REVIEW ARTICLE

Drugs Aging 2005; 22 (3): 231-255
1170-229X/05/0003-0231/$34.95/0

Assessing Medication Adherence in the Elderly

Which Tools to Use in Clinical Practice?

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Abstract

Adherence to prescribed medication regimens is difficult for all patients and particularly challenging for the elderly. Medication adherence demands a working

relationship between a patient or caregiver and prescriber that values open, honest discussion about medications, i.e. the administration schedule, intended benefits, adverse effects and costs.

Although nonadherence to medications may be common among the elderly, fundamental reasons leading to nonadherence vary among patients. Demographic characteristics may help to identify elderly patients who are at risk for nonadherence. Inadequate or marginal health literacy among the elderly is common and warrants assessment. The number of co-morbid conditions and presence of cognitive, vision and/or hearing impairment may predispose the elderly to nonadherence. Similarly, medications themselves may contribute to nonadherence secondary to adverse effects or costs. Especially worrisome is nonadherence to 'less forgiving' drugs that, when missed, may lead to an adverse event (e.g. withdrawal symptoms) or disease exacerbation.

Traditional methods for assessing medication adherence are unreliable. Direct questioning at the patient interview may not provide accurate assessments, especially if closed-ended, judgmental questions are posed. Prescription refill records and pill counts often overestimate true adherence rates. However, if elders are asked to describe how they take their medicines (using the Drug Regimen Unassisted Grading Scale or MedTake test tools), adherence problems can be identified in a nonthreatening manner.

Medication nonadherence should be suspected in elders who experience a decline in functional abilities. Predictors of medication nonadherence include specific disease states, such as cardiovascular diseases and depression. Technological aids to assessing medication adherence are available, but their utility is, thus far, primarily limited to a few research studies. These computerised devices, which assess adherence to oral and inhaled medications, may offer insight into difficult medication management problems. The most practical method of medication adherence assessment for most elderly patients may be through patient or caregiver interview using open-ended, nonthreatening and nonjudgmental questions.

The impact of medication nonadherence is staggering and often goes unrecognised. It is estimated that the true rate of adherence to medication regimens is only about 50%,[1-3] and ranges from 26–59% in persons aged ≥60 years.[4] Furthermore, one-half of filled prescriptions in daily clinical practice are incorrectly taken.[5] Conservative estimates suggest that medication nonadherence accounts for 10% of hospital admissions and 23% of nursing home admissions,[6] and thus may lead to significant clinical and economic consequences. While nonadherence is an important issue for all populations, it is particularly problematic for older persons who often experience a higher number of medical conditions and use more medications. Therefore, assessment of medication adherence in the elderly is essential.

Several methods to assess medication adherence are available. While some methods have been validated in clinical studies, they remain subjective and potentially biased.[1] Newer technological aids, while perhaps more objective, have not yet been validated in controlled clinical trials. Nevertheless, they are readily available and are marketed directly to consumers and caregivers to assess medication adherence in daily clinical practice.

1. Medication Adherence versus Medication Compliance

Medication adherence may be defined as the extent to which a patient's or caregiver's medication administration behaviour coincides with medical advice. Medication adherence generally refers specifi-

cally to administration of prescribed drugs. However, adherence to advice regarding over-the-counter (OTC) drugs, herbal and dietary supplements and lifestyle habits may substantially influence the efficacy of pharmacotherapeutic regimens. Ideally, these perspectives should be assessed along with adherence to prescribed medications. Successful medication adherence requires a collaborative relationship between the patient (or caregiver) and his/her healthcare provider(s). It includes all types of medications, diet, exercise and lifestyle activities that affect the safety and efficacy of medication regimens and the underlying disease states. However, the study of medication adherence has generally been limited to the administration of oral prescription drugs.

Medication 'adherence' is the preferred terminology, substituting for the older term 'compliance'. 'Compliance' is defined as the "act or process of complying to a desire, demand, or proposal to coercion" and a "disposition to yield to others".[7] Compliance implies a one-way relationship in which the healthcare provider gives directions with little or no input from the patient. Having possible paternalistic and omnipotent overtones, the notion of compliance is often viewed as being the sole responsibility of the patient. The patient is labeled as 'noncompliant' because he/she does not comply with the prescribed regimen no matter how complicated, unreasonable or expensive it may be. In fact, it may be the healthcare provider who does not comply with the lifestyle, health habits or economic means of the patient.[2] According to Haynes et al.,[1] "The term adherence is intended to be non judgmental, a statement of fact rather than of blame of the patient, prescriber, or treatment. Compliance and concordance are synonyms for adherence." Adherence emphasises two-way communication between patients and healthcare practitioners, which is essential for optimal adherence. Medication adherence implies that both prescriber and patient assume active roles in creating and executing a therapeutic regimen. An approach is agreed upon which is most likely to offer healthcare benefit with the least potential for adverse effects. Medication adherence is most likely to be achieved when an equal partnership exists between the patient and the healthcare team. Patients, caregivers, physicians, nurses and pharmacists all must work together to assess and then potentially improve medication adherence in the elderly.

2. Consequences of Medication Nonadherence in the Elderly

Very few patients of any age are able to adhere perfectly to a prescribed medication regimen. Studies reveal that one of six patients are able to maintain dosage intervals within the prescribed limits, adhere strictly to administration times, almost never miss a prescribed dose, and only occasionally take an extra dose.[8] Another one of three patients adheres satisfactorily, but occasionally omits one or more doses or occasionally takes an extra dose. Partial adherents, who make up another one of three patients, take >40% but <80–90% of the prescribed doses. Finally, one of six patients adheres poorly, administering <40% of prescribed doses at long, widely variable dosage intervals.[8]

The consequences of medication nonadherence in the elderly are profound. Col et al.[9] interviewed 315 patients ≥65 years of age upon hospital admission. Twenty-eight percent of admissions were drug related, with 11% being the result of nonadherence and 17% caused by adverse drug reactions. One-third of these elder patients gave a self-admitted history of nonadherence. Economic factors and adverse effects were the most commonly cited reasons for nonadherence leading to hospitalisation. In a more recent study of elderly patients ≥75 years of age, nonadherence, omission and cessation of drug therapy collectively accounted for 26% of hospital admissions.[10] Cardiovascular and CNS medications were involved in almost three-fourths of these events. The most frequent manifestations of nonadherence were falls, postural hypotension, heart failure and delirium.

Hospitalisations, re-hospitalisations, and nursing home admissions are recognised as direct costs of medication nonadherence in the elderly. However, medication nonadherence among the elderly may also result in disease progression, which can eventually exact a much greater human and economic toll. For example, 20% of patients who were experiencing partial vision loss as a result of glaucoma initiated at least one drug holiday period per month.[5]

Drug therapy was interrupted for ≥3 days and was unrecognised by physicians.

An estimated 40–45% of elderly individuals are unable to take their medications as prescribed.[11] Low medication adherence is increasingly recognised as a dominant feature in elderly patients.[12] This may result from forgetfulness, avoidance of troublesome adverse effects, cognitive decline, physical inability to self-administer medicines, economic limitations and intentional under dosage.

3. Effectiveness of Medication Adherence Improvement Programmes

Surprisingly, programmes designed to limit the health and economic toll of medication nonadherence did not undergo formal evaluation until the 1970s. Since then, no single method of medication adherence enhancement has proven to be superior or highly effective. Peterson et al.[6] evaluated 61 randomised studies of interventions to improve medication adherence. Each study reported on a minimum of ten subjects per intervention group, which was composed of either patients or caregivers. Only one-half of the studies reported patient age, and few randomised, controlled studies specifically targeted the elderly. Adherence definitions varied substantially across the studies with measures including percentage of adherent patients, percentage of patients achieving 70–90% adherence, and adherence score. The assessment methods used in these randomised studies mirrored the more traditional assessment methods reviewed in this article, i.e. patient self-report, pill counts and medication profile review. All three methods are known to overestimate medication adherence.[13] Overall, an increase in medication adherence of 4–11% was observed in the published studies.[6] The overall effect size of combined interventions (behavioural and educational) was 0.08 (95% CI 0.04, 0.12). As Haynes et al.[1] noted in a 2002 Cochrane review, there is little evidence that medication adherence can be consistently improved. Even the most effective interventions within randomised, controlled clinical trials did not produce large improvements in adherence and treatment outcomes. Furthermore, because the literature presents a publication bias toward positive studies, the effect size of adherence improvement methods is likely to have been overestimated.[1] However, the disappointing effect size of adherence improvement programmes does not rule out the possibility of occasional dramatic improvements in individual patients. Thus, prescribers, health maintenance organisations (HMOs) and pharmaceutical benefit managers continue to invest in methods to assess adherence and conduct follow-up medication adherence enhancement programmes.

Analysis of well-controlled medication adherence trials provides a framework for choosing an adherence assessment method which may be practical and useful in caring for the elderly. A diverse range of assessment tools was identified in the most recent Cochrane review of unconfounded, randomized, controlled trials of interventions to change adherence with medications, in which both adherence and treatment effects were measured.[1] Adherence assessment methods used within the controlled research environment included patient self-reports, observational checklist, observer subjective reports, pill counts (clinic and home), urine and serum drug concentrations, clinical measures (e.g. blood pressure, serum lipoprotein levels, hospitalisation rates, throat cultures, spirometry, depression symptoms and viral load), returned medications count, metered dose inhaler (MDI) canister weight, quality of life questionnaire data, electronic monitoring and prescription refill data.

Although newer technologies for assessing medication adherence, such as electronic monitoring, offer promise, most have not yet been evaluated in well-controlled clinical trials. Nevertheless, they may be useful in daily clinical practice. Before choosing the method(s) to assess medication adherence in a specific elder patient, however, the practitioner must first assess the potential reasons for possible nonadherence.

4. Understanding Fundamental Reasons for Nonadherence in the Elderly

Various underlying factors may affect medication adherence. These may be assigned to one of five categories using a modified classification scheme described by Balkrishnan:[14] (i) demographic; (ii) medical; (iii) medication; (iv) behavioural; and (v) economic (table I). Each of the five areas should be noted as being a potential positive or negative factor impacting the patient's ability to adhere to pre-

Table I. Potential factors that may affect medication adherence)[14]

Category	Factors
Demographic	Age
	Race
	Sex
	Occupation
	Educational level
	Health literacy
Medical	Type of disease
	Severity and duration of illness
	Number of co-morbid conditions
	Frequency of use of medical services
	Patient satisfaction with healthcare providers
	Quality of care
Medication	Dosing regimen
	Types of medication
	Number of concurrent medications
	Drug delivery system
	Use of adherence aids (e.g. pill box)
	Therapeutic regimen
	Adverse effects
Behavioural	Physician-patient interactions
	Patients' knowledge, understanding, and beliefs about their disease(s) and medications
	Caregiver knowledge and beliefs
Economic	Socioeconomic status
	Type of insurance coverage
	Costs of medication and medical care
	Patient income

scribed medication regimens. Most often a combination of these factors leads to medication nonadherence. Identification of patient-specific variables that influence medication adherence can be included in the comprehensive medical history and recorded in the patient's medical record in the same way that the family and social history are noted.

4.1 Demographic Variables

While increasing age is often assumed to be associated with decreased medication adherence, most data demonstrate that age is not a factor.[15,16] In fact, some studies suggest that advanced age (i.e. ≥65 years of age) may be positively correlated with adherence.[17,18] In a study of adherence to antihypertensive therapy among elderly Medicaid enrollees, patients who were ≥85 years of age demonstrated higher good adherence rates (≥80%), as assessed by prescription claims data, than those between 65 and 74 years of age (odds ratio [OR] 2.12; 95% CI 1.72, 2.60).[17] However, medication-taking behaviour varies across the aging continuum. Park et al.[19] observed that the old-old adults (≥71 years of age) showed more nonadherence than the young-old adults (≤70 years of age). The old-old adults were particularly prone to under adherence resulting from omission of medications.

Another factor contributing to medication nonadherence in the elderly is a high incidence of marginal or inadequate functional health literacy. Functional health literacy is defined as the ability to read, understand, and act on health information.[20] It includes the ability to read and understand a prescription label, a manufacturer's package insert, or patient-specific medication instructions. Functional health literacy is markedly lower in older persons even after adjusting for gender, race, ethnicity, cognition, visual acuity and years of schooling.[21] Up to 35% of English-speaking US Medicare-managed care enrollees demonstrated inadequate or marginal health literacy.[22] Inadequate functional health literacy among US Medicare enrollees was associated with never receiving the influenza vaccine (OR 1.4; 95% CI 1.1, 1.9) or pneumococcal vaccination (OR 1.3; 95% CI 1.1, 1.7).[23] Unfortunately, healthcare practitioners rarely assess the literacy skill of their older patients even though screening tools are available.[24] Because health literacy does not correlate well with years of schooling or education level, it is important that practitioners independently assess health literacy prior to prescribing medication regimens. One such screening tool, the Short Test of Functional Health Literacy in Adults, takes 7 minutes to complete and may be administered by office staff or a nursing assistant.[25] Alternatively, staff may ask a patient to read a short passage, knowing that illiterate patients will often avoid potential embarrassment by saying they forgot their eyeglasses or that they will read the material at a later date.

4.2 Medical Variables

Medical factors that may affect drug adherence include the type of disease(s), severity and duration of illness, number of co-morbid conditions, frequency of use of medical services, patient satisfaction with healthcare providers and quality of care.[14]

The elderly are at particularly high risk of nonadherence from medical-related factors. First, they often have decreased visual acuity, hearing and manual dexterity, which may make it difficult for them to read prescription labels, differentiate tablet colours and open prescription vials.[26] Secondly, other medical conditions which predict poor adherence are common in the elderly, e.g. cognitive impairment, increased psychological stress and depression.[16,26,27] It is important to note that the elderly often do not recall their own medical conditions. In a study of community-dwelling seniors, subjects reported a mean of 6.11 specific medical conditions.[28] However, only one-half of the conditions were spontaneously recalled by the seniors. The other one-half were identified by prompted recall when the interviewer asked if the senior had any of >50 specific medical conditions.

4.3 Medication-Related Variables

Medication-related factors that may influence adherence include administration regimen, type of medication, drug delivery system, therapeutic regimen and adverse effects (see also sections 6 and 7).[6,14]

Multiple studies involving patients with a range of ages and disease states have evaluated administration regimens and consistently found that administration frequencies that exceed twice daily are associated with decreased adherence.[29-37] No significant difference in adherence rates has generally been noted between once daily versus twice daily regimens. However, most of these studies involved relatively limited numbers of elderly patients, particularly those >75 years of age.[38] In a review of 26 adherence studies, adherence with once daily administration regimens was 73% versus 70% with twice daily regimens.[39] However, as the frequency of administration increased to more than twice daily, adherence decreased markedly with an average adherence rate of 52% with three times daily administration and 42% with four times daily administration ($p < 0.05$ for once daily and twice daily administration versus either three times daily or four times daily).

Since little difference in medication adherence has been noted between once or twice daily administration regimens, there may be little benefit, and possible harm, with switching from a twice daily to a once daily regimen.[38] Forgetting to take a single dose of a drug that is given once daily may place the patient at more risk than forgetting a single dose of a drug that is given twice daily. It would be ideal if any medication given on a once daily basis possessed capacity for 'forgiveness'. Forgiving drugs are those that, because of their pharmacokinetics or pharmacodynamics, have a blunted response when one or two doses are missed.[40] This may allow greater variability in timing of doses, and perhaps reduce the clinical consequence of a missed dose(s). An example of this phenomenon can be seen with intermediate-acting β-adrenoceptor antagonists (atenolol) and long-acting β-adrenoceptor antagonists (betaxolol).[41] The impact of missing a dose of betaxolol on blood pressure is significantly less than that of missing a dose of atenolol. Thus, betaxolol would be considered to be a more 'forgiving drug'.

Many pharmaceutical manufacturers are reformulating products to provide for extended administration frequencies (i.e. once-weekly administration). However, most studies assessing newly reformulated agents have focused on demonstrating equality in efficacy and safety, not enhanced adherence. Burris et al.[42] evaluated adherence with once weekly transdermal clonidine versus once daily sustained release oral verapamil, and found increased adherence with once weekly transdermal clonidine (96–100% vs 37–69%). In a 12-week study of once weekly versus once daily fluoxetine in 117 patients with depression, adherence rates during the first month were similar (85.4% vs 87.3%).[43] However, while adherence remained similar during the maintenance phase compared with the initial 1 month in the weekly dosed group (87.5%), there was a significant decline in adherence in those receiving once daily fluoxetine (79.4%, $p < 0.001$).

The number of concurrent medications a patient is taking may also impact on medication adherence. As noted earlier, the elderly are often afflicted with multiple chronic diseases. Thus, they will require several different medications to treat these. In one study, the mean number of different medications consumed by a cohort of well-educated community-dwelling seniors was 5.9 prescription medications, 3.5 OTC medications, and 0.4 herbal supplements.[28] The steady increase in consumption of

OTC and herbal medications is often overlooked when assessing medication adherence. Physicians are usually not aware of self-medication regimens, and patients and their caregivers are sometimes reluctant to volunteer such information. Thus, drug-drug and drug-disease interactions involving OTC and herbal products are difficult to detect. Consumption of OTC and herbal products may indicate that the patient is truly engaged in his/her medical therapy and is assuming a higher order of self-responsibility (with concurrent enhanced adherence). Alternatively, self-care using OTCs and herbal supplements may indicate enthusiasm for alternative medicines (and disappointment with traditional prescribed medicines), which may be associated with intentional nonadherence to prescription drug regimens. The cost of OTCs, herbal supplements and alternative medicine therapies may easily approach hundreds of dollars each month and further prompt the elderly to intentionally underdose prescribed medicines.

Use of numerous medications has been presumed to be associated with poor adherence,[44] and may be a risk factor for hospitalisation because of nonadherence.[9] However, in a study by Billups et al.,[18] both a high number of chronic conditions and use of a high number of concurrent drugs were positively correlated with adherence ($p < 0.001$ for both). Additionally, in a study of hypertensive patients by Sharkness and Snow,[45] use of more than one drug was associated with better pharmacy adherence. Thus, the relationship between the number of medications and adherence may be more complicated than generally appreciated.

4.4 Behaviour or Patient Belief Variables

Several different sociobehavioural characteristics and patient beliefs are associated with medication adherence. These include factors such as physician-patient interactions and the patient's knowledge, understanding, and beliefs about their disease(s) and medication.[14,45-48]

Patients' knowledge and beliefs about their medication and/or disease states appear to play a significant role in therapy adherence. Patients who understand their disease, the perceived need for treatment, and their medications generally have better adherence.[9,45,46] Knowledge about diseases and their consequences is presumed to be a positive factor influencing adherence. However, controlled studies clearly demonstrate that enhancing disease state knowledge alone does not improve medication adherence.[6] In addition, for conditions in which treatment may be targeted towards prophylaxis, asymptomatic treatment or symptomatic treatment, differences in adherence may be noted. In a study by Jackevicius et al.,[49] adherence to treatment with HMG-CoA reductase inhibitors (statins) was higher in patients with symptoms of acute coronary syndromes (40.1%) than in those with chronic coronary artery disease (36.1%) or when used for primary prevention (25.4%).

Several different behavioural patterns of nonadherence have been observed. Up to one-third of patients may take a drug 'holiday', during which time a medication is intentionally omitted for several consecutive days.[50] Full strength therapy is then resumed. Depending on the type of drug used, length of therapy and indication, such nonadherent behaviour may have serious deleterious consequences. Three adverse events are potentially associated with drug holidays. The initial cessation of therapy causes a drug-free period in which therapy is abruptly stopped. Therapeutic coverage is then lacking, such as when antiepileptic therapy is discontinued. Secondly, for some agents, such as antihypertensives (e.g. β-adrenoceptor antagonists and clonidine), the drug holiday may precipitate rebound disease manifestations and precipitate an acute exacerbation of the underlying disease. Thirdly, when therapy is resumed after several days of absent drug effect, excessive drug effect may occur. Patients do not re-titrate their medication upward, thus again precipitating first dose effects, such as the postural hypotension observed with ACE inhibitors. For other agents, such as cholinesterase inhibitors, the on-off nature of a drug holiday reintroduces adverse effects such as nausea and vomiting. The magnitude of such adverse effects is proportional to the pharmacodynamic half-life of the drug, the release mechanisms of the formulation, concurrent therapy and underlying pathophysiology.[40,41] Table II lists potential clinical consequences of elder-initiated drug holidays for commonly used drug classes. A final consequence of the drug holiday syndrome is financial. Drug holidays of less forgiving drugs,

Table II. Potential clinical consequences of elder-initiated drug holidays[a]

Drug type	Drug holiday syndrome
Paracetamol	Breakthrough pain prompting NSAID therapy and its associated renal, gastrointestinal and cardiovascular effects, increased use of opioids
ACE inhibitors	Rebound hypertension and ischaemic events, heart failure exacerbation and hospitalisation, first dose hypotension upon reinstitution, fluctuating electrolyte homeostasis
α-Adrenoceptor antagonists	Rebound hypertension or acute urinary retention as a result of underlying benign prostatic hypertrophy
Angiotensin II type 1 receptor antagonists	Rebound hypertension
Antibacterials	Infection relapse, drug resistance, warfarin drug interactions unpredictable
Anticholinergics	Acute urinary retention and many other adverse effects on reinstitution, underlying disease exacerbation (e.g. asthma, glaucoma etc)
Antidepressants (SSRIs, SNRIs, TCAs)	Depression relapse, withdrawal symptoms
Antiepileptic drugs	Seizure relapse, worsening of behaviours associated with dementia
Antidiabetic agents	Worsened glucose control
Antiplatelet agents	Coronary, peripheral and cerebrovascular events, including stent occlusion
Antipsychotics	Acute behavioural disturbances, falls, anticholinergic adverse effects on reinstitution
Antiretrovirals	Drug resistance accelerated, opportunistic infections in HIV patients, acute postherpetic neuralgia attacks
Antirheumatics	Flares, progressive disease with structural damage
Anxiolytics	Anxiety, panic attacks, behaviour disturbances
Asthma medications (oral and inhaled)	Acute exacerbation with potential hospitalisation
β-Adrenoceptor antagonists	Exacerbation of underlying heart disease, rebound hypertension, angina, tachycardia, loss of rate control in atrial fibrillation
Calcitonin	Pain breakthrough, fracture rehabilitation time lengthened
Calcium channel antagonists	Angina and hypertension exacerbation, reflex tachycardia
Cholinesterase inhibitors	Behavioural and psychological symptoms worsened, increased caregiver burden, functional decline, nausea and vomiting with need to re-titrate using escalating doses
Digoxin	Heart failure exacerbation, loss of rate control if used for atrial fibrillation
Diuretics	Heart failure exacerbation, hypertensive rebound
Fibre supplements	Exacerbation of diverticular disease, opioid-induced constipation, impaction
Glaucoma medications	Accelerated vision loss
Histamine H_2 antagonists	Reflux relapse, erosive oesophagitis, symptoms mimicking myocardial infarction
Hypnotics	Sleeplessness
Nitrates	Angina, heart failure exacerbation, headache upon reinstitution
NSAIDs	Recurrent pain, limited mobility and activities of daily living
Parkinson's disease medications	Motor fluctuations, re-titration difficult because of adverse events
Potassium supplements	Potassium fluctuations predispose to cardiac arrhythmias
Proton pump inhibitors	Gastroesophageal reflux disease relapse, erosive oesophagitis, symptoms mimicking myocardial infarction
Spironolactone	Heart failure exacerbation with hospitalisation, electrolyte imbalance
HMG-CoA reductase inhibitors (statins)	Increased coronary events
Warfarin	Thrombotic events, bleeding complications on reinstitution and dose re-titration, variable drug interactions leading to thrombosis or bleed

a A drug holiday is defined as 3 or more consecutive days without drug therapy resulting from patient self-initiation. All drug holidays may create variable and unpredictable drug interactions.

SNRIs = serotonin-norepinephrine reuptake inhibitors; **SSRIs** = selective serotonin reuptake inhibitors; **TCAs** = tricyclic antidepressants.

such as the cardiovascular agents, may have a significant economic impact because patient-initiated discontinuation of these drugs is clearly associated with increased physician visits and hospitalisations.[50]

Another commonly observed behaviour is improvement in medication adherence several days prior to a scheduled medical examination. This phenomenon, often termed 'white coat compliance'[8] or the 'tooth brush effect',[51] may substantially overestimate patient adherence. These behaviours in which the patient portrays good adherence reflect the desire to please the healthcare provider or to be perceived as a 'good patient'. This is particularly true for medications in which serum drug concentrations are to be drawn at a scheduled clinic visit.[52,53]

While poor medication adherence is often presumed to be nonintentional (e.g. as a result of forgetfulness), this may not always be the case. In a study by Cooper et al.,[15] 71% of nonadherence was intentional, whereas unintentional nonadherence accounted for <30%. Reasons cited for intentional nonadherence included perception that the medication was not needed (52%), adverse effects were occurring (15%), or the patient needed more of the prescribed drug than was prescribed (4%).

Utilising behavioural medicine principles, Garfield and Caro[54] have proposed that adherence may be improved and sustained by assessment and movement through the following stages-of-change: 'precontemplation' (patient is not intending to change), 'contemplation' (patient considers change), 'preparation' (small changes are initiated), 'action' (active behavioural changes are made), and 'maintenance' (sustained, long-term change in behaviour). In a study by Willey et al.,[55] the stages-of-change model was assessed for construct and predictive validity for assessing medication adherence using previously validated measures in patients with chronic disease (HIV and hypertension). In the 731 patients with hypertension (mean age 56.6 years), the Medical Outcome Study measure of adherence was strongly associated with stages-of-change ($p = 0.001$). Recognition of which stage a patient may be in enables the physician to recommend an appropriate intervention aimed at increasing adherence (e.g. use of a monitoring device for patients in the 'action' or 'maintenance' stage).

5. Methods of Assessing Adherence

Traditional adherence assessment methods, although still frequently used by healthcare providers, often yield inaccurate and unreliable data when used alone. These methods include patient or caregiver self-report, review of refill records and pill counts (see sections 5.1, 5.2 and 5.3).[1] Two other methods, i.e. inquiry into ability to pay for medicines and a pharmacist's adherence assessment using open-ended nonjudgmental questions, are modifications to the patient or caregiver self-report that may offer somewhat more reliable data (see sections 5.4 and 5.5).

5.1 Patient and Caregiver Self-Report

Clinicians traditionally rely upon self-report to assess medication adherence. During the interview, the patient or occasionally the caregiver will be asked a direct question regarding medication use. Healthcare professionals often pose a single closed-ended, judgmental question such as, "Do you take your medicines as prescribed?" Invariably, patients respond 'Yes' for fear of alienating their provider and because of discomfort in sharing difficulties associated with medication use. This direct method of questioning has been proven to be unreliable.[13] An alternative interview approach provides more complete and reliable information. By posing open-ended, nonjudgmental questions, interviewers may actually encourage patients to share their experiences with medications. Phrases such as, "Will you tell me how you take your medications?", have proven helpful in soliciting greater information.[28] Elderly patients may also be asked to show the interviewer how they take their medications.[56] This method allows the interviewer to assess the number of tablets or pills taken, the time of day the medication is taken, and the indication for use of each medicine. Table III lists several questions which may be useful when inquiring about medication use.

5.2 Prescription Refill Records

Prescription refill records are useful for assessing medication adherence only if the patient purchases their medications and the medications are obtained from a single source. Although still used by some managed care organisations and pharmacy benefits

Table III. Medication adherence inquiries

Tell me how you take your medicines
How do you schedule your meal and medication times?
Do you use a pill box or organiser to help you take your medicines?
How do you manage to pay for your medicines?
If possible, would you like me to simplify your medication regimen?
If possible, would you like to explore some options for reducing your out-of-pocket medication expenses?
Show me how you use your inhaler

managers, the information obtained with this approach is generally inadequate.[1] Merely obtaining a refill or renewing a prescription provides no information about the actual consumption of the medication. Patients may order refills, especially when prompted to do so by a phone call or post card, but they may also hoard medicines and have large stashes of unopened medications in their home.

5.3 Pill Counts

Once thought to be a useful method for assessing adherence, pill counts are also unreliable. In one study, measurement of adherence by returned pill counts grossly overestimated adherence as measured by a pharmacological indicator.[57] In a trial of patients taking two antihypertensives, weekly pill counts masked excessive medication taking immediately before the return visit.[58] This pattern of 'pill dumping' is more likely to occur when patients are aware that the prescriber suspects nonadherence. In an adherence assessment study of 91 diabetic patients using oral agents, both the return pill counts and prescription refill data overestimated adherence as assessed by electronic monitoring.[59]

5.4 Ability to Pay Assessment

Economic factors play an increasing role in medication adherence, particularly in countries with capitalistic healthcare systems (e.g. the US). In these countries, the patient's socioeconomic status, type of insurance coverage and costs of medications and general medical care may combine with rising medication co-payments to render prescription drugs unaffordable. In a 2-year period, more than 2 million elderly US Medicare beneficiaries did not adhere to drug treatment regimens because of cost, with associated worsening of hypertension and heart disease.[60] Programmes which help secure resources for medications may significantly improve adherence. In a study by Paris et al.,[61] development of such a programme for transplant patients significantly reduced nonadherence from 25% in patients who had been transplanted before the availability of such a programme to 10% ($p < 0.01$). Economic factors were cited as common reasons for hospitalisation as a result of nonadherence. Col et al.[9] found that patients in a medium income category who believed that medications were expensive had a higher rate of hospitalisations secondary to nonadherence.

Providing economic relief in the form of prescription medications may have a significant effect on adherence and clinical outcomes. In a study by Schoen et al.,[62] indigent patients with heart disease who were provided prescription medications free of charge showed significant improvements in drug adherence (48.5–72.6% at 6 months; $p < 0.001$), diastolic blood pressure, and low-density lipoprotein level. In addition, hospitalisations decreased from 85 admissions at baseline (0.52 ± 0.86 admissions/patient) to 49 admissions (0.31 ± 0.81 admissions/patient, $p < 0.05$) at 6 months. Thus, while some insurance plans may not cover prescription drugs because of perceived extra costs, such coverage may in fact improve adherence and lower overall health system costs as a result of improved disease control and decreased hospitalisations.

A simple method for assessing medication adherence may be direct inquiry regarding the patient's ability to pay for his/her medicines. Mojtabai and Olfson[60] found that 7% of Medicare beneficiaries reported poor adherence because of the cost of drugs. Thus, an open-ended question such as, "How do you pay for your medicines?", is likely to provide useful information. Prescribers must understand the availability and limitations of any insurance or drug card programme. One useful approach is to create a complete medication list, including OTCs and sup-

plements, and then record the patient's out-of-pocket expense for each medication. Prescribers are often surprised to learn that prescription co-pays alone can easily approach several hundred dollars each month. A follow-up question may then reveal patients who, for financial reasons, are intentionally not filling prescriptions or using drug holidays to stretch their medications. Prescribers should evaluate the complete therapeutic regimen. Single source branded drugs may have equally effective therapeutic alternatives. Prescribers should also have a general knowledge of the indigent drug programmes offered by pharmaceutical manufacturers.

5.5 Pharmacist Assessment of Adherence

Using a combination of approaches, pharmacists may be able to detect adherence difficulties that would otherwise go unrecognised. However, no single traditional method of assessing medication adherence is reliable even when used by pharmacists.[3,63] A direct interview starting with an open-ended statement is recommended, such as: "I know many people have difficulty taking their medicines, so please tell me how you manage all these drugs." The resulting conversation should solicit information about possible adverse effects, overly complicated medication schedules and inability to pay for medications.

Pharmacists may use refill information as a screening tool for nonadherence. However, with the increasing use of mail order and internet pharmacies, such face-to-face opportunities to discuss medication-taking behaviour with patients are rare. Furthermore, an increasing number of patients are being forced to use multiple pharmacies, such as mail order for long-term medications and a local pharmacy for short-term medications. Pharmacists are sometimes able to check the accuracy of filling a pill box by comparing its contents with the original prescription containers. Unfortunately, pharmacists may be unable to devote the time required for comprehensive medication adherence assessment, and they are generally not compensated for such evaluations.

5.6 Medication Management Assessment Tools for the Elderly

Several assessment tools may help evaluate older patients' medication management skills (table IV). Meyer and Schuna[64] described the use of their screening tool in 93 patients in both an inpatient and outpatient setting. Components of this tool included patient's self-report of medication management and the simulated ability to read labels, open safety vials, understand the requirements of taking medications according to a three times daily regimen, remove tablets and differentiate colours. However, the relationship between capacity to manage medications and medication adherence was not specifically evaluated. Ruscin and Semla[26] utilised Meyer and Schuna's assessment tool, adapted by excluding the component of opening a nonsafety capped vial, as part of a comprehensive medication history performed by a clinician-pharmacist in 83 outpatients. They found that having at least one physical dependency in activities of daily living or cognitive impairment (Mini-Mental State Examination [MMSE] <24), was an independent risk factor for poorer performance ($p < 0.001$). However, this tool has yet to be validated and the evaluation did not control for poor vision, colour blindness or arthritis.

Fitten et al.[65] described an adherence capability testing instrument which evaluated cognitive and functional abilities. Functional capacity, assessed by manual dexterity, ability to read and comprehend prescription labels, and subjects' understanding of two hypothetical situations, were compared between medically ill inpatients and outpatients, and an age-matched, independent group. Medically ill patients failed the hypothetical scenarios more often than controls (29% vs 5%). However, there was no difference in manual dexterity and ability to read and comprehend prescription labels. There was moderate to good correlation between MMSE score and performance on each scenario ($r = 0.7$ and $r = 0.69$, $p < 0.01$ for scenarios 1 and 2, respectively).

Another tool to evaluate medication management skills is the Drug Regimen Unassisted Grading Scale (DRUGS).[56] The DRUGS tool evaluates patients' ability to identify their own medication, open the container, remove the appropriate dosage and demonstrate the appropriate timing of administra-

Table IV. Medication management assessment tools

Author and screening tools	Meyer and Schuna[64]	Fitten et al.[65]	Edelberg et al.[66] DRUGS tool	Raehl et al.[28] MedTake tool
Overview	One composite score	Three independently scored tests	One composite score	One composite score
	Simulation	Simulation	Patient's own medications	Patient's own medications
Tool components	Ability to read a 12-point font prescription label	Test 1: ability to read and comprehend labeled prescription vials: 5 main labels and 2 auxiliary labels read aloud, the meaning of the labels described in the patient's own words	Identification: showing appropriate medications	Dose correctly stated
	Ability to open and close a child-resistant cap on a 7-dram vial	Test 2: test of manual dexterity to open, withdraw the proper amount of medication, and then close the medication vial	Access: opening appropriate containers	Indication correctly stated
	Ability to open and close a nonchild-resistant cap on a 7-dram vial	Test 3: test of ability to understand hypothetical medication regimens: 2 scenarios of varying difficulty followed by questions to test 3 areas (memory, estimation of consequences, and judgment)	Dosage: dispensing the correct number per dose	Food, water coingestion described appropriately
	Ability to remove 2 medication tablets from an opened 7-dram vial		Timing: demonstrating appropriate timing of doses	Regimen correctly described
	Ability to describe a 3 times daily regimen		Each task is performed for each medication that the patient takes	
	Ability to differentiate tablets by colour			
Detailed scoring method	1 point for performing the task	Test 1: 1 point for each correct label and explanation	1 point for each action for each medication	0–100% for each oral prescription medication
	0 points for uncompleted tasks	Maximum score = 14	0 points for each task the patient is unable to perform	Overall calculated mean score (MedTake) 0–100%
	Maximum score = 4	Test 2: 1 point for each task for 5 different types of vials	Maximum score = number of medications × 4	
		Maximum score = 15		
		Test 3: 3 points for correct answers without cueing, 2 points for correct answer with cueing, 1 point for partially correct answers with cueing, 0 points for incorrect answers		
		Maximum score for scenario 1 = 33		
		Maximum score for scenario 2 = 27		

DRUGS = Drug Regimen Unassisted Grading Scale.

tion of each of their own prescription and OTC medications. When Edelberg et al.[56] evaluated the DRUGS tool in 60 older outpatients, they found that patients' scores were inversely related to age and significantly lower in patients residing in an assisted living environment compared with those who lived at home. Patients' self-reported capacity to handle their own medications, including denial of aid in arranging, taking or remembering to take their medications, was correlated with DRUGS tool scores (94.8% able vs 86.2% unable to take medication independently by self report, $p = 0.047$). The DRUGS tool score and the patients' self-reported medication management capacities were positively associated with MMSE score ($p < 0.001$ and $p = 0.044$, respectively). No significant association between DRUGS scores and the actual number of medications or doses that a patient consumed was found. Both inter-rater and test-retest reliability were high (>0.90 for both, respectively). In a follow-up 12-month study, a move from independent living to an assisted living facility was associated with a significant decline in the DRUGS score.[66] The DRUGS tool may provide some insight into seniors' abilities to live independently and manage their own medications.

A fourth tool, the MedTake test,[28] is useful for assessing drug therapy adherence in the elderly. Like the DRUGS tool, the MedTake test asks seniors to describe how they take each of their oral prescription medications. Both the MedTake and DRUGS tools evaluate adherence to medication regimens prescribed for a specific patient and avoid simulated tests. Multivariate regression revealed that performance on the MedTake test was significantly related to MMSE score ($p = 0.002$) and need for Medicaid assistance within 10 years ($p = 0.21$).[28] Although the MedTake tool often detected nonadherence with the medication regimen, an additional 20% of seniors had potentially clinically significant medication problems identified by follow-up pharmacist evaluation of the medication regimen. Further study utilising medication management assessment tools is needed to establish their role in the routine assessment of adherence.

6. Disease and Drug-Based Adherence Assessment

In order to fully assess adherence, it is important to recognise disease specific and medication specific factors that may predict nonadherence. Disease characteristics such as cognitive and functional decline can profoundly affect adherence. Serum or urine physiological markers may prove useful for assessing adherence or therapeutic effect. Disease specific devices may be helpful in overcoming functional limitations which interfere with appropriate medication administration.

6.1 Decline in Functional Abilities

Diminished functional abilities may exert an adverse effect on adherence. Older patients may have difficulty distinguishing between tablet colours, particularly blue-green and yellow, as well as tablet or capsule size.[67,68] Older patients frequently have difficulty opening child-proof medication lids or smaller medication containers,[68,69] and they have diminished hearing. An evaluation of elderly patients' abilities to read and comprehend medication labelling combined with verbal instruction found that older age was associated with greater errors in recall and comprehension skills related to timing of medication administration, quantity to be taken, special administration instructions, indications and recording medication information (e.g. name of drug, dose, administration time).[70] Both the inability to read prescription labels and to open prescription vials are associated with nonadherence.[71]

Several interventions to help overcome functional challenges have been evaluated. An intervention trial evaluating the effects of mixed pictorial and traditional labelling of prescriptions versus traditional labelling of prescriptions alone found that mixed labelling was associated with poorer performance (i.e. more errors) by older subjects when asked to provide information on dosage, administration, indications, and special medication instructions compared with younger subjects ($p < 0.001$).[72] Increased errors were most likely a result of increased requirement for translation or manipulation of the pictorial data. Older patients may not devote adequate time to reading labels and, consequently, do not recall the information they contain.[72] Health-

care professionals should therefore devote more time to ensuring elder patient understanding and recall of newly prescribed medications.[70]

Medication adherence can be affected by how the prescription label directs the patient to schedule medications. Hanchak et al.[73] evaluated differences in patient understanding of dosage instructions (namely written dosage intervals) in 500 outpatients. Prescription dosage instructions written in hourly intervals, for example, every 6 hours, were more likely to be misinterpreted than instructions written in frequency per day, for example, three times daily (relative risk [RR] = 83; 95% CI 31, 200). Thus, medications requiring around-the-clock or hourly administration should be prescribed with specific times of the day to ensure clarity. This is a simple and inexpensive intervention that could be incorporated into standard practice.

Cognition is a determinant of medication adherence. Cognitive impairment (MMSE score <24 of 30) has been reported to be associated with both over and under adherence.[12] In addition, Isaac and Tamblyn[74] determined that visual memory skills also appear to correlate with adherence.

6.2 Targeted Disease State Adherence Enhancement

Determining factors that influence treatment adherence in specific diseases may provide insight into targeting interventions to improve adherence. This involves understanding differences in patient responses and beliefs related to symptomatic, asymptomatic and prophylactic therapy, factors associated with nonadherence in specific diseases, and appropriate use of adherence aids. A number of studies have identified potential predictors of adherence or nonadherence in chronic disease states common in the elderly, such as chronic obstructive pulmonary disease (COPD), breast cancer, cardiovascular disease (e.g. hypertension, congestive heart failure) and glaucoma.

6.2.1 Predictors of Adherence in Chronic Obstructive Pulmonary Disease

COPD is a common disorder in the elderly. When Turner et al.[75] evaluated 985 patients with COPD who were receiving nebuliser therapy, patient characteristics which predicted adherence included older age, higher education level, White race, marital status, less tobacco consumption, less alcohol consumption, serum theophylline levels ≥9 μg/mL, moderate-to-severe shortness of breath, and lower post-forced expiratory volume in 1 second. The overall adherence rate, defined as average nebuliser use ≥25 minutes/day, was 50.6%. A logistic regression accounted for 62% of the variation in patient adherence.

Predictors for incorrect inhaler technique, a factor that may also predict nonadherence in older patients receiving MDIs for COPD, have also been studied. When Gray et al.[76] studied 72 subjects who were either inhaler naive or had not received MDI therapy over the previous 6 months, predictors of nonadherence included lower hand strength (despite all patients being able to depress the MDI canister), male gender and an MMSE score <24.

6.2.2 Predictors of Adherence in Breast Cancer

Partridge et al.[77] studied 2378 subjects, average age 75 years, who were receiving tamoxifen for treatment of primary breast cancer. They found that 77% of patients were adherent during year 1 of therapy, but only 50% of patients remained adherent by year 4 of follow-up. Patients falling into the age extremes (<45 years of age or >85 years of age), non-Whites, patients who were postmastectomy, and those who had not seen an oncologist within 1 year prior to initiating therapy were more likely to be nonadherent to tamoxifen.

6.2.3 Predictors of Adherence in Cardiovascular Diseases

ACE inhibitors are widely used in the elderly for hypertension and chronic heart failure. Roe et al.[78] evaluated adherence with ACE inhibitors 6 months before and after hospitalisation for heart failure in the hope of identifying factors that may predict adherence. Adherence was greater posthospitalisation in males and in patients who demonstrated higher medication possession ratios (supply of medication in days/number of days evaluated) prior to hospitalisation. Unlike some studies that found improvement in adherence with physician visits, lower adherence postdischarge was noted in patients who had seen a cardiologist in the 6 months prior to hospitalisation. It was postulated that this counterin-

tuitive finding may have been related to undiagnosed depression.[78]

Depression is recognised as a common co-morbidity of cardiovascular diseases.[79] After controlling for potential confounders (i.e. demographic variables, use of thiazide diuretics, presence of comorbid conditions and locus of control orientation), depression was associated with lower adherence.[80] Similarly, Ziegelstein et al.[81] noted poorer adherence to lifestyle modifications in postmyocardial infarction patients with elevated depressive symptoms (Beck Depression Inventory scores >8) at the time of the event. In summary, depression is associated with medication nonadherence,[82] and depression screening is therefore warranted when nonadherence is suspected.

6.2.4 Predictors of Adherence in Glaucoma

In a study by Gurwitz et al.,[83] prescription data were evaluated to assess adherence to glaucoma medications in 616 newly treated patients. Although fewer ophthalmological visits during year 1 of follow-up was associated with greater nonadherence, few other characteristics were identified that might assist in predicting nonadherence in this population. Adherence did not appear to be significantly influenced by indicators of greater disease severity (e.g. higher intraocular pressures or visual field testing abnormalities). Indeed, it was proposed that using intraocular pressure as a measure of adherence might be misleading, as this measurement samples a finite point in time and may be representative of adherence immediately preceding an ophthalmological appointment (i.e. 'white coat compliance').

Nonadherence with eye drop regimens varies from 21% to 70%, with reported problems including fear of poking the eye, difficulties opening the tamper proof seal, difficulties with aim, difficulties squeezing the dropper bottle and problems with patients' ability to raise their arms and appropriately tilt their heads.[84-86] Several eye drop administration aid devices are available. These include the Easidrop® [1] and Auto-drop® devices, which help primarily with aim, as well as the Opticare® eye drop dispenser, which aids both aiming and squeezing of the bottle.[84] All devices are reusable, available over the Internet and sell for approximately $US4.00–10.00.[87-93]

The Opticare® eye drop delivery system was evaluated by Averns et al.[86] in 30 patients with rheumatoid arthritis and symptoms of keratoconjunctivitis sicca. Use of the device was associated with a significant improvement in ability to squeeze and administer drops ($p = 0.001$ and $p = 0.003$, respectively). Problems observed with the use of the eye drop bottle without the assistive device included touching the bottle tip to the eye and/or conjunctiva or blinking away drops. Thus, use of an eye drop assistive device for elderly patients with glaucoma may be quite beneficial, particularly in the context of appropriate medication administration adherence.

6.3 Drug Class Adherence Assessment and Enhancement

Blood, urine and plasma drug concentrations are sometimes useful when assessing adherence to specific medication regimens. However, adherence assessment using urine assays is plagued with difficulties, including the impact of sample collection time on results and inaccurate drug assays.[94] Similarly, assessment of adherence based on plasma drug concentrations may be misleading as adherence may improve immediately prior to an expected blood draw. Taggart et al.[34] did not find noteworthy differences in digoxin levels despite significant changes observed in adherence to twice daily versus four times daily therapy. This was most likely a result of the very long elimination half-life of digoxin, and shows that evaluation of adherence by measuring blood drug concentrations is less sensitive for detecting intermittent administration.

Because of the possible shortcomings of plasma drug concentrations as a measure of adherence, the potential role of various disease markers has been studied. Struthers et al.[95] evaluated markers for adherence to ACE inhibitors in 39 patients with congestive heart failure. All disease markers studied (serum ACE activity via plasma *N*-acetyl-seryl-aspartyl-lysl-proline [AcSDKP] levels, plasma angiotensin II [AII] : angiotensin I [AI] ratio, plasma AI levels and plasma AII levels) were able to distinguish between complete adherence and complete

1 The use of trade names is for product identification purposes only and does not imply endorsement.

nonadherence. However, only plasma AcSDKP was able to distinguish between full adherence and partial nonadherence.

7. Technological Aids to Adherence Assessment

Older patients are more likely to use medication adherence aids. One of the most commonly used devices is the weekly pill box which has separate compartments corresponding to breakfast, lunch, dinner and bedtime for each day of the week. One study found that a pillbox is used by 70% of community dwelling elders.[28] Many elders fill their own weekly pill boxes, but at least 20% receive help from family members, friends or home health aids. Elders are also more likely to use a calendar as a medication reminder or create their own unique reminder system, such as coding prescription vials with large letters or coloured labels. Thus, in order to assess medication adherence by an elder, the practitioner must inquire about the use of these aids, how they are used by the patient, and who fills them; the pill box contents also need to be compared with the administration details on the current prescription containers.

While relatively low technology methods for adherence assessment (e.g. pill boxes, pill counts) are most commonly used, newer products and tools utilising computer technology have been developed. These include computerised refill reminder programs, electronic prescription vial monitoring systems, MDI aids, interactive electronic health and medication monitors, and automated pill boxes. Table V lists several electronic adherence devices currently available.

7.1 Automated Refill Reminders

Automated refill reminder programs vary in complexity from automatic refilling of a maintenance medication to automated messages sent to a home telephone or e-mail account. The effectiveness of automated refill reminders is unproven.[108,109] Unclaimed prescriptions may signal nonadherence, but no intervention (i.e. postcards to patients, postcards to prescribers, telephone calls to patients or telephone calls to prescribers) increased pick-up of unclaimed prescriptions in one study.[63] However, some studies have suggested a positive impact with use of automated refill reminders.[110,111] Practitioners in the US should also keep in mind that new Health Insurance Portability and Accountability Act rules prohibit use of personal healthcare information for marketing purposes. Refill reminders designed to increase sales of products or services would need the patient's written permission and must be conveyed in a confidential manner.[112]

7.2 Medication Event Monitoring System

The Medication-Events-Monitoring System (MEMS®) is a device that fits on a standard pharmacy vial and contains microelectronics that record the date and time the vial is opened (see figure 1a). Depending on the model chosen, the cap can also display information such as how many times the vial has been opened each day and how many hours since it was last opened. Some MEMS® units may also be programmed with up to six alerts per day to remind the patient to take the medication.[113,114] When connected to the communicator (see figure 1b) and a computer with the appropriate software, the MEMS® device yields information such as administration calendar plots, administration intervals, and exact times at which doses were removed from the vial. Thus, the device has the capability to identify various nonadherent behaviours, such as drug holidays, 'pill dumping' and 'white coat compliance'.

Several studies have compared the effectiveness of the MEMS® device to that of other measures of adherence such as pill counts and self-reports.[33,52,115-122] In a study by Straka et al.,[119] the MEMS® device was compared with patient self-reports (using diaries) in 68 patients (mean age 67 years) taking isosorbide dinitrate three times daily.[119] Each patient was given their medication in a MEMS®-fitted container and instructed to record the date and time a dose was taken. After 3 weeks, the average medication adherence was reported as 71% according to patient diaries and 55% according to the MEMS® device ($p = 0.001$). Patient diaries overestimated adherence in 37 patients (67%).

Cramer et al.[52] assessed the MEMS® device and measured serum drug concentrations in 20 patients receiving antiepileptics at a Veterans Affairs clinic. Adherence rates were highest 5 days before and 5

Table V. Electronic medication adherence devices

Product	Description	Price and availability
Walgreens Auto-Refill System	Automated refill reminder. Vary in complexity from automatic refilling of medication to automated telephone or e-mail messages	Typically no charge
MEMS®	Fits on a standard pharmacy vial and records the date and time the vial is opened. Depending on the model chosen, the cap can also display the number of openings per day and the number of hours since last opening. Some can be programmed to issue up to six reminder alerts per day. Can download data via communicator for interpretation by computer with appropriate software	$US80.00–142.00[a] per cap $US365.00[a] for communicator $US406.00–3200.00[a] depending on software package
MDILog™	Electronic device that attaches to an MDI. Records the date and time of each actuation of the inhaler. Currently available for research purposes only	$US295.00[b] for compliance module $US495.00 for docking station $US595.00 for software
Doser™	Electronic device that fits on top of a standard MDI canister. Records the number of actuations per day (for 30 days) and the number of actuations remaining in the canister	$US27.95[96]
SmartMist™	Electronic MDI aid. Not currently available for consumer use	Currently not marketed[c]
CompuMed®	Weekly pill box that automatically dispenses medication at programmed intervals. Emits an audible tone reminding patients to take their medications. Optional extras include a modem which can be programmed to telephone the patient or caregiver when a dose is missed, voice module (customised message in a familiar voice), and strobe light for the hearing-impaired	$US895.00 for dispenser and rental rate of $US100.00 per month[97]
Health Buddy®	Pager-like device that reminds patients to take their medication. Can be programmed to monitor different disease states with daily interactive questions to the patient about medication use, symptoms, lifestyle etc. Patients' answers are conveniently entered into the device and can be transferred via telephone line to any person (e.g. physician, researcher, etc.)	Information not available
Beep N' Tell™	Vial cap beeps to remind patient to take their medicine. The cap is reset when removed then replaced by the patient. The base of the device has a red button that will play a 60 second message/instructions recorded by a caregiver	$US49.95–99.95[98]
HealthWatch™ 100	Digital watch that works with personal computer. Up to 8 daily reminders can be set. Watch has an alarm and also displays a text message for each reminder	$US249.95[99]
Home Monitoring Services	Many home monitoring services have medical services available as well, including scheduled devices that remind patients to take their medication. If the device is not touched by the patient (indicating that the dose has been taken), the patient is called on the telephone or a caregiver can be contacted	Prices vary depending on the service plan[100,101]
Kind Remind™	Visual reminder with magnetic backing. Can be set to remind either once or twice daily. Device has a blinking red light that requires the patient to press a button to indicate he/she has taken the dose	$US24.95–29.95[102]
LogPad®	Handheld electronic device that is used primarily as a patient diary but can also be programmed with alarms. The device time stamps patient interactions. It is highly customisable. The device is primarily being used in clinical trials	$US 400.00–1000.00[d] per device (includes fees for programming, modems, and other necessary costs)[103]

Continued next page

Table V. Contd

Product	Description	Price and availability
MEDGlider™	Combination pill box and alarm. Has voice alarm, beep alarm and visual alarm. Can hold up to 4 doses per day	$US19.95[104]
Med-ic™	Blister packaging that contains a microchip that records the time and date the blister is broken. Information is uploaded by scanning the packaging	~$US15.00 per package ~$US600.00 for the scanner and software[105]
Med-Time®	Automated, lockable pill box/alarm clock combination. Tray has 28 compartments and can be set up to 4 times per day. When alarm sounds only the compartment for that dose is opened. Once the patient removes the dose, the alarm is reset	$US232.95–349.00[106]
WatchMinder® 01110	Digital alarm watch with larger than usual display. Has 16 daily alarms, 2 vibrate modes and comes with 75 pre-programmed text messages	$US99.95[107]

a Wells M, personal communication.

b Taccini T, personal communication.

c Keenan C, personal communication.

d Rocci S, personal communication.

days after a clinic appointment (88.3% ± 17% and 86.4% ± 17%, respectively). However, 1 month after a clinic visit, adherence declined significantly (72.8% ± 22%, $p = 0.01$). At clinic appointments, all serum antiepileptic levels were considered within the therapeutic range or appropriate for the prescribed dose. Thus, practitioners cannot rely solely on serum drug concentrations as a measure of adherence, since these often overestimate such medication taking behaviours.

In a double-blinded study by Matsuyama et al.,[121] medication adherence was compared in patients using the MEMS® device versus those using traditional pill counts. In this 60-day study, 32 patients (mean age 64 years) with type 2 diabetes mellitus were grouped as having either poor or fair control with oral antidiabetic agents. There was no statistically significant difference in adherence or diabetes control (as assessed by glycosylated haemoglobin [HbA_{1c}] level) between the pill count or MEMS® group (35% vs. 60% and 12.1% vs 12.7%, respectively). It is important to note that HbA_{1c} was measured at 60 days and thus may not have provided an accurate indication of long-term blood glucose control. However, while there was no

Fig. 1. Medication-Events-Monitoring System (MEMS®) device: (a) MEMS®V Smart Cap, with display showing that two doses have been taken; (b) MEMS® V Communication Device (photographs courtesy of AARDEX® Ltd./Aprex).

statistically significant difference in adherence between the two groups, use of the MEMS® device resulted in significantly more recommendations for patient education as opposed to pharmacological adjustment (7% vs 2%, p = 0.028). Thus, in addition to providing a measure of adherence, the MEMS® device may stimulate alternative interventions, such as patient education, rather than unnecessary pharmacological changes.[121]

While the MEMS® device offers several advantages in assessing adherence, it also has limitations. First, opening a medication vial does not necessarily mean the dose was taken. Secondly, the MEMS® device is not useful for many elders who use pill boxes. Thirdly, the device itself may interfere with established routines and deter adherence.[122] Finally, the price may be prohibitive for individual patient use, particularly when multiple medications are involved. MEMS® caps range from $US80.00 to $US142.00 per cap (Wells M, personal communication). The communicator necessary for downloading data costs $US365.00 and the software to interpret the data costs at least $US406.00.

7.3 Metered Dose Inhaler Adherence Aids

Measuring adherence to MDIs is difficult. Currently, no MDI allows direct visualisation of medication or determination of the exact number of actuations taken. Within the last few decades, several electronic MDI aids have been developed. When attached to a traditional canister, these devices may record the date and time of each actuation, actuation technique (e.g. depressing the canister with insufficient force), the number of actuations per day and the number of remaining doses.[123,124] Presently, the majority of these devices are only available for research purposes.

The MDILog™ (formally known as Nebulizer Chronolog™) contains microelectronics that record the date and time of each actuation of the MDI (figure 2).[123] In a study by Nides et al.,[123] the Nebulizer Chronolog™ was used in 251 patients with early COPD (average age 49.9 years). All patients were issued an inhaler fitted with the device and assigned to either a feedback group to whom information was provided based on data obtained from the device (e.g. number of actuations used, date and time of each actuation, patterns of use) or a control group who were aware only that the device recorded the number of actuations used and who were given no specific feedback. Adherence information was collected by self-report, from canister weight and by data obtained from the device (number of actuations per dose, percentage of prescribed actuations taken and percentage of days adherent). After 4 months, there were significant differences in doses used per day (1.95 ± 0.68 in the feedback group vs 1.63 ± 0.82 in the control group,

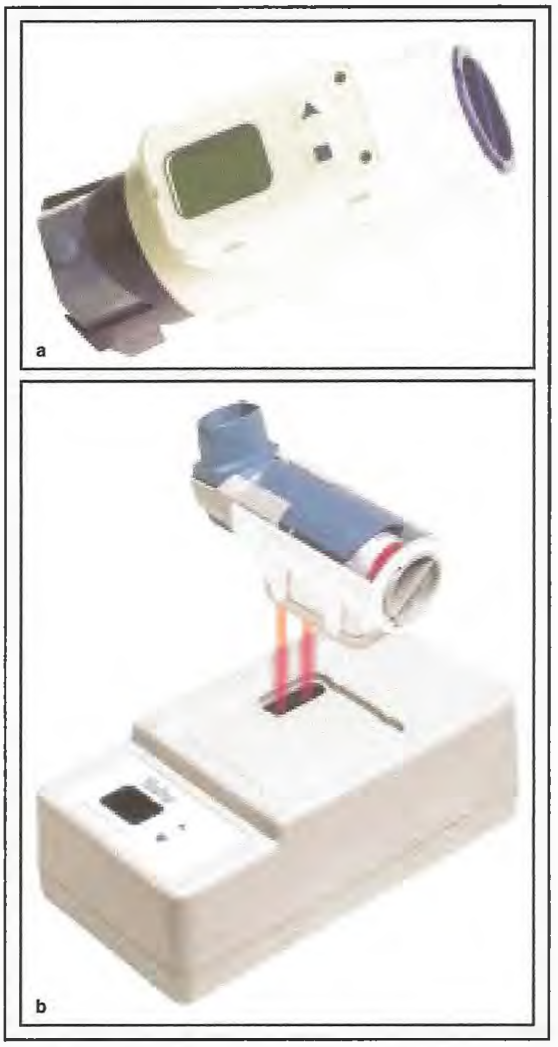

Fig. 2. MDILog™ metered dose inhaler (MDI) adherence measuring device: (a) MDILog™ attached to MDI; (b) MDILog™ and Docking Station (photographs courtesy of Westmed™ Inc.).

p = 0.003), percent of prescribed actuations taken (88.8 ± 9.6 feedback group vs 68.8 ± 25.7 control group, p < 0.0001), and percentage of days adherent to therapy (60.2 ± 25.9 feedback group vs 40.4 ± 28.2 control group, p < 0.0001). 'Canister dumping', where patients repeatedly actuate the canister within a short period of time in order to simulate adherence, occurred in 15% of the control group versus 0% in the feedback group (p < 0.0001). The device verified 44% of self-reported administrations in the feedback group compared with 25% in the control group (p < 0.007). In a long-term COPD continuation study by Simmons et al.,[125] 231 patients were issued with an MDI with attached Nebulizer Chronolog™ and followed for 2 years. At months 4 and 24, significant differences were noted in the number of doses used per day between the control group and feedback group (1.6 ± 0.83 vs 1.93 ± 0.69, p = 0.0035 and 1.16 ± 0.95 versus 1.65 ± 0.89, p = 0.0006, respectively). Interestingly, both the control group and the feedback group exhibited improved adherence immediately following a scheduled follow-up visit (p = 0.028 and p = 0.0001 for within group comparisons).

The accuracy of three electronic monitors for MDIs – MDILog™, Doser CT™ and SmartMist™ – were compared by Julius et al.[124] The inhalers were actuated one, two and four times twice daily (e.g. '1 puff twice daily', '2 puffs twice daily', and '4 puffs twice daily') for 30 days. Two devices were used for each administration schedule. The total accuracy of the devices were 91.8 ± 8.0% and 90.1 ± 6.9% for the MDILog™, 100% and 94.3 ± 2.9% for the Doser CT™, and 100% and 100% for the SmartMist™, at 15 and 30 days, respectively. Errors noted with the MDILog™ and Doser CT™ were extra reported inhalations which were thought to be secondary to battery decay. Thus, while two of the products did record erroneous actuations, the overall performance of all three devices appeared to be sufficient to monitor adherence.

The only currently available electronic MDI aid available for consumer use is the Doser™. The Doser™ fits atop a standard MDI canister, is relatively inexpensive $US27.95,[96] and records the number of actuations per day (for 30 days) and the number of actuations remaining in the canister (figure 3). This information could be clinically useful in that it may allow some assessment of adherence (analogous to pill counts). Additionally, patients may readily determine how many actuations are left in a canister, a task that is often difficult given the construction of most MDIs.

7.4 Electronic Medication Adherence Aids

Several different electronic medication reminder systems are available. CompuMed® is a weekly pill box that automatically dispenses medication at programmed intervals (figure 4).[126] It emits an audible tone reminding patients to take their medication. Optional components include a modem which can be programmed to telephone the patient or a caregiver when a dose is missed, a 'voice module' which can record a customised message with a familiar voice, and a strobe light for the hearing impaired.[97] In a study by Winland-Brown and Valiente[126] involving 61 elderly patients residing in an independent living environment, medication adherence was compared in patients using the CompuMed®, a pre-filled pill box or self administration (control group). Patients were chosen for the study on the basis of fulfilling one of three criteria: hospitalisation as a result of medication-related misadventures, a medication mismanagement episode or disease state in which medication adherence was

Fig. 3. Doser™ (**a**) attached to a metered dose inhaler and (**b**) not attached to a metered dose inhaler (photograph courtesy of MediTrack™ Products).

Fig. 4. CompuMed® electronic medication reminder system (photograph courtesy of e-pill® Medication Reminders).

considered essential. After 6 months, there were significantly fewer missed doses with the CompuMed® device (mean 1.7) than with the pre-poured pill box (mean 15.1, $p < 0.01$) or the control group (mean 19.7, $p < 0.01$). There was no significant difference between the pill box and self administration groups. It is important to note that patients were visited weekly by a member of the investigative team, a potential confounder. The CompuMed® device may be a useful tool for patients needing to take complex medication regimens. However, its large size (approximately 7 inches [18cm] wide, 6 inches [15cm] high and 11 inches [28cm] deep, weight (approximately 7 lbs [3.2kg]), and price ($US895.00 for the dispenser and a rental rate of $US100.00 per month)[97] limit its portability and widespread use.

The Health Buddy® is a pager-like device that can remind patients to take their medication (figure 5). This device can be programmed to monitor different disease states with the use of interactive prompts. Each day the device may deliver a specific set of questions to the patient regarding their medication use, symptoms, diet and other aspects of their health. The patient answers the questions by pressing down one of four large buttons on the device. Responses are transferred daily via a standard telephone line to selected professionals caring for the patient (e.g. physician, nurse, researcher, etc.). Questions are delivered by text and, therefore, may be adapted to other languages. In a comparative cohort study by Cherry et al.,[127] the Health Buddy® system was used to monitor medication adherence and symptoms of disease in 169 indigent or economically disadvantaged patients with diabetes. After 1 year, use of the Health Buddy® together with concurrent interaction with study nurses had significantly decreased outpatient visits by 49% compared with historical controls ($p < 0.001$). There were no statistically significant differences in inpatient admissions (0.50 vs 0.73, $p < 0.07$), emergency room visits (0.40 vs 0.61, $p < 0.06$) or post discharge care visits (0.10 vs 0.18, $p < 0.28$).

8. Conclusion

Routine assessment of medication adherence in the elderly is rarely performed in everyday clinical practice. This may reflect both the inherent difficulty of accurately measuring medication administration and the general ineffectiveness of programmes designed to improve medication adherence. However, adherence remains vital to achieving optimal outcomes with most medication regimens.

Several methods to assess medication adherence already exist. However, no single method is suffi-

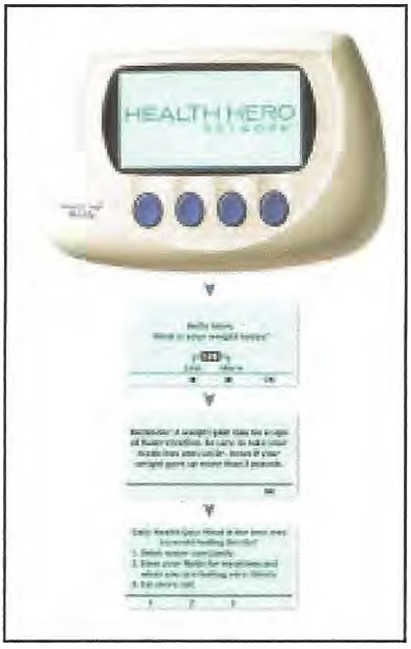

Fig. 5. Health Buddy® electronic medication reminder system, with example of interactive question for the patient (photograph courtesy of Health Hero®).

ciently reliable and accurate.[1] Thus, a combination of assessment methods may be preferred.[4] Medication adherence tools may be categorised as traditional methods (e.g. pill counts, interviews, etc.), formally designed medication management assessment tests based on patient interview and direct observation of medication consumption (e.g. DRUGS, MedTake), and newer technological aids (e.g. MEMS® and MDILog™). Traditional medication assessment methods such as pill counts and patient self-report are known to significantly overestimate medication adherence.[13] Likewise, prescription refill records are inaccurate and often do not reflect true medication taking behaviour.[1] Markers such as serum or urine drug levels also overestimate adherence because patients often try to improve adherence immediately before a physician's visit or scheduled blood draw.[52,53]

Several medication management assessment tools specifically designed for elderly populations have been developed and tested in small clinical trials.[28,64-66] Tools such as the DRUGS and MedTake test are based on patient interview and direct observation. Both are easy to administer, but require patient and healthcare provider time. Because they assess patients' adherence to their own prescribed medication regimens (versus a contrived hypothetical medication regimen) they may be more accurate. However, they are also subject to observer bias and may not reflect patients' behaviours at home. The electronic MEMS® device represented a significant improvement in adherence assessment methodology, particularly in the context of conducting adherence research. However, it may be impractical for routine clinical use and thus remains primarily a research tool. In contrast, a number of technological aids designed to help patients adhere to medication schedules are currently being marketed directly to patients and their caregivers. Designed to be patient friendly and low cost, these technological aids are not supported by adequate reliability and validity data. Controlled trials comparing these new aids with more established systems, such as the MEMS device, are lacking.

Each day, clinicians face the quandary of trying to determine how closely their elder patients adhere to their prescribed medication regimens. Clinicians can now select one or more methods of assessing medication adherence but they must do so without the benefit of supporting data, particularly in the older population. Perhaps the best approach for assessing medication adherence is to select both a medication adherence monitoring method and a companion clinical outcome. Monitoring of clinical outcomes (e.g. blood pressure) may complement adherence measures (e.g. refill data, patient self-report), so that adherence is considered as a factor when deciding upon initiation or adjustment of medication regimens. Future research is needed to identify accurate and reliable methods for assessing and enhancing adherence in order to improve medication-related health outcomes.

Acknowledgements

No sources of funding were used to assist in the preparation of the manuscript, and no author has any potential conflicts of interest directly relevant to the contents of the review

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Medicaid Beneficiaries With Congestive Heart Failure: Association of Medication Adherence With Healthcare Use and Costs

Dominick Esposito, PhD; Ann D. Bagchi, PhD; James M. Verdier, JD; Deo S. Bencio, BS; and Myoung S. Kim, PhD

Objectives: To examine the association of medication adherence with healthcare use and costs among Medicaid beneficiaries with congestive heart failure (CHF), to investigate whether the association was a graded one, and to estimate the potential savings due to improved adherence.

Study Design: Using Medicare and Medicaid data for 4 states, adherence was estimated using the medication possession ratio (MPR).

Methods: Multivariate logistic and 2-part general linear models were estimated to study the primary objectives. The MPR was specified in multiple ways to examine its association with healthcare use and costs.

Results: Adherent beneficiaries were less likely to have a hospitalization (0.4 percentage points), had fewer hospitalizations (13%), had in excess of 2 fewer inpatient days (25%), were less likely to have an emergency department (ED) visit (3%), and had fewer ED visits (10%) than nonadherent beneficiaries. Total healthcare costs were $5910 (23%) less per year for adherent beneficiaries compared with nonadherent beneficiaries. The relationship between medication adherence and healthcare costs was graded. For example, beneficiaries with adherence rates of 95% or higher had about 15% lower healthcare costs than those with adherence rates between 80% and less than 95% ($17,665 vs $20,747, $P < .01$). The relationship between adherence and total healthcare costs was even more stark when the most adherent beneficiaries were segmented into finer subgroups.

Conclusions: Healthcare costs among Medicaid beneficiaries with CHF would be lower if more patients were adherent to prescribed medication regimens. Researchers should reconsider whether a binary threshold for adherence is sufficient to examine the association of adherence with outcomes and healthcare costs.

(Am J Manag Care. 2009;15(7):437-445)

Congestive heart failure (CHF) is a leading cause of hospitalization and mortality in the United States, affecting more than 5 million people at an expected cost of $34.8 billion in 2008.[1] The Centers for Medicare & Medicaid Services (CMS) has prioritized improved treatment of CHF, among other chronic conditions, through demonstrations and pilot programs for its beneficiaries.[2-4] The prevalence of CHF is as high as 2.6% among Medicaid beneficiaries and 10.7% among those dually enrolled in Medicare and Medicaid (dual eligibles).[5] Patients with CHF account for a disproportionate share of CMS spending. In 1999, 14% of fee-for-service Medicare beneficiaries with CHF accounted for 43% of total spending.[2]

Patients with CHF are generally at increased risk for heart attack, stroke, emergency department (ED) visits, hospitalization, and death.[6-8] To minimize their risk, most patients with CHF should use 1 or more drugs from different therapeutic subclasses, including loop diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and β-blockers.[9-11] However, medication nonadherence is common among patients with CHF, and Medicaid beneficiaries' drug use is often inconsistent with practice guidelines.[12-17]

Despite evidence that poor adherence leads to higher hospitalization rates, few studies[18-20] have examined the relationship between adherence and healthcare costs for patients with CHF, although hospitalization accounts for their highest share of expenditures. If higher CHF drug adherence is associated with lower hospitalization risk, it stands to reason that it is also associated with lower healthcare costs.

This study had 3 primary objectives. The first objective was to examine the association of CHF medication adherence with healthcare use and costs in a Medicaid population. The second objective was to investigate whether the association between drug adherence and outcomes was a graded one. Throughout the literature, the primary threshold used to represent adherent behavior is a medication possession ratio (MPR) of 80%, but we hypothesized that the relationship was more likely graded. The third objective was to estimate the potential savings to Medicaid based on any findings that suggested an association between CHF medication adherence and healthcare costs.

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METHODS

Data and Sample Selection

This study used medical and phar-

For author information and disclosures, see end of text.

Take-Away Points

Higher adherence to congestive heart failure (CHF) medications was associated with lower healthcare utilization and lower costs among Medicaid beneficiaries.

- The relationship between medication adherence and healthcare costs was a graded one. Beneficiaries with near-perfect drug adherence had lower healthcare costs than beneficiaries with only slightly lower adherence.
- Overall Medicare outlays could be considerably lower if more enrollees with CHF were adherent.
- Researchers should reconsider whether a simple binary threshold for adherence (eg, a medication possession ratio of 80%) is sufficient for examining the association of drug adherence with outcomes and healthcare costs.

macy claims data from the 1998 State Medicaid Research Files, the 1999 Medicaid Analytic eXtract, and the 1999 Medicare Standard Analytic File for Medicaid beneficiaries residing in Arkansas, California, Indiana, and New Jersey. We selected these states because they are geographically and demographically diverse and because they had limited or no capitated managed care for the disabled and older Medicaid population in 1998 and 1999. In addition, CHF drug utilization differences across these states were not due to differences in copayments or benefit designs.[17]

The research sample included noninstitutionalized beneficiaries with at least 1 CHF drug claim in 1999, medical claims for CHF, and continuous enrollment in fee-for-service Medicaid with pharmacy benefit coverage. The CHF medications were identified using First DataBank's Master Drug Data Base[21] therapeutic classification system and included the following drug groups: antianginals, β-blockers, calcium channel blockers, antiarrhythmics, antihypertensives, and diuretics. Beneficiaries were identified as having CHF if they were hospitalized with a CHF diagnosis in 1998 or had at least 2 ambulatory visits in 1998 with a CHF diagnosis (*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 402.xx, 404.xx, and 428.x).

Medication Adherence

We used the MPR to measure CHF medication adherence in 1999.[22] Using all CHF drug claims, the MPR was calculated by dividing a patient's total days' supply of medication by the number of days between the date of the patient's first fill and the last day on which the patient had medication available. Days during which a patient stayed in a hospital are excluded from the calculation, and days for which more than 1 CHF drugs were available are counted only once. Using multiple CHF drug subclasses to examine adherence is more lenient than focusing on 1 subclass and is appropriate for a Medicaid population, as research indicates considerable underutilization of CHF drugs from any single subclass.[15,17]

This study considers multiple MPR specifications. First, the threshold of 80% is used to deem patients as adherent (≥80%) or as nonadherent (<80%). This value is borrowed from established literature on cardiovascular disease and from previous adherence research.[6,23-31] However, there is no clinical evidence to support using this ratio or any other value as the threshold for medication adherence. Second, in a sensitivity analysis we also specified the MPR as a continuous variable. Third, we specified the MPR as 4 different ordinal variables. The first ordinal variable has 3 levels, segmenting patients with an MPR of 95% or higher from patients with an MPR between 80% and less than 95% and from patients with an MPR below 80%. We also specified 3 different 5-level ordinal variables. First, we examined the MPR by adherence quintile (eg, the first quintile is 0%-20%, and the last quintile is 80%-100%). Second, we segmented the MPR by quintile such that roughly 20% of the sample fell into each group. Third, we specified an ordinal variable to examine adherence for patients with a near-perfect MPR (with each subgroup containing ≥10% of the sample). The 5 levels were 99% or higher, 95% to less than 99%, 80% to less than 95%, 50% to less than 80%, and less than 50%.

Outcome Variables and Regression Analyses

We examined healthcare costs and utilization in 1999. Cost outcomes included total healthcare (including and excluding drug costs) and drug, inpatient, outpatient, and other medical costs (skilled nursing facility, hospice, ED, and durable medical equipment). Utilization included any hospital use, the number of hospital admissions, the number of hospital days, any ED use, and the number of ED visits. Regression analyses examined the association in 1999 between CHF drug adherence and outcomes.

The distribution of costs dictated regression specifications for models in which costs were the dependent variables. For cost data with only nonzero values (total costs, including drug costs), we estimated a generalized linear model (GLM). For skewed data with many zero values, we used a 2-stage procedure.[32,33] We first estimated a logistic regression to model the likelihood of having a nonzero cost and then estimated costs with a GLM, multiplying cost estimates by the predicted probability of having nonzero costs to obtain final cost estimates. For all GLM equations, we used the modified Park test to determine the appropriate link function.[33] We estimated costs through the method of recycled predictions, setting all sample members as adherent or as nonadherent, while keeping all other individual characteristics constant.

Table 1. Study Population Characteristics and Congestive Heart Failure (CHF) Drug Use[a]

Variable	Total (N = 37,408)	Adherent to CHF Drug Regimens (n = 19,912)
Age, y, %		
≤64	35.9	34.5
65-74	24.4	26.1
75-84	24.7	25.4
≥85	15.1	14.0
Residence, %		
Arkansas	9.8	8.8
California	63.0	61.9
Indiana	8.9	9.8
New Jersey	18.3	19.5
Race/ethnicity, %		
African American	25.5	18.4
Other or unknown	20.9	32.0
White	53.6	49.7
Female sex, %	72.8	70.1
Dually enrolled in Medicare, %	72.0	69.9
Disabled, %	52.5	55.4
Had coronary artery disease, %	29.1	28.6
Had diabetes, %	29.8	28.6
Hospitalized for CHF in 1998, %	37.5	40.2
Hospitalized for other conditions in 1998, %	38.4	34.7
Chronic Illness and Disability Payment System risk score	1.07	0.98
No. of CHF prescriptions per month	1.2	1.7
No. of CHF drugs patients using, %[b]		
1	25.2	12.0
2-3	49.6	51.1
≥4	25.3	37.0
CHF medication possession ratio, %		
90-100	36.6	68.6
80-89	16.7	31.3
70-79	9.9	NA
0-69	36.9	NA

NA indicates not applicable.
[a]From the 1998 State Medicaid Research Files and the 1999 Medicaid Analytic eXtract. Beneficiaries are classified as adherent if their medication possession ratio is 80% or higher.
[b]Representing a drug subclass as defined by Master Drug Data Base, version 2, developed by Wolters Kluwer Health (http://www.medispan.com/master-drug-database.aspx).

For models in which adherence was specified as a 3-level or 5-level variable, we estimated costs for each of the 3 to 5 subgroups separately.

We estimated logit models for hospital admissions and ED visits and least squares regressions for the number of hospitalizations, the number of hospital days, and the number of ED visits. All utilization outcomes were estimated through recycled predictions. We estimated all regressions using commercially available statistical software (STATA, release 9; StataCorp LP, College Station, TX).[34]

Independent Variables

The independent variable of interest was the MPR. Regression analyses also included demographic characteristics,

Table 2. Regression-Adjusted Healthcare Utilization and Costs for Medicaid Beneficiaries Adherent and Nonadherent to Congestive Heart Failure Drug Regimens[a]

Variable	Adherent (n = 19,912)	Nonadherent (n = 17,496)	Difference[b]
Healthcare utilization			
Any hospitalization, %	47.5	47.9	–0.4
No. of hospitalizations	1.4	1.6	–0.2
No. of hospital days	5.9	8.0	–2.1
Any emergency department visit, %	43.7	45.1	–1.4
No. of emergency department visits	3.6	4.0	–0.4
Healthcare costs, $			
Total costs, including drug costs	19,402	25,312	–5910
Total costs, excluding drug costs	16,338	23,101	–6763
Drug costs	3516	2322	1194
Inpatient costs	7809	10,686	–2877
Outpatient costs	7766	9267	–1501
Other costs[c]	1313	1347	–34

[a]From the 1998 State Medicaid Research Files, the 1999 Medicaid Analytic eXtract, and the 1999 Medicare Standard Analytic File. Beneficiaries are classified as adherent if their medication possession ratio is 80% or higher.
[b]All significantly different from 0 at $P < .01$ (2-tailed t test) except for "Other costs" under "Healthcare costs."
[c]Include hospice, skilled nursing facility, home health, and emergency department.

health risk factors, and CHF comorbidities. Demographic characteristics included a dual-eligible indicator, age (≤64, 65-74, 75-84, and ≥85 years), sex, state of residence, and race/ethnicity (white, African American, or other). Health risk factors and comorbidities included whether the beneficiary also had diagnosed coronary artery disease or diabetes mellitus and whether the beneficiary had any hospitalizations related or unrelated to CHF during 1998, as well as a diagnostic risk adjustor based on the Chronic Illness and Disability Payment System[35] using 1998 medical claims data.

Potential Savings to Medicare

To estimate the potential savings to Medicare from higher CHF medication adherence, we extrapolated study findings on an aggregate level. This was based on published estimates of the number of beneficiaries with CHF and on assumptions about their mean medication adherence.[36]

RESULTS

In the 4 study states, 37,408 of Medicaid beneficiaries met the inclusion criteria (Table 1). About 36% were younger than 65 years, and 15% were 85 years or older. Slightly more than half were white, and roughly a quarter were African American. Almost three-fourths were female, 72% were dual eligibles, and about half were classified as disabled (and about half of these were also dual eligibles [data not shown]). Many beneficiaries had medical claims for other cardiovascular conditions in addition to CHF, including coronary artery disease (29%) and diabetes (30%). In 1998, 38% of the sample had a hospitalization for CHF, and 38% had a hospitalization for other conditions. In 1999, beneficiaries averaged 1.2 CHF drug claims per month. The most common CHF drug subclasses in the sample were diuretics (59% of patients), ACE inhibitors (45%), and antianginals (35%) (data not shown). Among adherent sample members as specified by an MPR threshold of 80%, the demographic profile was similar to that of the entire research sample, but the number of drug fills was higher.

Hospital and ED Use

Hospital and ED outcomes were always lower for adherent beneficiaries compared with nonadherent beneficiaries, and all differences were significant at $P = .01$ (Table 2). Adherent beneficiaries were less likely to have a hospitalization (0.4 percentage points), had fewer hospitalizations per beneficiary (13%), had in excess of 2 fewer days spent in the hospital (25%), were less likely to have an ED visit (3%), and had fewer ED visits per beneficiary (10%). When medication adherence was specified as an ordinal variable (at 3 or 5 levels), all healthcare utilization outcomes were generally least likely or lowest for beneficiaries with the highest MPR (data not shown).

Healthcare Costs

Except for total drug costs, healthcare costs were lower for adherent beneficiaries than for nonadherent beneficiaries ($P < .01$ for most comparisons) (Table 2). Total healthcare costs (including drug costs) were $5910 (23%) less per year. When the MPR was specified with 3 or more levels, the relationship between adherence and healthcare costs was graded (Table 3). For example, beneficiaries with adherence rates of 95% or higher had about 15% lower total healthcare costs, including drug costs, than those with adherence rates between 80% and less than 95% ($17,665 vs $20,747, $P < .01$). The same pattern was evident when the sample was split into quintiles by adherence level (20% intervals of the MPR) or by

Table 3. Regression-Adjusted Healthcare Costs for Medicaid Beneficiaries by Various Specifications of Medication Adherence[a]

Variable, %	Sample Size	Total Costs, $	Total Costs, Excluding Drug Costs, $	Inpatient Costs, $	Outpatient Costs, $
3 Level					
≥95	8527	17,665	14,418	7094	7196
80 to <95	11,385	20,747[b]	17,832[b]	8335[b]	8189[b]
<80	17,496	25,324[b]	23,112[b]	10,693[b]	9274[b]
5 Level					
≥99	3878	16,989	13,691	7084	6449
95 to <99	4649	18,141[b]	14,733[b]	7093	7776[b]
80 to <95	11,385	20,730[b]	17,675[b]	8332[b]	8180[b]
50 to <80	8989	24,350[b]	21,768[b]	10,424[b]	8231[b]
<50	8507	26,486[b]	24,349[b]	11,033[b]	10,414[b]

[a]From the 1998 State Medicaid Research Files, the 1999 Medicaid Analytic eXtract, and the 1999 Medicare Standard Analytic File. For regression specifications in which the medication possession ratio was split into quintiles, annual healthcare costs were always lowest for the quintiles with the highest adherence rates.
[b]Significantly higher than costs for the group with the highest adherence rates at $P < .01$ (2-tailed t test).

sample size (20% of the sample in each quintile). A specification by decile was also used, but the data are not shown.

The relationship between medication adherence rates and total healthcare costs was stronger when the most adherent beneficiaries were segmented into finer subgroups (Table 3). Beneficiaries with adherence rates of 99% or higher (near-perfect adherence) had 6% lower total healthcare costs, including drug costs, than patients with adherence rates between 95% and less than 99% ($16,989 vs $18,141, $P < .01$). The association of CHF medication adherence with costs was higher in absolute US dollars for dual-eligible beneficiaries adherent patients had annual costs (Table 4). Among dual-eligible beneficiaries, adherent patients had annual costs (including drug costs) that were $7913 lower than annual costs of nonadherent patients, or 24% of the nonadherent mean ($P < .01$). However, the difference between adherent and nonadherent beneficiaries among non–dual-eligible beneficiaries was only $2859 or 19% of the nonadherent mean ($P < .01$).

Potential Savings to Medicare From Improved Adherence

In 2002, approximately 13% of community-dwelling Medicare beneficiaries had CHF, and their mean healthcare costs were about $24,000.[36] Because more than 90% of Medicare enrollees reside in the community and the total number of enrollees in 2002 was about 40 million, roughly 5 million community-dwelling beneficiaries had CHF. Based on the association between medication adherence and healthcare costs for dual-eligible beneficiaries in this study, we estimated total costs to Medicare assuming that a fixed proportion of enrollees were adherent (≥80% MPR).

Because the mean annual healthcare costs for nonadherent dual eligibles were 23% higher than those for adherent dual eligibles, we estimated that the mean annual healthcare costs among nonadherent beneficiaries were $28,374 compared with $21,750 for adherent beneficiaries. If 60% of enrollees with CHF were adherent and that percentage rose to 80%, Medicare costs would be $6.6 billion lower, or about 2% of total Medicare spending. This estimate is sensitive to the initial proportion of beneficiaries who are presumed to be adherent. If 65% are adherent, then savings are about $5 billion. Moreover, these savings assume that Medicare could achieve higher mean patient adherence at little or no cost. However, because we had only 1 year of data, it is impossible to estimate the effect of persistent medication adherence from one year to the next.

Sensitivity Analyses

We conducted sensitivity analyses by specific drug subclass and by the number of distinct subclasses filled by beneficiaries. First, we specified the MPR as a continuous variable and estimated costs at various MPR levels (50%, 75%, 80%, 85%, 95%, and 99%). Consistent with our primary results, healthcare costs decrease monotonically as the MPR rises (Table 5). Second, we estimated regressions for the top 4 CHF drug subclasses (ranked by the proportion of patients with ≥1 fill) in the sample (ACE inhibitors, antianginals, β-blockers, and diuretics) using only the MPR calculated for that drug subclass. Results for this analysis were qualitatively similar to those of the main analysis.

A potential analytical limitation is that our measure of mean adherence depends on the number of CHF medica-

Table 4. Regression-Adjusted Healthcare Costs for Dual-Eligible and Non–Dual-Eligible Medicaid Beneficiaries by Medication Adherence[a]

	Dual-Eligible Beneficiaries, $			Non–Dual-Eligible Beneficiaries, $		
Variable	Adherent (n = 13,923)	Nonadherent (n = 10,690)	Difference	Adherent (n = 5989)	Nonadherent (n = 6806)	Difference
Total costs, including drug costs	24,506	32,419	−7913[b]	12,398	15,257	−2859[b]
Total costs, excluding drug costs	21,087	30,033	−8946[b]	9769	13,336	−3567[b]
Drug costs	3808	2491	1316[b]	3157	2124	1033[b]
Inpatient costs	9915	14,025	−4110[b]	4140	4826	−687[b]
Outpatient costs	8763	9867	−1104[b]	6334	8380	−2046[b]
Other costs[c]	2716	2750	−35	380	401	−21

[a]From the 1998 State Medicaid Research Files, the 1999 Medicaid Analytic eXtract, and the 1999 Medicare Standard Analytic File. Beneficiaries are classified as adherent if their medication possession ratio is 80% or higher.
[b]Significantly different from 0 at $P < .01$ (2-tailed t test).
[c]Include hospice, skilled nursing facility, home health, and emergency department

tions a patient fills. To test whether the association between healthcare costs and medication adherence varied among patients with differing numbers of unique drugs filled, we estimated regressions for the subgroups of patients with 1, 2, 3, and 4 or more unique CHF drugs filled. Across all 4 groups, results were qualitatively consistent with those of the main analysis (Table 5).

The final sensitivity analysis examined the decision to estimate the relationship between medication adherence and healthcare costs contemporaneously. Estimating models in this way cannot account for the potential of reverse causality that healthcare outcomes cause changes in medication adherence rather than vice versa. Although the results of this research do not suggest that better adherence results in fewer adverse health events and lower healthcare costs, the inclusion of healthy sample members who adhere regularly to medications and have few medical problems other than CHF might bias our results. To test this hypothesis, we examined 1998 healthcare use and estimated 4 separate models for patients with a (1) a Chronic Illness and Disability Payment System score of 1 or higher, (2) a diabetes diagnosis, (3) a diagnosis of coronary artery disease, and (4) hospitalization for any condition. For all 4 models, the association between the MPR and healthcare expenditures was qualitatively the same as that in the primary analysis.

DISCUSSION

In our study, higher medication adherence among Medicaid beneficiaries with CHF and those dually enrolled in Medicare was associated with a lower likelihood of hospitalization and ED use. This study's finding that adherent patients were slightly less likely to have a hospitalization is lower in magnitude than previous results among patients with CHF in which magnitudes were 8 to 10 percentage points[6] and 6.1% to 8.7%.[23] Findings on ED use were also lower in magnitude, although qualitatively similar.[8] Unlike other research on patients with CHF that did not find or did not examine other outcomes, this study also finds an association between CHF drug adherence and the number of hospitalizations, hospital days, and ED visits. That nonadherent beneficiaries are more likely than adherent beneficiaries to experience more of these adverse health events is likely important to state Medicaid agencies and to the federal government, as these events are expensive. Among patients in this research sample, the mean inpatient costs in 1999 among those with at least 1 visit were $19,432, or more than $6000 per visit. Given the persistent financial problems plaguing Medicare and the high mean cost of inpatient visits, improvement of CHF drug adherence among its beneficiaries (particularly dual eligibles) could result in considerable savings.

The relationship between CHF drug adherence and total costs was stark. When the MPR threshold of 80% was used, total costs for adherent patients were almost $6000 lower per year (Table 2). Although no other research has reported such a relationship for patients with CHF, one other study[6] found differences for commercially insured patients with hypertension and hypercholesterolemia.

This study also finds that the association between total healthcare expenditures and patient adherence is a graded one, challenging the 80% threshold used throughout the literature on medication adherence. Total healthcare costs of patients with adherence rates of 95% or higher were more than $3000 lower (almost 15%) than those of patients with adherence rates between 80% and less than 95% (Table 3). This result suggests that Medicaid agencies and the CMS could benefit substantially from interventions that improve beneficiaries' adherence to CHF drug therapy (as long as the

Table 5. Regression-Adjusted Sensitivity Analyses[a]

Healthcare Costs by Adherence to Specific Subclasses of CHF Drugs				
Drug Subclass	**Sample Size**	**Adherent, $**	**Nonadherent, $**	**Difference, $[b]**
Diuretics	23,925	21,247	23,763	–2516
ACE inhibitors	20,303	17,890	25,553	–7663
Antianginals	15,348	24,738	28,573	–3835
β-Blockers	12,013	17,978	25,695	–7717
Healthcare Costs by No. of CHF Drug Subclasses Patients Using				
No. of CHF Drug Subclasses Patients Using	**Sample Size**	**Adherent, $**	**Nonadherent, $**	**Difference, $[b]**
1	9419	13,638	19,783	–6145
2	9989	17,363	21,480	–4117
3	8552	18,761	27,774	–9013
≥4	9448	25,271	36,991	–11,720
Healthcare Costs by Medication Possession Ratio Level[c]				
Adherence Level, %	**Total Costs, Excluding Drugs, $**	**Total Costs, Including Drugs, $**	**Inpatient Costs, $**	**Outpatient Costs, $**
50	18,398	20,996	17,455	8196
75	15,866	18,761	14,800	7350
80	15,403	18,343	14,319	7192
85	14,953	17,934	13,854	7037
95	14,093	17,145	12,970	6737
99	13,763	16,838	12,632	6621

CHF indicates congestive heart failure.
[a]From the 1998 State Medicaid Research Files, the 1999 Medicaid Analytic eXtract, and the 1999 Medicare Standard Analytic File. Beneficiaries are classified as adherent if their medication possession ratio is 80% or higher.
[b]All significantly different from 0 at $P < .01$ (2-tailed t test).
[c]Estimated with the medication possession ratio specified as a continuous variable. Values represent cost estimates at these particular adherence levels.

cost of these interventions does not exceed their potential savings).

Total healthcare costs of patients with near-perfect medication adherence (≥99%) compared with patients whose medication adherence was slightly lower (95% to <99%) were about $1150 per year (6%) less than those of patients with slightly lower medication adherence (Table 3). Whether it would be cost-effective for Medicaid agencies or the CMS to encourage near-perfect adherence compared with adherence at least 95% of the time is dependent on how much more costly it is to these agencies to achieve near-perfect adherence rates among their beneficiaries. Future research should consider quantifying how much it might cost these agencies to improve medication adherence for patients with CHF who are already very adherent.

There are some limitations related to the use of administrative claims data and reverse causality. First, using pharmacy data to measure adherence can inform us that a prescription was filled but cannot confirm that patients take medications as directed. As in other medication adherence studies, we cannot account for this bias. Further research is needed on the association of patients' estimated medication adherence from claims with their reported adherence, possibly from surveys. Second, it was impossible to determine the severity of illness among patients with CHF by any means other than proxy measures. The association of medication adherence with healthcare utilization and costs might be different among patients having lower CHF severity compared with patients having higher severity. Future research should carefully address the association of CHF severity to inform policy makers of the risks of medication nonadherence among beneficiaries in the poorest of health. Third, our data did not allow us to account for important socioeconomic factors such as income or years of education. Because these factors are likely associated with drug adherence, their inclusion may have explained some of the variation in medication adherence across the sample. In particular, some research suggests that adherence to physician-recommended drug regimens (including adherence to a placebo) is associated with enhanced patient outcomes, indicating that researchers should

attempt (whenever feasible) to examine as many factors as possible when estimating the association between adherence and patient outcomes.[37-40]

An additional limitation to this study concerns our inability to determine whether it is truly medication adherence that is the only factor associated with lower healthcare utilization and costs. It is possible that patients who are adherent to medications are also adherent to other types of treatments (such as exercise and diet), but it is impossible with these data to assess adherence to these treatments. Further research should attempt to compare adherence to pharmaceutical and nonpharmaceutical therapies versus their joint association with healthcare utilization and costs.

Finally, because we measured medication adherence, healthcare use, and healthcare costs contemporaneously, our results might be biased by reverse causality that high healthcare costs could cause low medication adherence. However, the intent was not to suggest a direction of causality but merely an association. Moreover, if the primary results were biased in some way, we should expect to find no significant association between medication adherence and healthcare costs among patients in poor health at baseline. Yet, sensitivity analyses dispute this hypothesis.

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Author Disclosure: The authors (DE, ADB, JMV, DSB, MSK) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Funding Source: This research was funded by the Centers for Medicare & Medicaid Services under contract 500-00-0047.

Authorship Information: Concept and design (DE, ADB, JMV, MSK); acquisition of data (DSB, MSK); analysis and interpretation of data (DE, JMV, MSK); drafting of the manuscript (DE, ADB, JMV); critical revision of the manuscript for important intellectual content (ADB, JMV); statistical analysis (DE, MSK); administrative, technical, or logistic support (DSB); supervision (JMV); and programming (DSB).

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Incidence and Preventability of Adverse Drug Events Among Older Persons in the Ambulatory Setting

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Context Adverse drug events, especially those that may be preventable, are among the most serious concerns about medication use in older persons cared for in the ambulatory clinical setting.

Objective To assess the incidence and preventability of adverse drug events among older persons in the ambulatory clinical setting.

Design, Setting, and Patients Cohort study of all Medicare enrollees (30 397 person-years of observation) cared for by a multispecialty group practice during a 12-month study period (July 1, 1999, through June 30, 2000), in which possible drug-related incidents occurring in the ambulatory clinical setting were detected using multiple methods, including reports from health care providers; review of hospital discharge summaries; review of emergency department notes; computer-generated signals; automated free-text review of electronic clinic notes; and review of administrative incident reports concerning medication errors.

Main Outcome Measures Number of adverse drug events, severity of the events (classified as significant, serious, life-threatening, or fatal), and whether the events were preventable.

Results There were 1523 identified adverse drug events, of which 27.6% (421) were considered preventable. The overall rate of adverse drug events was 50.1 per 1000 person-years, with a rate of 13.8 preventable adverse drug events per 1000 person-years. Of the adverse drug events, 578 (38.0%) were categorized as serious, life-threatening, or fatal; 244 (42.2%) of these more severe events were deemed preventable compared with 177 (18.7%) of the 945 significant adverse drug events. Errors associated with preventable adverse drug events occurred most often at the stages of prescribing (n=246, 58.4%) and monitoring (n=256, 60.8%), and errors involving patient adherence (n=89, 21.1%) also were common. Cardiovascular medications (24.5%), followed by diuretics (22.1%), nonopioid analgesics (15.4%), hypoglycemics (10.9%), and anticoagulants (10.2%) were the most common medication categories associated with preventable adverse drug events. Electrolyte/renal (26.6%), gastrointestinal tract (21.1%), hemorrhagic (15.9%), metabolic/endocrine (13.8%), and neuropsychiatric (8.6%) events were the most common types of preventable adverse drug events.

Conclusions Adverse drug events are common and often preventable among older persons in the ambulatory clinical setting. More serious adverse drug events are more likely to be preventable. Prevention strategies should target the prescribing and monitoring stages of pharmaceutical care. Interventions focused on improving patient adherence with prescribed regimens and monitoring of prescribed medications also may be beneficial.

JAMA. 2003;289:1107-1116 www.jama.com

ALTHOUGH NUMEROUS STUDIES have evaluated the patterns and quality of prescription medication use among the elderly,[1-5] information related to the incidence of preventable adverse drug events in the ambulatory geriatric population is limited. Even though most medication errors do not result in injury,[6,7] the extensive use of medications by the geriatric population suggests that sizeable numbers of older persons are affected. The prevalence of prescription medication use among the ambulatory adult population increases with advancing age. A recent national survey of the US noninstitutionalized adult population indicated that more than 90% of persons aged 65 years or older used at least 1 medication per week.[8] More than 40% used 5 or more different medications per week, and

For editorial comment see p 1154.

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12% used 10 or more different medications per week.

During recent years, the knowledge base relating to adverse drug events in hospitals and in nursing home settings has grown substantially.[9-12] However, only limited efforts have been made to systematically examine the problem of drug-related injury among the older population in the ambulatory setting. Therefore, we conducted a study of a large population of Medicare enrollees cared for in the ambulatory setting to evaluate the incidence and preventability of adverse drug events among ambulatory geriatric patients; to categorize adverse drug events by drug class, severity, and clinical effects; and to classify preventable events by the stage of the pharmaceutical care process at which the error occurred. We expect this research to inform the development and testing of interventions designed to reduce the risk of adverse drug events experienced by older persons who are receiving care in the outpatient setting.

METHODS

Study Setting and Population

This study was conducted in the setting of a large multispecialty group practice that provides care to members of a New England–based health maintenance organization. The group practice provides health care to more than 30000 persons aged 65 years or older, approximately 90% of whom are enrolled in a Medicare+Choice Plan (Medicare risk contract with the health plan), with the remainder being traditional fee-for-service Medicare enrollees. All Medicare+Choice Plan enrollees had a drug benefit plan during the study. Traditional fee-for-service Medicare enrollees did not have a drug benefit plan under Medicare, but they may have independently purchased plans.

Box 1. Computer-Generated Signals of Possible Drug-Related Incidents

Serum Drug Levels

Quinidine >5 µg/mL
Valproate >120 µg/mL
Theophylline >20 µg/mL
Procainamide >12 µg/mL
Phenobarbital >10.4 mg/L (>45 µg/mL)
Phenytoin >20 µg/mL
Cyclosporine >400 ng/L
Digoxin >2.0 ng/mL (>2.56 nmol/L)
Carbamazepine >13.0 µg/mL

Diagnoses (*ICD-9-CM* Codes)

Poisoning by
- Psychotropic agents (969)
- Analgesics and antipyretics (965)
- Agents that affect blood (964)
- Antibiotics (960)
- Other anti-infectives (961)
- Hormones and synthetic substitutes (962)
- Anticonvulsants/antiparkinsonian drugs (966)
- Sedatives and hypnotics (967)
- Other central nervous system depressants (968)
- Central nervous system stimulants (970)
- Drugs primarily affecting the autonomic nervous system (971)
- Cardiovascular drugs (972)
- Gastrointestinal tract drugs (973)
- Water, mineral, and uric acid metabolism drugs (974)
- Agents acting on muscles and respiratory tract systems (975)
- Topical agents (976)
- Other and unspecified drugs (977)

Late effects of drugs (909)
Dermatitis due to substances taken internally (693)
Allergic contact dermatitis (692)
Neuropathy due to drugs (357.6)
Urticaria (708)
Gastritis (535.4)

Laboratory Results (Including Drug-Laboratory Combinations)

Serum alkaline phosphatase >350 U/L
Serum bilirubin >4.0 mg/dL (>68.4 µmol/L)
Serum potassium <2.9 or >6.0 mEq/L
Blood eosinophils >9%
Serum aspartate aminotransferase >84 U/L
Serum alanine aminotransferase >80 U/L
Serum urea nitrogen >60 mg/dL (>21.42 mmol/L)
International normalized ratio >5
Platelet count $<50 \times 10^3$/µL
Serum creatinine >2.5 mg/dL (221 µmol/L)
Thyroxine and TSH <0.3 µU/mL
Clozapine and white blood cell count $<3 \times 10^3$/µL
Clostridium difficile testing
Glucocorticoid and hemoglobin A_{1c} >6%
Ganciclovir and white blood cell count $<3 \times 10^3$/µL

Antidotes/Treatments

Prednisone and diphenhydramine
Phytonadione (vitamin K)
Naloxone
Sodium polystyrene sulfonate
Protamine sulfate
Digoxin immune antigen-binding fragments
Flumazenil
Glucagon
Hydroxyzine and prednisone
Oral vancomycin
Nystatin

Abbreviations: *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; TSH, thyroid-stimulating hormone.

Subjects for this study included all persons aged 65 years or older receiving health care services delivered by the group practice in the ambulatory setting from July 1, 1999, through June 30, 2000. Residents of long-term care facilities were excluded from the study.

The project was approved by the institutional review board of the University of Massachusetts Medical School, Worcester, and the institutional review board of the group practice and the health maintenance organization. The study was carried out under the auspices of the health plan and medical group quality management committees, as part of peer review and quality improvement activities. Study personnel had no direct contact with either patients or health care providers (which include physicians, advanced practitioners, nurses, and pharmacists) during the study.

Case-Finding Definitions and Classification of Events

Our study was limited to drug-related incidents occurring in the ambulatory clinical setting. Drug-related incidents were detected using the following methods: (1) reports from health care providers (via an intranet reporting system, adverse drug event telephone hot line, or reporting cards sent by mail); (2) review of hospital discharge summaries; (3) review of emergency department notes; (4) computer-generated signals; (5) automated free-text review of electronic clinic notes; and (6) review of administrative incident reports concerning medication errors. Ambulatory medical records were selected for review based on information derived from the various detection methods listed above. Medical record reviews and abstractions were performed by trained clinical pharmacist investigators (K.D., A.C.S., Ms Auger, and Ms Garber).

All available discharge summaries relating to hospitalizations for the study population during the study were obtained for review. The information contained in these discharge summaries was reviewed for evidence of a drug-related incident that led to an admission to the hospital. Drug-related incidents occurring during the course of a hospitalization were not considered in the context of this study. Similarly, all available emergency department notes were reviewed for evidence of a drug-related incident leading to an emergency department visit, but drug-related incidents that occurred during emergency department visits were excluded. Reviews of the discharge summaries and emergency department notes were performed by the trained clinical pharmacist investigators.

Computer-generated signals of possible drug-related incidents were derived from automated data. Such signals included elevated drug levels, abnormal laboratory results, the use of medications considered to be antidotes, and diagnoses (*International Classification of Diseases, Ninth Revision [ICD-9]*)[13] associated with health care claims that could reflect an adverse drug event. A complete list of these computer-generated signals is provided in Box 1.

Most outpatient clinic notes (>80%) were available in electronic form as part of an electronic medical record. Free-text searching, using a computer program to identify potential drug-related incidents, was conducted, as previously described by Honigman et al.[14,15] This effort involved the examination of clinic notes electronically using an adaptation of the Micromedex M^2D_2 medical data dictionary.[14,15] This data-mining tool is a clinical lexicon server consisting of a controlled vocabulary of medical concepts and drug terminology that allows for multiple relationships between multiple medical terms and events. A program was developed that semantically linked drugs and drug classes to known and reported adverse effects and their synonyms. To limit the number of false positives, links that were pursued as possible drug-related incidents by the clinical pharmacist investigators at least 15% of the time (this rate was arbitrary), during a 2-month trial period, were used in this study. Examples of drug-adverse effect links are included in Box 2.

Box 2. Examples of Drug–Adverse Effect Links

ACE inhibitors and cough
Antibiotics and diarrhea
β-Blockers and bradycardia
Calcium channel blockers and peripheral edema
Digoxin and nausea
Diuretics and hyponatremia
Diuretics and hypotension
Hypoglycemics and hypoglycemia
Hypoglycemics and tremor
NSAIDs and bleeding
NSAIDs and gastrointestinal tract complaints
NSAIDs and nausea
NSAIDs and renal insufficiency/failure
Opioids and constipation
Proton pump inhibitors and diarrhea
Selected antidepressants and anorexia
Selected antidepressants and constipation
Selected antidepressants and dry mouth
Selected antidepressants and hypotension
Selected antidepressants and insomnia
Selected antidepressants and nervousness
Warfarin and bleeding

Abbreviations: ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

Outcome Measures

The primary outcome of the study was an *adverse drug event*, defined as an injury resulting from the use of a drug. This definition is consistent with definitions used in previous studies.[9,10,12,16] Adverse drug events may have resulted from medication errors (ie, errors in prescribing, dispensing, patient adherence, and monitoring) or from adverse drug reactions in which there was no error.

After an extensive training period, we assessed reliability between clinical pharmacist investigators on the decision to select possible drug-related incidents for

Table 1. Characteristics of Medicare+ Choice Plan Enrollees

Characteristics	Enrollees, No. (%) (N = 27 617)
Age, mean (SD), y	74.7 (6.7)
Age group, y	
65-69	7110 (25.7)
70-74	7748 (28.1)
75-79	6296 (22.8)
80-84	3920 (14.2)
85-89	1871 (6.8)
≥90	672 (2.4)
Sex	
Male	11 411 (41.3)
Female	16 206 (58.7)
Length of time enrolled in health plan, mean (SD), d	351 (51)
No. of outpatient physician visits, mean (SD)	5.2 (5.2)
Outpatient physician visits	
0	3442 (12.5)
1-2	5963 (21.6)
3-4	5845 (21.2)
5-6	4206 (15.2)
>6	8161 (29.6)
No. of prescription drug dispensings, mean (SD)	21.1 (20.6)
Prescription drug dispensings	
0	3361 (12.2)
1-5	3489 (12.6)
6-15	6617 (24.0)
16-30	7273 (26.3)
>30	6877 (24.9)
No. of prescription medication categories, mean (SD)	3.8 (2.7)
Prescription medication categories	
0	3361 (12.1)
1	2689 (9.7)
2	3876 (14.0)
3	4073 (14.8)
4	3707 (13.4)
>4	9911 (35.9)

full ambulatory medical record review and abstraction. For 80 signals of possible drug-related incidents, clinical pharmacist investigators agreed 84% of the time (κ=0.67). Four clinical pharmacist investigators were involved during the study. The agreement percentage and κ relate to pairs of clinical pharmacist investigators.

All possible drug-related incidents were presented by a clinical pharmacist investigator to pairs of physician-reviewers selected from among 4 of the authors (J.H.G., D.W.B., L.R.H., and J.R.). These physician-reviewers independently classified incidents using structured implicit review according to the following criteria: whether an adverse drug event was present, the severity of the event, whether the event was preventable, and the effects of the event on the patient. In determining whether an adverse drug event had occurred, the physician-reviewers considered the temporal relation between the drug exposure and the event, as well as whether the event reflected a known effect of the drug. The structured implicit review process has been used in numerous prior studies relating to adverse drug events across various clinical settings.[9,12,16-19]

Severity of adverse events was categorized as significant, serious, life-threatening, or fatal.[9,12] Examples of significant events include a nonurticarial skin rash, a fall without associated fracture, hemorrhage not requiring transfusion or hospitalization, and oversedation. Examples of serious events include urticaria, a fall with an associated fracture, hemorrhage requiring transfusion or hospitalization but without hypotension, and delirium. Examples of life-threatening events include hemorrhage with associated hypotension, hypoglycemic encephalopathy, profound hyponatremia, and acute renal failure requiring hospitalization. Adverse drug events were considered to be preventable if they were due to an error and were preventable by any means available.[9] Preventability was categorized as preventable, probably preventable, probably not preventable, or definitely not preventable; results were collapsed into preventable and nonpreventable categories in the analyses.[9] The effects of adverse drug events on the patients were categorized as abnormal laboratory results without signs and symptoms, symptoms of less than 1 day in duration, symptoms of 1 day and longer in duration, nonpermanent disability, permanent disability, and death. Physician-reviewers characterized an event as causing permanent disability based on the potential for a drug-induced injury with permanent effects to cause physical disability or deficits in functioning.[20]

We also classified the stages of pharmaceutical care during which an error leading to a preventable adverse drug event had occurred. The stages of pharmaceutical care in the ambulatory clinical setting were classified as prescribing, dispensing, patient adherence (eg, adherence to documented dosing or monitoring instructions provided by health care professionals), and monitoring. Monitoring stage errors include inadequate laboratory monitoring of drug therapies or a delayed response or failure to respond to signs or symptoms or laboratory evidence of drug toxicity. For a single adverse drug event, it was possible to identify errors at more than 1 stage of pharmaceutical care and/or to identify more than 1 error within a single stage of care.

When the physician-reviewers disagreed on the classification of an incident regarding the presence of an adverse drug event, its severity, or its preventability, they met and reached consensus; consensus was reached in all instances where there was initial disagreement. We compared all the initial assessments of the physician-reviewers and calculated interrater reliability using the κ statistic. For judgments about the presence of an adverse drug event, the κ was 0.81; for preventability, 0.67; and for severity, 0.66. A κ score between 0.6 and 0.8 reflects "substantial" agreement and a κ score between 0.8 and 1.0 is considered "almost perfect."[21]

Statistical Analysis

During the 12-month study, we estimated that the group practice was responsible for 30 397 person-years of health care to individuals aged 65 years or older, based on the monthly census of persons cared for by the group practice during the study, including both Medicare+Choice Plan enrollees and traditional fee-for-service Medicare patients. To determine crude rates of events, the numbers of adverse drug events were divided by the total number of person-years. Ninety-five percent confidence intervals were calculated for rate estimates.[22] We did not discount person-time from the denominator in our calculation of rates for either in-hospital stays or for short stays

in skilled nursing or rehabilitation facilities. However, long-term care residents of nursing homes were excluded from the denominator. Comparisons between categorical variables were performed using the χ^2 test. $P<.05$ was considered significant. Analyses were performed using SAS, version 8.0 (SAS Institute Inc, Cary, NC).

Administrative data regarding outpatient health service utilization and prescription medication use were available for the 27 617 Medicare+Choice Plan enrollees, who were followed by the group practice at any time during the study. Comparable data for traditional fee-for-service Medicare patients were not available. To provide additional context for this study relative to other patient populations and settings, we determined age and sex characteristics, mean length of enrollment in the health plan during the study, information on frequency of outpatient physician visits, and use of prescription medications for these Medicare+Choice Plan enrollees. We also compared this population with national estimates of the overall US population aged 65 years or older (at the midpoint of the study period) with regard to age and sex distribution.

RESULTS

The characteristics and specific prescription medication categories of the 27 617 Medicare+Choice Plan enrollees who were followed by the group practice at any time during the study are summarized in TABLES 1 and 2. Comparing this population to the overall US population aged 65 years and older[23] demonstrated very similar age and sex characteristics; those in age groups 65 to 74 years, 75 to 84 years, and 85 years and older comprised 53.8%, 37.0%, and 9.2% of persons in our population, respectively, compared with 52.4%, 35.3%, and 12.3% of the US population in these respective age categories. Of the US population in these age groups, 58.5% were women compared with 58.7% in our population.

The clinical pharmacist investigators identified, by the various screening methods, a total of 2268 possible drug-related incidents, of which 32.8% (745) were not characterized as adverse drug events by the physician-reviewers. Of the 1523 adverse drug events, 11.0% (168) were identified from reports submitted by health care providers, 10.8% (164) through review of hospital discharge summaries, 12.1% (184) through review of emergency department notes, 28.7% (437) through computer-generated signals, 37.1% (565) through automated free-text searching of electronic clinic notes, and less than 1% (5) through administrative incident reports concerning medication errors.

The overall rate of adverse drug events was 50.1 per 1000 person-years, with a rate of 13.8 preventable adverse drug events per 1000 person-years (TABLE 3). Of the 1523 adverse drug events, 27.6% (421) were judged preventable. Of the 578 serious, life-threatening, or fatal adverse drug events, 42.2% (244) were deemed preventable, compared with 18.7% (177) of the 945 significant adverse drug events (Table 2). Overall, more severe adverse drug events were significantly more likely to be considered preventable (relative risk, 2.25; 95% confidence interval, 1.91-2.65, $P<.001$).

Most adverse drug events (>70%) resulted in symptoms of more than 1 day in duration (TABLE 4). Sixteen events resulted in permanent disability (n=5, 0.3%) or death (n=11, 0.7%). Events resulting in permanent disability included 1 stroke, 2 intracranial bleeding events, 1 hemorrhagic injury to the eye, and 1 drug-induced pulmonary injury. Deaths in this study were related to the following: 4 fatal bleeding, 1 peptic ulcer, 1 neutropenia/infection, 1 hypoglycemia, 1 drug toxicity relating to lithium, 1 drug toxicity relating to digoxin, 1 anaphylaxis, and 1 from complications of antibiotic-associated diarrhea.

The 1523 adverse drug events were associated with a wide variety of different drug classes (TABLE 5). Cardiovascular drugs were the most frequently implicated agents (26.0%), followed by antibiotics/anti-infectives (14.7%), diuretics (13.3%), nonopioid analgesics (11.8%), anticoagulants (7.9%), hypoglycemics (6.8%), steroids (5.3%), and opioids (4.9%). Psychoactive drugs were relatively in-

Table 2. Characteristics of Medicare+Choice Plan Enrollees

Specific Prescription Medication Categories	Enrollees, No. (%) (N = 27 617)
Cardiovascular	14 691 (53.2)
Antibiotics/anti-infectives	12 299 (44.5)
Diuretics	8139 (29.5)
Opioids	6055 (21.9)
Antihyperlipidemic	5983 (21.7)
Nonopioid analgesics	5477 (19.8)
Gastrointestinal tract	5237 (19.0)
Respiratory tract	4303 (15.6)
Dermatologic	4093 (14.8)
Antidepressants	3634 (13.2)
Sedatives/hypnotics	3554 (12.9)
Nutrients/supplements	3387 (12.3)
Hypoglycemics	3180 (11.5)
Steroids	2683 (9.7)
Ophthalmics	2645 (9.6)
Thyroid	2585 (9.4)
Antihistamines	2546 (9.2)
Hormones	2514 (9.1)
Anticoagulants	1935 (7.0)
Muscle relaxants	1503 (5.4)
Osteoporosis	1457 (5.3)
Antiseizure	950 (3.4)
Antigout	893 (3.2)
Antineoplastics	764 (2.8)
Antiplatelets	369 (1.3)
Antipsychotics	325 (1.2)
Antiparkinsonians	243 (0.9)
Alzheimer disease	235 (0.9)
Immunomodulators	12 (0.04)

Table 3. Rates and Severity of Adverse Drug Events

	Type of Adverse Drug Event		
	Overall (N = 1523)	Preventable (n = 421)	Nonpreventable (n = 1102)
Rate per 1000 person-years (95% CI)	50.1 (47.6-52.6)	13.8 (12.5-15.2)	36.3 (34.1-38.4)
Category of severity, No. (%)			
Fatal	11 (0.7)	5 (1.2)	6 (0.5)
Life-threatening	136 (8.9)	72 (17.1)	64 (5.8)
Serious	431 (28.3)	167 (39.7)	264 (24.0)
Significant	945 (62.0)	177 (42.0)	768 (69.7)

Abbreviation: CI, confidence interval.

Table 4. Effects of Adverse Drug Events

	Type of Adverse Drug Event, No. (%)		
	Overall (N = 1523)	Preventable (n = 421)	Nonpreventable (n = 1102)
Abnormal laboratory results without symptoms	203 (13.3)	72 (17.1)	131 (11.9)
Duration of symptoms, d			
<1	220 (14.6)	64 (15.4)	156 (14.2)
≥1	1071 (70.3)	275 (65.3)	796 (72.1)
Disability*			
Nonpermanent	13 (0.9)	3 (0.7)	10 (0.9)
Permanent	5 (0.3)	2 (0.2)	3 (0.3)
Death	11 (0.7)	5 (1.2)	6 (0.5)

*An event was characterized as causing permanent disability based on the potential for a drug-induced injury with permanent effects to cause physical disability or deficits in functioning.

Table 5. Frequency of Adverse Drug Events by Drug Class*

	Adverse Drug Events, No. (%)		
Prescription Drug Class	Overall (N = 1523)	Preventable (n = 421)	Nonpreventable (n = 1102)
Cardiovascular	396 (26.0)	103 (24.5)	293 (26.6)
Antibiotics/anti-infectives	224 (14.7)	13 (3.1)	211 (19.1)
Diuretics	203 (13.3)	93 (22.1)	110 (10.0)
Nonopioid analgesics	180 (11.8)	65 (15.4)	115 (10.4)
Anticoagulants	121 (7.9)	43 (10.2)	78 (7.1)
Hypoglycemics	103 (6.8)	46 (10.9)	57 (5.2)
Steroids	80 (5.3)	11 (2.6)	69 (6.3)
Opioids	74 (4.9)	28 (6.7)	46 (4.2)
Antidepressants	48 (3.2)	15 (3.6)	33 (3.0)
Antiseizure	35 (2.3)	19 (4.5)	16 (1.5)
Antihyperlipidemics	30 (2.0)	2 (0.5)	28 (2.5)
Antineoplastics	26 (1.7)	1 (0.2)	25 (2.3)
Gastrointestinal tract	20 (1.3)	1 (0.2)	19 (1.7)
Nutrients/supplements	20 (1.3)	5 (1.2)	15 (1.4)
Antiplatelets	18 (1.2)	7 (1.7)	11 (1.0)
Respiratory tract	12 (0.8)	4 (1.0)	8 (0.7)
Sedatives/hypnotics	9 (0.6)	6 (1.4)	3 (0.3)
Antipsychotics	8 (0.5)	4 (1.0)	4 (0.4)
Hormones	8 (0.5)	2 (0.5)	6 (0.5)
Osteoporosis	8 (0.5)	1 (0.2)	7 (0.6)
Muscle relaxants	7 (0.5)	3 (0.7)	4 (0.4)
Thyroid	7 (0.5)	4 (1.0)	3 (0.3)
Antigout	6 (0.4)	1 (0.2)	5 (0.5)
Antiparkinsonians	4 (0.3)	0	4 (0.4)
Dermatologic	2 (1.3)	0	2 (1.8)
Alzheimer disease	2 (0.1)	1 (0.2)	1 (0.1)
Antihistamines	2 (0.1)	1 (0.2)	1 (0.1)
Immunomodulators	2 (0.1)	0	2 (0.2)
Ophthalmics	2 (0.1)	1 (0.2)	1 (0.1)
Vaccines	1 (0.1)	0	1 (0.1)

*Drugs in more than 1 category were associated with some events. Frequencies in each column sum to greater than the total number of events.

frequently implicated in adverse drug events in this population: antidepressants were associated with 3.2% of events, sedatives/hypnotics with 0.6%, and antipsychotics with 0.5%. The frequencies of adverse drug events by drug class reflected the prevalence of use of prescription medications in the source population in most, but not all, cases. Cardiovascular medications were the most frequently used prescription drug class (53.2%), followed by antibiotics/anti-infectives (44.5%), diuretics (29.5%), and opioids (21.9%) (Table 1). Antidepressants and sedatives/hypnotics were used by more than 10% of the population, yet they were implicated in few of the identified adverse events (3.2% and 0.6%, respectively).

Among the 421 preventable adverse drug events, cardiovascular drugs also were the most frequently implicated (24.5%), followed by diuretics (22.1%), nonopioid analgesics (15.4%), hypoglycemics (10.9%), anticoagulants (10.2%), and opioids (6.7%) (Table 4). While antibiotics/anti-infectives were the second most common cause of adverse drug events overall, they were associated with only 3.1% of all preventable adverse drug events. Most antibiotic/anti-infective-associated adverse drug events were rashes or diarrhea caused by *Clostridium difficile*.

Gastrointestinal tract events (eg, nausea, vomiting, diarrhea, constipation, and abdominal pain) were the most common type of adverse drug event (22.1%) and the second most common preventable adverse drug event (21.1%) after electrolyte/renal events (26.6%) (TABLE 6). Also among the most frequently identified types of preventable adverse drug events were hemorrhagic (15.9%), metabolic/endocrine (13.8%), and neuropsychiatric (8.6%) events (Table 5).

Among the 421 preventable adverse drug events, 246 (58.4%) errors were identified in the prescribing stage and 256 (60.8%) in the monitoring stage of pharmaceutical care. Of note, many preventable adverse drug events also related to errors in patient adher-

ence (n=89, 21.1%). Examples of identified errors in patient adherence include taking the wrong dose, continuing to take medication despite instructions by the physician to discontinue drug therapy, refusal to take a needed medication, continuing to take a medication despite recognized adverse effects or drug interactions known to the patient, and taking another person's medication. Dispensing errors causing preventable adverse drug events were rarely identified (<2%).

Among the preventable prescribing stage errors, wrong drug/wrong therapeutic choice errors were most common among the 421 preventable adverse drug events (n=114, 27.1%), followed by wrong dose errors (n=101, 24.0%). Inadequate patient education concerning medication use was cited as an error in 18% (75) of preventable adverse drug events. The prescription of a drug for which there was a well-established, clinically important interaction with another drug (eg, drug interaction with warfarin) also was a common error (n=56, 13.3%).

Monitoring stage errors generally represented inadequate laboratory monitoring of drug therapies or a delayed response or failure to respond to signs or symptoms of drug toxicity or laboratory evidence of drug toxicity. Failure to act on available information relating to clinical findings or laboratory results was the most common error that occurred at the monitoring stage (n=154, 36.6%), followed closely by inadequate monitoring (n=152, 36.1%). Examples of monitoring errors include inadequate frequency of monitoring of warfarin leading to an elevated international normalized ratio value associated with bleeding, and failure to respond promptly to symptoms suggestive of digoxin toxicity (eg, nausea, vomiting, and anorexia).

COMMENT

We found that adverse drug events were common among ambulatory geriatric patients, and that more than a quarter were preventable. Serious, life-threatening, and fatal adverse drug events were more likely to be preventable than less severe events. The types of medications most commonly involved in adverse drug events relate closely to those most frequently prescribed in the ambulatory setting, with cardiovascular drugs and antibiotics/anti-infectives being the most frequently used and implicated drug categories. While most adverse drug events had few long-term consequences, disability and some deaths occurred.

Although it is difficult to directly compare event rates observed in the present study with studies performed in other clinical settings involving different patient populations, some comparisons are of interest. Bates et al[9] identified adverse drug events occurring during 4031 nonobstetrical adult admissions to 2 Boston tertiary care hospitals during a 6-month period. Of the 247 adverse drug events identified in that study (6.5 adverse drug events per 100 admissions), 1% were fatal, 12% were life-threatening, 30% were serious, and 57% were significant; and 28% of these were judged preventable. Of the serious and life-threatening adverse events, 42% were judged preventable compared with 18% of significant adverse drug events. Gurwitz et al[12] identified 546 adverse drug events during 2403 nursing home resident-years of observation (227 adverse drug events per 1000 resident-years) in 18 Massachusetts nursing homes. Of the adverse drug events, 1 was fatal, 6% were life-threatening, 38% were serious, and 56% were significant; and 51% of these were judged preventable. Of the serious, life-threatening, and fatal events, 72% were judged preventable compared with 34% of the significant events. In the ambulatory setting, the percentage of adverse drug events that were deemed preventable more closely mirrored the hospital setting (28%). Consistent with

Table 6. Frequency of Types of Adverse Drug Events*

Type	Adverse Drug Events, No. (%)		
	Overall (N = 1523)	Preventable (n = 421)	Nonpreventable (n = 1102)
Gastrointestinal tract	336 (22.1)	89 (21.1)	247 (22.4)
Electrolyte/renal	255 (16.7)	112 (26.6)	143 (13.0)
Hemorrhagic	194 (12.7)	67 (15.9)	127 (11.5)
Metabolic/endocrine	145 (9.5)	58 (13.8)	87 (7.9)
Dermatologic/allergic	120 (7.9)	9 (2.1)	111 (10.1)
Infection	91 (6.0)	2 (0.5)	89 (8.1)
Respiratory tract	83 (5.4)	12 (2.9)	71 (6.4)
Neuropsychiatric	75 (4.9)	36 (8.6)	39 (3.5)
Edema	72 (4.7)	6 (1.4)	66 (6.0)
Syncope/dizziness	72 (4.7)	20 (4.8)	52 (4.7)
Cardiovascular	66 (4.3)	25 (5.9)	41 (3.7)
Hepatic	23 (1.5)	3 (0.7)	20 (1.8)
Anorexia/weight loss	18 (1.2)	8 (1.9)	10 (0.9)
Ataxia/difficulty with gait	15 (1.0)	6 (1.4)	9 (0.8)
Falls without injury	15 (1.0)	10 (2.4)	5 (0.5)
Hematologic	14 (0.9)	1 (0.2)	13 (1.2)
Anticholinergic†	12 (0.8)	4 (1.0)	8 (0.7)
Fall with injury	8 (0.5)	4 (1.0)	4 (0.4)
Musculoskeletal	5 (0.3)	1 (0.2)	4 (0.4)
Extrapyramidal symptoms/tardive dyskinesia	4 (0.3)	0	4 (0.4)
Functional decline‡	3 (0.2)	1 (0.2)	2 (0.2)
Incontinence	1 (0.1)	0	1 (0.1)

*Adverse drug events could manifest as more than 1 type.
†Anticholinergic effects include dry mouth, dry eyes, urinary retention, and constipation.
‡Adverse drug event manifested only as decline in activities of daily living without any other more specific type of event. Other types of events may have been associated with functional decline.

both the hospital and nursing home settings, more serious events were more likely to be judged preventable.

Electrolyte/renal, gastrointestinal tract, hemorrhagic, and metabolic/endocrine events were the most common types of preventable adverse drug events identified in our study. Some of these types of events may be more amenable to prevention efforts than others. Technological approaches, such as computerization of prescribing with clinical decision support, have the potential to reduce the occurrence of drug-induced nephrotoxicity, dehydration, and electrolyte abnormalities.[24,25] Computerized physician order entry with decision support provides the potential to prevent or to warn against prescribing drugs with known interactions, or to warn the prescriber of a need to increase the frequency of monitoring. Active prompting of the prescriber to perform follow-up laboratory testing in the case of prescribing anticoagulants, thyroid medications, antiseizure medications, and certain cardiovascular drug therapies (eg, digoxin and angiotensin-converting enzyme inhibitors) is feasible. While there is evidence to support the benefits of this approach in the inpatient setting,[26] less than 5% of US hospitals have computerized physician order entry.[27,28] Use of such systems in the ambulatory setting is even more limited; while this approach may be equally useful in the ambulatory setting, evidence supporting the benefits remains largely anecdotal.[29]

Anticoagulants were responsible for 121 of the 1523 adverse drug events, fully a third of which were considered preventable. A more systematic approach to decision making about the use of warfarin for stroke prevention in older persons is required, as is a more consistent approach to management of anticoagulant therapy. While more widespread use of specialized clinics for anticoagulation therapy to provide coordinated care has been promoted to improve the effectiveness and safety of warfarin in elderly patients,[30] to date the benefits of this approach relative to usual care have not been established.[31]

While most antibiotic-associated events were characterized as nonpreventable, it is widely recognized that these agents are commonly overused, particularly in the ambulatory setting.[32] Many antibiotic-associated events (eg, rashes and diarrhea) might have been deemed preventable if the decision to implement therapy had been more rigidly scrutinized.

Most errors associated with preventable adverse drug events occurred at the prescribing and monitoring stages. However, problems with patient adherence were cited as a contributing factor in more than 20% of cases. The issue of patient adherence has received very little attention in the literature on patient safety relevant to preventing adverse drug events, but this issue is clearly very important.[26,33] In studies of preventable adverse drug events conducted in hospital and long-term care settings, errors involving patient adherence have not been identified as an important issue. In those clinical settings, all aspects of pharmaceutical care are presumed to be supervised; generally the patient is given little, if any, responsibility relating to medication administration or monitoring. In contrast, in the ambulatory setting, such responsibilities do extend to the patient and/or family members. While the adverse effects of patient nonadherence on the therapeutic benefits of drug therapies have been increasingly recognized,[34] the effect of nonadherence on the risk of adverse drug events has not been widely considered. As patient education is an essential component of most efforts to improve patient adherence, it is informative that our study identified inadequate patient education about medication use as a frequent error in preventable adverse drug events.

Our study was conducted in the context of a single multispecialty group practice providing care to older persons aged 65 years or older residing in a single geographic area, and the vast proportion of the study population was composed of Medicare+Choice Plan enrollees. This particular setting is ideal for such research, as automated data on prescription medications, laboratory results, and electronic clinic notes are readily available. At the time of our study, while only 17% of all Medicare beneficiaries nationally were Medicare+Choice Plan enrollees,[35] the age and sex characteristics of the study population closely mirrored the overall US population aged 65 years or older.[23]

If the findings of the present study are generalized to the population of all Medicare enrollees, then more than 1 900 000 adverse drug events—more than a quarter of which are preventable—occur each year among 38 million Medicare enrollees; furthermore, estimates based on our study suggest that there are in excess of 180 000 life-threatening or fatal adverse drug events per year, of which more than 50% may be preventable. For a number of reasons, these estimates are likely to be conservative. In our study, while most outpatient notes (>80%) were available in electronic form as part of an electronic medical record, handwritten notes were not systematically searched, which likely reduced complete ascertainment of adverse events. To ascertain information on drug-related incidents, we relied solely on information contained in ambulatory medical records. The clinical pharmacist investigators were cued to review ambulatory medical records by a variety of information sources including automated signals, hospital discharge summaries, emergency department notes, spontaneous reports by health care providers, and administrative incident reports, but they did not review every medical record. However, a systematic, periodic review of all medical records would likely have provided the opportunity to identify even more adverse drug events. In addition, in some cases, information contained in ambulatory records was limited, and adequate information was not available to allow physician-reviewers to classify incidents as adverse drug events. There was no direct patient contact in this study; interviews of patients would have provided the opportunity to identify additional events.[36]

We did not discount person-time from the denominator in our calculation of rates for time spent in hospital or for short stays in skilled nursing or rehabilitation facilities. However, we suspect that this would modestly affect our estimates, even if such adjustments were made. For example, recently published data from the National Center for Health Statistics indicate that for the year 2000 in the United States, persons aged 65 years or older had an average of 2 days of hospital care.[37]

The interrater reliability of implicit judgments about adverse events caused by medical care, based on medical record review, has been criticized.[38] However, in the present study, we found a high level of agreement between the physician-reviewers. Several authors have been highly critical of estimates of numbers of deaths caused by medical error, citing a need to be certain that the adverse event caused death in a patient who otherwise would have survived.[39-41] Our study was not designed to focus on death as a primary outcome measure. As Hayward and Hofer have written, "Whether errors warrant systems changes should not be based on the impact of the errors but, rather, on a careful examination of specific errors and the effectiveness and costs of a policy directed at error prevention."[42]

How should the findings of this study be applied to improve the quality of care for older persons in the ambulatory setting? Fortunately, many health care systems are moving toward an approach to dealing with medical error by addressing failure in the design of systems of care that contribute to error.[7,43,44] Enhanced surveillance and reporting systems for adverse drug events in the ambulatory setting are required. Efforts as intensive as those described in the present study would not be feasible on an ongoing basis because of their expense, but automated monitoring of some type may be practical as electronic medical record systems are more widely adopted. However, almost no such monitoring currently takes place in the outpatient setting.

Prescribing and monitoring errors in the ambulatory setting may be particularly amenable to prevention strategies using systems-based approaches. Broader testing of computerized physician order entry with clinical decision support to reduce the risk of medication errors is required before advocating for large-scale implementation in the outpatient setting. Further development and testing of new approaches to enhance collaborations between those who prescribe drugs and those who know the most about the specific drugs, that is, clinical pharmacists, should be pursued in the ambulatory setting.[16,45]

The increased involvement of older persons in their pharmaceutical care also has the potential to be particularly beneficial in reducing medication errors. Complex medication regimens can lead to confusion for elderly patients and family members. Physicians and pharmacists are generally relied on to provide accurate and complete drug instructions for administration and monitoring to patients and their families. However, these interactions are often hurried, leading to the provision of incomplete information.[46] As Kaushal et al[29] have advocated for use by parents of pediatric patients, World Wide Web–based information could supplement verbal information provided by physicians and pharmacists. Personalized Web pages could provide information regarding a specific medication regimen and enhance patient adherence.

In summary, adverse drug events are common and often preventable among older persons in the outpatient setting. Our study provides additional evidence of the need to develop and evaluate new strategies to reduce the risk of drug-related injury in the ambulatory geriatric patient population.

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Financial Disclosure: Dr Bates is a consultant and serves on the advisory board for McKesson MedManagement, a company that assists hospitals in preventing adverse drug events; he has received honoraria for speaking from Automated Healthcare, which makes robots that dispense medications; and he is a consultant for Alaris, which makes intravenous drug delivery systems.
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Administrative, Technical or Material Support: Gurwitz, Field, Harrold, Rothschild, DeBellis, Seger, Cadoret, Fish, Garber, Kelleher, Bates.
Study supervision: Gurwitz.
Funding/Support: This work was supported by research grant AG 15979, cofunded by the National Institute on Aging and the Agency for Healthcare Research and Quality.
Disclaimer: The contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institute on Aging and the Agency for Healthcare Research and Quality.
Acknowledgment: We thank Jill Auger, RPh, and Leslie Garber, RPh, for assistance with data collection relevant to this study; Mary Ellen Stansky and Jackie Cernieux, MPH, for their assistance with technical aspects of this study; and Bessie Petropoulos for assistance with manuscript preparation.

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. . . we do not know a truth without knowing its cause.
—Aristotle (384-322 BCE)

ORIGINAL ARTICLES

Drug related medical emergencies in the elderly: role of adverse drug reactions and non-compliance

S Malhotra, R S Karan, P Pandhi, S Jain

Abstract

***Background*—Adverse drug reactions and non-compliance are important causes of admissions in the elderly to medical clinics. The contribution of adverse drug reactions and non-compliance to admission by the medical emergency department was analysed.**

***Methods*—A total of 578 consecutive elderly patients admitted to the medical emergency department were interviewed to determine the percentage of admissions due to adverse drug reactions or non-compliance with medication regimens, their causes, consequences, and predictors.**

***Results*—Eighty three (14.4%) of the 578 admissions were drug related: 39 (6.7%) caused by adverse drug reactions and 44 (7.6%) caused by non-compliance with medication. One hundred ninety two (33.2%) patients had a history of non-compliance. Factors associated with an increased risk of admission because of an adverse drug reaction were patients with diabetes or neoplasms, and patients using numerous different medications. Factors associated with a higher risk of hospitalisation because of non-compliance were poor recall of the medication regimen, seeing numerous physicians, female sex, polypharmacy, drug costs, and switching over to non-conventional forms of treatment.**

***Conclusion*—Many elderly admissions are drug related, with non-compliance accounting for a substantial fraction of these. Elderly people at high risk of suffering a drug related medical emergency are identified and suitable interventions may be planned by the healthcare policymakers to target them.**

(*Postgrad Med J* 2001;77:703–707)

Keywords: adverse drug reactions; non-compliance; drug related medical emergencies; elderly

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Submitted 10 January 2001
Accepted 27 March 2001

Of all the people who have ever lived to age 65, more than two thirds are currently alive. As individuals age, they are more likely to suffer from disease, disability, and drug side effects.[1] Adverse drug reactions (ADRs) are an important cause of morbidity and hospital admissions among the elderly.[2] In a large, multicentre study, adverse reactions were a contributing cause in 10.5% of consecutive geriatric admissions.[3] Although some studies have shown that the incidence of ADRs may be as high as 25%, a rate that is twofold or threefold higher than in younger patients, the notion that age is a critical predisposing determinant of adverse reactions is controversial.[4 5] In fact, the incidence of ADRs increased with age in only five of 12 studies that evaluated age as a variable.[4] However, elderly patients may have multiple disease states and may use a wide variety of drugs, increasing the potential for altered responsiveness to drugs and a higher incidence of adverse effects compared with younger patients.[6] Moreover, a substantial proportion of the elderly are non-compliant; estimates vary from 26% to 59%.[7–10] While several studies have attempted to identify characteristics that predict non-compliance, results have been contradictory. For example, one study found higher rates of non-compliance among elderly people who were over 75 years of age, living alone, less educated, and with more diagnoses[10]; another study found no significant differences using these same variables.[8]

The current study was designed specifically to address the drug taking behaviour of the elderly, taking into consideration variables such as living situation, cost of medications, and number of physicians seen regularly. Our objectives were to determine the proportion of medical emergency admissions that are secondary to ADRs or non-compliance and the causes and predictors of non-compliance and ADRs.

Patients and methods

The study was conducted in the medical emergency department of a 1200 bed tertiary care referral hospital in north India. All patients 65 years and over who were admitted to the department between January and July 2000 were included in the study. The total sample size was 578.

All patients were interviewed, usually within 24 hours of admission. The methods followed have been described.[11] Briefly, information obtained included the patient's age, sex, assistance in taking their medications, number of physicians seen on a regular basis, medications taken on admission, history of non-compliance, and reasons for non-compliance. Determining a patient's history of non-compliance was attempted in a non-judgmental way. The question was asked as

follows: "Many patients that are taking different medications over long periods of time will occasionally not take one or more of their medications. Were you able to take all the medications regularly? Do you ever take more or less of the amount prescribed for any reason?".

Medical records were used to obtain diagnosis at admission, drug history, and to corroborate information provided by patients during the interview. Patients' knowledge of their medication regimen was determined by asking them to recite their regimen and comparing this response with information in their medical records. Whenever possible, family members were consulted for further corroboration. For confused or unresponsive patients, the required information was obtained from family members.

Each patient in the study was evaluated by one of us to determine if the admission was drug related, whether non-compliance or an ADR was a causative factor in each admission, and what drug(s) was (were) implicated. The strength of the casual relationship was also assessed, whether ADR or non-compliance was a definite, probable, possible, or contributing factor in that admission.

During the course of the study, 47 patients died or were discharged before they could be interviewed, two were either uncommunicative or too confused to be interviewed, with no family members available; this left a total study group of 578 admissions. The χ^2 test and two tailed Fisher's exact test were used to determine if there were statistically significant differences between proportions.

DEFINITIONS

The definitions used in this study, as described in similar studies, were:

Adverse drug reaction—Any response that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or treatment, excluding a failure to accomplish the intended purpose.[12]

Drug related hospital admission—Admission caused by any undesirable clinical manifestation that is consequent to and caused by the administration of a particular drug. The clinical manifestation may be a clinical sign, symptom, or abnormal laboratory test or it may be a cluster of abnormal signs, symptoms, or tests.[11 13]

Drug non-compliance—The extent to which the patient's drug taking behaviour (in terms of taking medication) coincides with the prescription.[14]

Definitions used in assessing causality were (1) definite or probable: the reaction commonly known to occur, with clear cut temporal association or laboratory confirmation; signs and symptoms were improved by dose adjustment, stopping or reinstating the drug; the signs and symptoms could not reasonably be explained by the known characteristics of the patients clinical condition or by the effects of other drugs; (2) possible: reaction known to occur with less clear cut temporal relationship; other causes also possible; the signs and symptoms were improved by dose adjustment, stopping, or reinstitution of the drug therapy; (3) contributing factor: there is a definite or probable link between drug treatment and admitting diagnosis; however, there are other complications that are unrelated to drug treatment, which are also a cause of admission.

Table 1 Characteristics of the study population

Mean (SD) age, years	72.5 (4.7)
Living alone, %	13.6
Completed high school, %	32.7
Average number of different medications prescribed*	4.1
Average number of pills taken per day†	5.9
Average monthly cost of medications	$4.3

*Including medications taken as needed.
†Including only medications prescribed by physician.

Results

The mean age of the study groups was 72.5 years, ranging from 65 to 91 years. The mean age for men was 71.6 years and for women 73.2 years. There was a slight preponderance of females (52.9%). More than 10% of the elderly were living alone and about one fourth completed high school. On average, these patients were taking between five and six medications a day and had four to five different medications prescribed (table 1). Eighty three (14.4%) of the 578 admissions to the medical emergency department were judged to be drug related: 39 admissions (6.7%) were caused by ADRs and 44 (7.6%) were related to medication non-compliance. Of 83 admissions, the causal relationship was considered to be definite or probable in 23, possible in 44, and a contributing factor in 16. The total hospital cost of all drug related admissions in the department was US $3775 (1 US $ = 46 Indian rupees); $1471 for admissions related to ADRs and $2304 for admissions related to non-compliance.

Among the 39 admissions related to ADRs, hypoglycaemia induced by oral hypoglycaemic agents was the commonest (30.8%). Other drugs most commonly implicated were non-steroidal anti-inflammatory drugs (NSAIDs) and anticancer drugs (table 2). There was no sex related difference in ADR related admissions. The greater the number of different medications prescribed, the greater the cost of admissions related to ADRs ($p<0.01$) (table 3).

Table 2 Medications (or therapeutic groups) implicated in emergency admissions related to ADRs

Medication (or therapeutic groups)	*No of times cited*
Oral hypoglycaemics*	12
NSAIDs†	6
Cancer chemotherapy‡	5
Antitubercular drugs§	5
Penicillins¶	2
Digoxin	2
Phenytoin	2
Others	5

*Includes glibenclamide (8), gliclazide (3), and glipizide (1).
†Includes indomethacin (4), aspirin (2).
‡Includes cyclophosphamide (2), methotrexate (2), 5-fluorouracil (1).
§Includes isoniazid and rifampicin combination.
¶Includes crystalline penicillin and ampicillin.

Table 3 Proportion of patients admitted with ADRs

Characteristic	*No of patients interviewed*	*No (%) of admissions for ADRs*
No of different prescribed medications*		
0	41	2 (4.9)
1–3	355	15 (4.2)
4–10	166	16 (9.6)
11 or more	16	6 (37.6)
Monthly cost of treatment†		
$0–4	431	17 (3.9)
$5–10	104	12 (11.5)
>$10	43	10 (23.2)

*Not including medications taken as needed.
†Cost in US dollars, $1 = 46 Indian rupees (approximately).

The proportion of patients whose admission was related to an ADR also varied with the monthly cost of medication: about one fourth of patients paying $10 or more per month had an ADR compared with 5.2% for those paying less than this amount ($p<0.05$). When controlling for the number of different medications, ADRs were 2.4 times more prevalent among those paying over $5 a month on medications (95% confidence interval 1.1 to 6.3) and 3.7 times more prevalent among those paying over $10 a month (95% confidence interval 1.3 to 12.7).

Stepwise logistic regression analysis found the following variables to be associated with admissions due to ADRs: the number of different prescription medications used, the number of physicians seen regularly, and patients living alone. The greater the number of different prescriptions drugs taken, the greater the risk of emergency admission related to an ADR—the odds ratio for those taking three or more different medications compared with those taking less than three was 4.3. Patients who were regularly seeing more than three physicians were at higher risk of presenting to the medical emergency compared with those seeing three or less (odds ratio 5.7). Patients who were living alone were more likely to attend medical emergency because of an ADR as compared to those living with families (odds ratio 4.3).

NON-COMPLIANCE

Among the study group, 192 (33.2%) reported a history of non-compliance within the past year. The most common form of non-compliance was underuse, accounting for 71% of all non-compliance, followed by overuse (17%) and misuse (2%). Sixty three per cent of all non-compliance was reported as being intentional and 37% reported as being unintentional.

Table 4 Main causes of medication non-compliance

Stated causes	*No (%) with past history of non- compliance**	*No (%) with current admission related to non- compliance**
Cost	53 (27.6)	16 (36.4)
Inadequate instruction	18 (9.4)	11 (25.0)
Switch to unconventional prescription	23 (12.0)	10 (22.7)
Side effects	38 (20.0)	5 (11.4)
Forgetfulness	41 (21.3)	3 (6.8)
Perceived as not necessary	15 (7.8)	3 (6.8)
Dislikes taking medicines	7 (3.6)	3 (6.8)
Others	9 (4.7)	0
Total	192	44

*Some respondents gave more than one response.

Table 5 Drug groups and drugs implicated in hospitalisations due to non-compliance

Medication	*No of times cited*
Antihypertensives	24
Enalapril	8
Amlodipine	8
Atenolol	2
Others	6
Antiasthmatics	8
Theophylline	3
Steroids	3
β_2-agonists	2
Antidiabetics	5
Insulin	4
Glibenclamide	1
Anticonvulsants	4
Phenyoin	3
Valproate	1
Antianginals	3
Isosorbide dinitrate	2
Nitroglycerin	1

The most common cause of non-compliance among patients with a history of non-compliance was cost (27.6% of respondents) followed by forgetfulness (21.3%), side effects (20.0%), and patients switching to unconventional forms of treatment (12.0%) (table 4). Among patients whose current admission was related to non-compliance, cost was again the most common cause (36.5%) followed by inadequate instruction (25.4%) and switch to non-conventional treatment (22.7%). The drug classes most commonly implicated in hospitalisation due to non-compliance were antihypertensives and antiasthmatics (table 5).

The proportion of patients with a history of non-compliance was highest among cardiac admissions (51.7%), followed by respiratory diseases (43.5%), metabolic abnormalities (26.4%), and central nervous system complaints (19.7%). In contrast, among patients whose present admission was related to non-compliance, including only definite/probable and contributing factors as causative factors, the highest proportion was seen among those with cardiovascular diseases (15.3%), followed by respiratory diseases (7.4%), metabolic disturbances (6.9%), and central nervous system disorders (3.3%).

Several characteristics were found to be associated with admissions related to non-compliance (table 6). Women accounted for a higher proportion of non-compliant admissions than did men (8.5% *v* 6.6%, $p<0.05$). Patients' ability to recall their medication regimen was found to be associated with the rate of non-compliant admissions—those patients who could not recall their regimen had a higher rate of non-compliant admissions than those who could (9.2% *v* 3.6%), while those patients who could only partially recall their regimens had the highest rate of non-compliant admissions (18.4%, $p<0.001$). The greater the number of physicians seen regularly by the patients, the greater the proportion of non-compliant admissions ($p<0.01$). The odds ratio for non-compliance admissions patients seeing more than three physicians regularly compared with those seeing fewer than three was 5.0. The greater the number of different medications prescribed, the greater the proportion of non-compliant admissions

Table 6 Proportions of patients admitted in the medical emergency for non-compliance

	No of patients interviewed	*No (%) of non-compliant admissions*	
Total	578	44 (7.6)	
Male	272	18 (6.6)	
Female	306	26 (8.5)	p<0.05
Recall of medication regimen			
Patient recalls regimen	334	12 (3.6)	
Patients cannot recall regimen	141	13 (9.2)	
Patients with only partial recall of regimen	103	19 (18.4)	p<0.01
No of physicians seen regularly			
0–1	427	14 (3.3)	
2–3	106	17 (16.0)	
>3	45	13 (28.9)	p<0.01
No of different prescribed medications			
0–1	41	0	
1–2	31	12 (3.8)	
≥3	220	32 (14.5)	p<0.01

(p<0.01). The odds ratio for those taking three or more different medications compared with those taking fewer than three was 4.3. The odds ratio for patients hospitalised for non-compliance with only partial recall for their medication regimen was 5.1 compared with those with total recall.

Discussion

Our study, which prospectively identified all drug related visits to a multidisciplinary medical emergency department showed that approximately 14% of all elderly admissions to the department were drug related. Only a few studies have analysed emergency department visits potentially related to the complications of drug therapy.[15–18] Most of these studies included only ADRs, were focused on specialised hospital units, and patients of all age groups were included. Consequently, the proportion of admissions caused by drug related issues ranged from 2.3% to 27% and in a meta-analysis a weighted estimate of 5.1% of drug related admissions was derived.[19]

Sulfonylureas were responsible for hypoglycaemic reactions, this ADR is known to occur in 4% of patients, and is a particular problem in elderly.[20] Severe acute gastritis, with or without gastric bleed, is a known complication of NSAID therapy,[21] and NSAIDs have been identified as one of the areas of particular concern in others studies as well.[15 17] Cancer chemotherapy was the other leading cause of ADR related emergency admission as in some other studies.[11] Several factors may contribute to ADRs in the elderly. A progressive decline in many parameters of physiological function occurs with aging and may influence the disposition of drugs in geriatric patients. Impaired organ function, which may result from prior disease as well as from aging, alters drug kinetics, organ responses, and homoeostatic counter-regulation to drug effect.[22]

The direct relation between number of drugs prescribed and admissions due to ADR proves that the likelihood of toxicity increases as the number of drug prescribed rises. The independent association between ADRs and medication costs seen in our and some other studies could reflect the use of newer medications that are more costly. Those with higher medication costs could be using the more costly, recently introduced drugs for which there may be more side effects, more drug interactions, and, most importantly, less experience in the elderly, leading to incorrect dosage.

Our results also show that nearly 8% of all elderly admissions to the medical emergency department were related to non-compliance. This finding is comparable with what has been described in the literature (2.9%, 7.4%, and 10.5%),[23] even though other studies included all age groups, used differing definitions of non-compliance and considered medical (and not emergency) admissions. The percentage of hospitalised elders having a history of non-compliance (33.2%) falls within the range of estimates produced by other studies (25% to 50%). However, this may be an underestimate of the compliance as determination of a patient's history of non-compliance relies on self admission. There may an error in recall or the patient may be unwilling to disclose non-compliance. We used the interview method, which although problematic, has been validated as a practical and reasonably accurate means of determining whether a patient has been non-compliant.[24–26]

Cost was the frequently stated cause for non-compliance both in patients and with a history of non-compliance and those whose current hospitalisation was related to non-compliance. This is different to what has been reported in other studies where side effects and forgetfulness were the most common causes for non-compliance.[11 16–18] This may be due to the fact that many patients who visit our hospital have poor socioeconomic background and cannot afford medications. Inadequate instruction and patients switching over to non-conventional forms of therapy on their own were two important causes for non-compliance among patients whose admission was related to non-compliance. Ours being a tertiary care, referral hospital, many patients are referred by the registered medical practitioners or from peripheral hospitals where they may not be receiving proper instructions regarding use of medications. Moreover, most patients in our study were suffering from chronic illnesses, requiring life long treatment and because of illiteracy, poverty and misconceptions, started visiting providers of non-conventional therapies and may even stop conventional medications. This was an important reason for non-compliance and had not been reported in previous studies. While using the other stated reasons for non-compliance on which to base policy interventions is problematic, it is the last one (switching to unconventional forms of therapy), which may be targeted for intervention by the policymakers.

It is not surprising that more complicated medication regimens, an inability to properly recall the regimen, the greater number of physicians consulted regularly, and the greater number of preparations used were associated with increased risk of non-compliance and increased risk of a hospitalisation related to non-compliance. Moreover, patients with a partial recall of their medication regimen were at higher risk than those with no recall. It is difficult to explain but perhaps patients with no

recall seek assistance more readily than those with partial recall.

The results of our study help identify several characteristics that can be used by health providers to identify elders at risk of suffering a drug related medical emergency. These include elderly diabetics; patients with neoplasms; patients on several medications concurrently with complicated regimens; patients who have only partial recall of their medication regimens; and those who are receiving expensive medications. Our results once again highlight the well known principle of geriatric clinical pharmacology: prescribe simpler regimens with fewer pills to be taken each day. Also, monitoring of prescriptions of the registered medical practitioners practising in the peripheral areas may help curtail drug related emergencies among the elderly. More importantly, our results suggest that better patient education about drug side effects and the pros and cons of unconventional therapies should help in decreasing noncompliance.

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Impact of Medication Adherence on Hospitalization Risk and Healthcare Cost

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Objective: The objective of this study was to evaluate the impact of medication adherence on healthcare utilization and cost for 4 chronic conditions that are major drivers of drug spending: diabetes, hypertension, hypercholesterolemia, and congestive heart failure.

Research Design: The authors conducted a retrospective cohort observation of patients who were continuously enrolled in medical and prescription benefit plans from June 1997 through May 1999. Patients were identified for disease-specific analysis based on claims for outpatient, emergency room, or inpatient services during the first 12 months of the study. Using an integrated analysis of administrative claims data, medical and drug utilization were measured during the 12-month period after patient identification. Medication adherence was defined by days' supply of maintenance medications for each condition.

Patients: The study consisted of a population-based sample of 137,277 patients under age 65.

Measures: Disease-related and all-cause medical costs, drug costs, and hospitalization risk were measured. Using regression analysis, these measures were modeled at varying levels of medication adherence.

Results: For diabetes and hypercholesterolemia, a high level of medication adherence was associated with lower disease-related medical costs. For these conditions, higher medication costs were more than offset by medical cost reductions, producing a net reduction in overall healthcare costs. For diabetes, hypercholesterolemia, and hypertension, cost offsets were observed for all-cause medical costs at high levels of medication adherence. For all 4 conditions, hospitalization rates were significantly lower for patients with high medication adherence.

Conclusions: For some chronic conditions, increased drug utilization can provide a net economic return when it is driven by improved adherence with guidelines-based therapy.

Key Words: adherence, drug utilization, healthcare costs, hospitalization, pharmaceutical care

(*Med Care* 2005;43: 521–530)

Prescription drug expenditures are the fastest growing component of healthcare costs in the United States.[1,2] National outpatient drug spending has increased by 13% to 16% per year during the past few years,[2] and it is expected to continue to grow by 9% to 13% per year during the coming decade.[2] Much of the growth in drug spending is the result of increased use (more drugs prescribed for more people for more indications); this accounts for more than 50% of the growth in drug spending for many common conditions, including diabetes and hypercholesterolemia.[1,3] In an effort to manage this growth, health plan sponsors and plan managers have responded with a variety of programs aimed at containing utilization and cost. Some patients in prescription benefit plans have experienced higher copayments and tighter utilization controls, and physicians have been under increasing pressure to factor drug costs and coverage limits into their treatment decisions. All of the participants in the healthcare system face a common dilemma: are the benefits of prescription drugs worth the increased cost?

For many medical conditions, there is strong evidence that prescription drugs provide *clinical* value. Based on that evidence, pharmacotherapy has become an integral component of the treatment guidelines for many high-prevalence diseases, including diabetes,[4] hypertension,[5] hypercholesterolemia,[6] and congestive heart failure (CHF).[7] The more difficult question is whether prescription drugs provide net *economic* value to those who pay for health care. Does drug treatment reduce overall healthcare costs by reducing patients' need for expensive medical services such as hospitalization and emergency room (ER) treatment? Results of this kind have been demonstrated for several medical condi-

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This research was designed and conducted by the authors as part of their employment with Medco Health Solutions, Inc. The manuscript was reviewed through an internal publications review process to ensure data integrity and editorial quality. The research was not funded by, or subject to the review of, any outside company or organization.

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ISSN: 0025-7079/05/4306-0521

tions.[8–13] For example, lipid-lowering drugs are generally cost-effective in secondary prevention of heart disease; by reducing the risk of cardiovascular events, they can produce a net return on investment.[10] This type of cost offset is a welcome benefit, but it may not be found for all high-prevalence conditions for which drug therapy is recommended. Some drug treatments may show a medical cost offset (in the short term or long term), and some may not show an offset at all.[14]

The therapeutic and economic benefits of drug treatment are often demonstrated in the controlled settings of clinical trials. These benefits may not be realized in day-to-day practice, especially for patients who are only partially compliant with their prescribed therapy. Adherence with medication therapy is generally low—approximately 50% to 65%, on average, for common chronic conditions such as hypertension and diabetes.[15,16] When conditions are treated suboptimally, symptoms and complications may worsen, leading to increased use of hospital and ER services, office visits, and other medical resources.[16,17] This suggests that higher levels of medication adherence may have positive economic value for some chronic conditions. Increased adherence may generate medical savings that more than offset the associated increases in drug costs. For some chronic conditions, there is evidence to support this hypothesis.[14,18–23]

There has been relatively little research assessing the cost impact of medication adherence for treatments provided under benefit plans in population-based settings. Some studies have assessed how healthcare costs are affected when patients reduce their drug use in response to coverage limits or copayment requirements. In a study of coverage limits in a Medicaid population, there was a net *increase* in total healthcare costs when patients were limited to a maximum of 3 prescriptions per month; many patients cut back on medications for chronic conditions (such as diabetes and CHF), and their use of medical services increased.[24,25] Medical utilization may also increase when patients cut back on drug use in response to copayment requirements.[26–29] These studies suggest that if patients' adherence levels drop as a result of benefit plan changes, medical utilization for some conditions may increase, and the increased medical costs may exceed the savings in drug costs.[14]

In this observational study, we evaluate the relationships among medication adherence, medical utilization, and healthcare cost in a large population of patients with combined benefit eligibility for prescription drugs and medical services. Drug cost, medical cost, and utilization are measured using pharmacy claims data and medical claims data, integrated at the patient level. After adjusting for age, comorbidity, and other factors, we estimate healthcare cost and hospitalization risk as a function of medication adherence. The analysis covers 4 high-prevalence conditions for which prescription drugs play a key role: diabetes, hypertension, hypercholesterolemia, and CHF. These conditions are generally chronic in presentation and often require long-term medication therapy.

METHODS

Study Population

Patients were participants in medical and drug benefit plans sponsored by a large manufacturing employer. Patients were initially identified for the study population if they had continuous medical and drug benefit eligibility during the period of the study, June 1997 through May 1999. Medical plan types included a health maintenance organization (HMO), a preferred provider organization (PPO), and a traditional fee-for-service (FFS) plan; participants in a small, capitated managed care plan were excluded because full medical cost data were not available at the patient level. Patients aged 65 and older (n = 73,997) were excluded because medical claims data were not available for their primary benefit plan (Medicare). A total of 137,277 patients (employees and dependents) met the inclusion criteria for the final study population. Age in the study population was distributed as follows: 0–18 (20.0%), 19–39 (16.0%), and 40–64 (64.0%). The population was 48.9% female and 51.1% male.

Medical data for the study population were drawn from an administrative claims database maintained by a health plan organization for all medical plan types. Drug utilization data were drawn from a prescription claims database maintained by Medco Health, the pharmacy benefits management company that manages the prescription benefit plan for this population.

Sample Selection

Separate study samples were drawn from the study population for purposes of analysis. A study sample was identified for each of the 4 conditions under study: diabetes, hypertension, hypercholesterolemia, and CHF. Patients were identified for a study sample if they used medical services for the condition and if they received prescription drugs for the condition. Patients were included in multiple study samples if they met the inclusion criteria for more than 1 of the medical conditions under study. Specific inclusion criteria were as follows.

Medical Claims

Patients were initially identified for a study sample if they received medical services for the condition during the first 12 months of the study period. To minimize false-positives, patients were identified for a study sample if they had 2 or more medical claims for outpatient services on different dates during the year, or if they had 1 or more claims for hospitalization or ER service during the year; outpatient services included physician office visits and outpatient de-

partment visits. For each medical condition under study, medical services were identified using primary and secondary International Classification of Diseases, 9th Revision (ICD-9) codes[30] in patients' claim records (Appendix).

Drug Claims

Patients were included in the final study sample if they received 1 or more prescriptions for the target condition during the 12 months after their first medical index claim (the first of 2 or more dates of outpatient service for the target condition, or the first of 1 or more dates of inpatient or ER service). The study did not include patients who were diagnosed with a condition but who were not using medications to treat it.

Data Collection

Utilization Data

Medical and drug claims were tracked concurrently during a 12-month analysis period for the patients in each study sample. For each patient, the analysis period began on the date of the first index claim, as defined previously.

Sociodemographic Data

Data on age, sex, employment group, and medical plan type were drawn from an eligibility database maintained by the health plan organization. Employment group was hourly or salaried (benefit plans differed for these 2 groups). Medical plan type was HMO, PPO, or FFS.

Adherence

Medication adherence was measured by patients' overall exposure to medications used to treat a given condition. Adherence was defined as the percentage of days during the analysis period that patients had a supply of *1 or more* maintenance medications for the condition (based on "days' supply" data in patients' prescription claim records). This measurement strategy reduces the risk of overestimating adherence (eg, in cases in which patients have overlapping prescriptions as a result of a change in therapy). For prescriptions extending beyond the end of the analysis period, days' supply was truncated at the end of the period. Patients in each study sample were stratified into 5 categories based on their adherence score: 1–19%, 20–39%, 40–59%, 60–79%, or 80–100%.

Comorbidity

Two comorbidity scores were derived for the patients in each study sample. The Charlson score was based on ICD-9 codes in patients' medical claims during the analysis period; it was computed using a Deyo-adapted Charlson scale.[31] A chronic disease index (CDI) was computed from patients' prescription claims during the analysis period. The CDI is a composite measure of drug use across a broad range of chronic conditions; a related index has been validated in previous studies.[32,33] For each analysis, the CDI score excluded the target medications for the condition under study; this precluded any confounding with the primary predictor of interest (medication adherence). The 2 comorbidity scores differ in their data source (medical vs. drug claims) and in the medical conditions they assess. The measures are positively correlated but not colinear. Significant positive correlations were observed for all 4 study samples ($r = 0.40$, diabetes; 0.42, hypertension; 0.38, hypercholesterolemia; 0.38, CHF; $P < 0.0001$).

Disease Subtype

For each target condition, specific ICD-9 codes were used as indicators of disease subtype. If any medical claim during the follow-up period contained 1 of these codes, the indicator was scored "1" for that patient; otherwise, it was scored "0". Scores were derived independently for each indicator.

Outcome Measures

The primary economic measures were total *medical costs* and *prescription drug costs* during the 12-month analysis period. Total *healthcare costs* were defined as the sum of medical costs and drug costs. Medical costs included outpatient services, ER services, and hospitalization; nursing home and home care services were not included. Drug costs included all ambulatory prescriptions (dispensed by outpatient, community-based, or mail-service pharmacies). Cost was defined as net cost to the plan sponsor; patient copayments and deductibles were not included.

Two types of cost were measured from the claims data: all-cause costs and disease-related costs. *All-cause costs* were medical or drug costs associated with *any* condition during the 12-month period. *Disease-related costs* were costs associated with treatment of the target condition; they were a subset of all-cause costs. For medical services, disease-related costs were identified by primary and secondary ICD-9 codes in medical claims data (Appendix). For hypertension and hypercholesterolemia, disease-related medical costs were identified by a broader set of cardiovascular codes that included common sequelae of the target condition (such as myocardial infarction or stroke). In many settings, these acute sequelae are more likely to be used for diagnostic coding, especially in cases of hospitalization or ER treatment. If claims analysis is restricted to diagnostic codes for the underlying condition (such as hypercholesterolemia), medical utilization and cost can be seriously underestimated. For drugs, disease-related costs were identified by drug classes in prescription claims data (Appendix).

The primary measure of medical utilization was *hospitalization risk*. This was defined as the probability of 1 or more hospitalizations during a 12-month period, expressed as

a percentage. Observed probability values were derived from medical claims data during the analysis period.

Data Analysis

We used multiple linear regression to evaluate the association between medication adherence and healthcare costs for each target condition. Cost estimates were adjusted for age, sex, comorbidity, disease subtype, employment group, and medical plan type. The following primary covariates were used in the regression model: age, sex, Charlson score, CDI score, employment group, PPO participation, HMO participation, and the ICD-9-based subtype indicators for the target condition. To adjust for possible nonlinearities in functional form, 3 interaction terms were used: age*age, age*sex, and CDI-score*sex. For each study sample, separate analyses were conducted for each category of cost (disease-related medical, disease-related drug, all-cause medical, and all-cause drug).

We used a logistic regression model to estimate the relationship between medication adherence and hospitalization risk for each target condition, adjusting for the same covariates as in the cost models described previously. For each condition, we estimated hospitalization risk as a function of adherence level.

Statistical Analysis

Overall fit of the regression models was tested using F-value and adjusted r-square (cost models) and Wald χ^2 (hospitalization models). Differences between adherence levels were evaluated for the 2 primary outcome measures: medical cost and hospitalization risk. The statistical significance of these differences was tested using 2-tailed t tests (medical cost) and χ^2 tests (hospitalization risk). The outcome for the highest adherence level (80–100%) was used as the reference for each pairwise comparison. Correlations among measures were evaluated using Pearson product moment correlation coefficients.

RESULTS

Patient Characteristics

The characteristics of patients in each study sample are shown in Table 1.

Disease-Related Measures

Estimated disease-related outcomes are shown in Table 2 for each target condition and adherence level. These estimates represent relative levels of cost and utilization after adjustment for all covariates.

Disease-Related Costs

For diabetes and hypercholesterolemia, high levels of medication adherence were associated with lower disease-related medical costs. These differences were statistically significant for most adherence levels when compared with the highest level of adherence ($P < 0.05$). For both of these conditions, *total* healthcare costs tended to decrease at high levels of medication adherence, despite the increased drug costs. For diabetes, disease-related healthcare costs decreased monotonically as a function of exposure to diabetes medications (Fig. 1). For hypercholesterolemia, healthcare costs were generally lowest for patients with 80% to 100% adherence, although the results were more variable than for diabetes. Medical costs for hypertension tended to be lowest at 80% to 100% adherence, but the differences were generally not significant. Differences for CHF were not significant.

Hospitalization Risk

For all 4 conditions, patients who maintained 80% to 100% medication adherence were significantly less likely to be hospitalized compared with patients with lower levels of adherence. These differences were statistically significant for most of the adherence levels tested ($P < 0.05$). For diabetes, there was a monotonic decrease in hospitalization risk as adherence to drug treatment increased (Fig. 1).

TABLE 1. Characteristics of Study Samples

Condition	Sample Size (n)	Mean Age (SD)	Percent Female	Mean Comorbidity Scores (SD)		Plan Type		Percent Salaried
				Charlson	CDI	Percent PPO	Percent HMO	
Diabetes	3260	53.9 (9.1)	45.4	4.4 (3.4)	0.6 (0.9)	10.0	11.0	32.3
Hypertension	7981	54.2 (7.7)	46.7	3.4 (2.9)	0.7 (1.0)	9.7	12.0	37.7
Hypercholesterolemia	2981	54.5 (7.5)	44.3	3.2 (2.9)	0.6 (0.9)	9.3	12.9	54.3
CHF	863	55.7 (7.9)	45.3	4.7 (3.1)	1.4 (1.2)	8.7	10.7	17.2

SD indicates standard deviation; CDI, chronic disease index; PPO, preferred provider organization; HMO, health maintenance organization; CHF, congestive heart failure.

TABLE 2. Disease-Related Healthcare Costs and Hospitalization Risk at Varying Levels of Medication Adherence

Condition	Adherence Level	N	Medical Cost ($)	Drug Cost ($)	Total Cost ($)	Hospitalization Risk (%)
Diabetes	1–19	182	8812*	55	8867	30*
	20–39	259	6959*	165	7124	26*
	40–59	419	6237*	285	6522	25*
	60–79	599	5887*	404	6291	20*
	80–100	1801	3808	763	4570	13
			F = 36.62†	**F = 88.57†**		**χ^2 (25 df) = 543.6†**
			Adj. r^2 = 0.18	**Adj. r^2 = 0.36**		
Hypertension	1–19	350	4847	31	4878	28*
	20–39	344	5973*	89	6062	24*
	40–59	562	5113	184	5297	24*
	60–79	921	4977	285	5262	20
	80–100	5804	4383	489	4871	19
			F = 46.44†	**F = 171.98†**		**χ^2 (31 df) = 1256.3†**
			Adj. r^2 = 0.13	**Adj. r^2 = 0.37**		
Hypercholesterolemia	1–19	167	6810*	78	6888	15*
	20–39	216	4786*	213	4999	13
	40–59	324	3452	373	3825	15*
	60–79	520	4938*	603	5541	14*
	80–100	1754	3124	801	3924	12
			F = 18.99†	**F = 320.08†**		**χ^2 (25 df) = 474.7†**
			Adj. r^2 = 0.10	**Adj. r^2 = 0.65**		
CHF	1–19	86	9826	15	9841	58
	20–39	70	7643	90	7733	63*
	40–59	82	11,244	134	11,378	65*
	60–79	107	13,766	158	13,924	64*
	80–100	518	12,261	437	12,698	57
			F = 5.33†	**F = 25.73†**		**χ^2 (24 df) = 169.7†**
			Adj. r^2 = 0.08	**Adj. r^2 = 0.34**		

*Indicates that the outcome is significantly higher than the outcome for the 80–100% adherence group ($P < 0.05$). Differences were tested for medical cost and hospitalization risk.

†$P < 0.0001$.

CHF indicates congestive heart failure.

All-Cause Measures

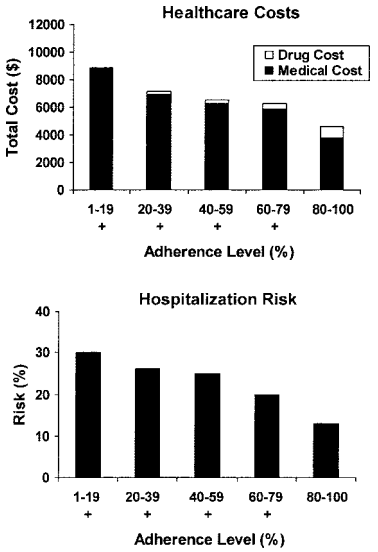
Estimated all-cause outcomes are shown in Table 3 for each target condition and adherence level.

All-Cause Costs

For diabetes, hypertension, and hypercholesterolemia, high levels of adherence with condition-specific drugs were associated with lower medical costs across *all* of the patients' treated conditions. These differences were statistically significant for most adherence levels ($P < 0.05$). For all 3 conditions, *total* healthcare costs tended to decrease at high levels of drug adherence, despite the increased drug costs. For diabetes, all-cause healthcare costs decreased monotonically with exposure to diabetes medications. Similar, although less uniform, patterns were observed for hypertension (Fig. 2) and hypercholesterolemia; healthcare costs were generally lowest for patients with 80% to 100% adherence. Differences for CHF were not significant.

Hospitalization Risk

For all 4 conditions, all-cause hospitalization rates were lowest for patients who had the highest level of medication adherence. These differences were statistically significant for all adherence levels ($P < 0.05$). For diabetes and hypertension, there was a monotonic decrease in hospitalization rates as medication adherence increased (Fig. 2, hypertension).



Estimated diabetes-related healthcare costs and hospitalization risk based on regression analyses. A plus sign (+) under a column denotes a value that is significantly higher than the outcome for the 80-100% adherence group ($P < 0.05$).

FIGURE 1. Diabetes: impact of medication adherence on disease-related healthcare costs and hospitalization risk.

Covariates

Cost and hospitalization risk showed significant positive associations with Charlson score and CDI score in most of the models tested ($P < 0.05$). Many of the disease subtype indicators also contributed significantly to model fit in these analyses. For most conditions, medical costs and hospitalization risk were significantly higher for hourly employees ($P < 0.05$). Age, sex, medical plan type, and the interaction terms generally had no effect on the outcome measures. CDI scores showed significant positive correlations with adherence (r = 0.15, diabetes; 0.28, hypertension; 0.16, hypercholesterolemia; 0.19, CHF; $P < 0.0001$). Correlations between Charlson scores and adherence were generally weak and nonsignificant (r = 0.00–0.07).

DISCUSSION

For diabetes and hypercholesterolemia, high levels of medication adherence are generally associated with a net economic benefit in disease-related costs. Higher drug costs are more than offset by reductions in medical costs, yielding a net reduction in overall healthcare costs. This pattern is observed at all adherence levels for diabetes and at most adherence levels for hypercholesterolemia. These results are consistent with earlier studies that have reported linkages between medication adherence and health outcomes for these conditions.[21,34–37] For hypertension, medical costs tended to be lowest at high levels of medication adherence, but offsets in total healthcare costs were generally not found. The cost impacts of adherence may be less salient for conditions like hypertension, for which a large fraction of the treated population has a relatively low risk of near-term complications.[14] No significant associations between cost and adherence were observed for CHF. Adherence-related differences in hospitalization risk were relatively small for these patients, and cost variability in the CHF study sample was exceptionally high.

To our knowledge, the current study is the first to demonstrate this pattern of cost offsets for diabetes and hypercholesterolemia in a large benefit plan population. Given the chronic nature of these conditions, it is likely that most patients in these study samples had been receiving medication treatment for an extended period before the analysis period began. The observed savings probably reflect the cumulative effects of adherence levels sustained over several years. Adherence rates in this study were typical of the rates often reported for chronic conditions.[15,16,34,38] Observed adherence rates (defined as the proportion of patients with 80–100% adherence) ranged between 55% and 73% for the 4 conditions in this study.

Although a formal cost–benefit analysis is not possible in an observational study of this type, the return on investment (ROI) can be estimated by comparing costs across adherence ranges (quintiles) in the disease-related analyses. For diabetes, the average incremental drug cost for a 20% increase in drug utilization is $177 and the associated disease-related medical cost reduction is $1251, for a net savings of $1074 per patient (an average ROI of 7.1:1). For cardiovascular conditions, the average ROI for a 20% increase in drug utilization is 4.0:1 (hypertension) and 5.1:1 (hypercholesterolemia). The results for diabetes (Fig. 1) suggest that there may be an inverse linear relationship between adherence and cost for some conditions; this should be tested systematically in future research.

Medication adherence is associated with net savings in *all-cause* healthcare costs for diabetes, hypertension, and hypercholesterolemia. For people with diabetes, all-cause medical costs decrease monotonically as adherence with hypoglycemic drugs increases. These savings probably reflect the effects of improved glycemic control on related conditions (such as microvascular disease and neuropathy), reducing the need for medical services.[39–42] Similarly, for the cardiovascular conditions, the cost offsets at high levels of medication adherence probably reflect the impact of cardiovascular medications on related conditions; for example, improved control of hypertension can slow the progression of renal disease.[5]

Adherence-based savings in medical costs appear to be driven primarily by reductions in hospitalization rates at higher levels of medication adherence. For all of the conditions studied here, hospitalization rates were lowest for patients who had high levels of adherence. Hospitalization is the largest component of medical costs in these study samples, so it is likely that the changes in hospitalization risk are the

TABLE 3. All-Cause Healthcare Costs and Hospitalization Risk at Varying Levels of Medication Adherence

Condition	Adherence Level	N	Medical Cost ($)	Drug Cost ($)	Total Cost ($)	Hospitalization Risk (%)
Diabetes	1–19	182	15,186*	1312	16,498	55*
	20–39	259	11,200*	1877	13,077	47*
	40–59	419	11,008*	1970	12,978	42*
	60–79	599	9363*	2121	11,484	39*
	80–100	1801	6377	2510	8886	30
			F = 51.33†	**F = 51.38†**		**χ^2 (25 df) = 695.3†**
			Adj. r^2 = 0.24	**Adj. r^2 = 0.24**		
Hypertension	1–19	350	8831*	916	9747	44*
	20–39	344	10,286*	952	11,238	39*
	40–59	562	8368*	1123	9491	36*
	60–79	921	7658	1271	8929	30*
	80–100	5804	6570	1817	8386	27
			F = 66.51†	**F = 50.94†**		**χ^2 (31 df) = 1573.2†**
			Adj. r^2 = 0.18	**Adj. r^2 = 0.14**		
Hypercholesterolemia	1–19	167	9849*	1067	10,916	26*
	20–39	216	6830*	1152	7982	18*
	40–59	324	5509*	1247	6756	20*
	60–79	520	6676*	1736	8412	21*
	80–100	1754	4780	1972	6752	16
			F = 22.37†	**F = 101.14†**		**χ^2 (25 df) = 500.7†**
			Adj. r^2 = 0.11	**Adj. r^2 = 0.37**		
CHF	1–19	86	22,003	1961	23,964	83*
	20–39	70	17,133	2055	19,188	81*
	40–59	82	24,103	2208	26,311	85*
	60–79	107	26,373	3412	29,785	84*
	80–100	518	19,056	3107	22,164	75
			F = 7.69†	**F = 11.71†**		**χ^2 (24 df) = 108.7†**
			Adj. r^2 = 0.12	**Adj. r^2 = 0.18**		

*Indicates that the outcome is significantly higher than the outcome for the 80–100% adherence group ($P < 0.05$). Differences were tested for medical cost and hospitalization risk.

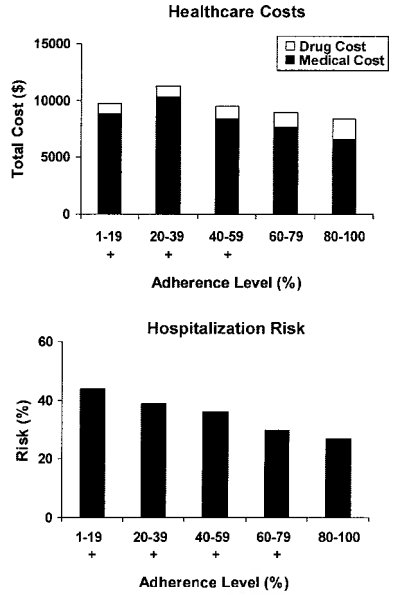
†$P < 0.0001$.

CHF indicates congestive heart failure.

primary driver of the cost savings observed at higher levels of adherence. This is consistent with results reported elsewhere on the impact of pharmacotherapy on hospitalization rates.[8,12,43,44]

This study was observational, so it is not possible to draw definite conclusions about the causal relationships among adherence, utilization, and cost. The cross-sectional nature of the design also poses some interpretive problems, because it yields some heterogeneity in the groups under study; for example, the "low-adherence" groups may include some patients who received short-term therapy or who started drug therapy late in the analysis period. However, given the chronic nature of the conditions under study, it is likely that most patients were continuing medication users (ie, it is likely that their treatment had started before the analysis period began). In cohort-based samples of patients with chronic conditions, most patients are prevalent (not incident) cases. The study can provide a good indication of the typical benefits of medication adherence in continuing patients with chronic disease. The study was not designed to track the time course of treatment of newly diagnosed patients, so it cannot define how quickly after the start of therapy the benefits of adherence begin to accrue.

The inclusion criteria for the study samples may limit the generalizability of the findings reported here. To reduce the risk of false-positives, at least 2 disease-specific claims were required when patients were identified based on outpatient claims. A single outpatient claim could indicate an office visit for evaluation; 2 claims are more likely to indicate a positive diagnosis. However, this selection methodology may



Estimated all-cause healthcare costs and hospitalization risk based on regression analyses. A plus sign (+) under a column denotes a value that is significantly higher than the outcome for the 80-100% adherence group ($P < 0.05$).

FIGURE 2. Hypertension: impact of medication adherence on all-cause healthcare costs and hospitalization risk.

produce a study sample that is weighted toward patients with more advanced disease or higher comorbidity, because it may exclude some patients who visit their doctors infrequently. A selection effect of this kind is suggested by the relatively high hospitalization rates for patients in these study samples; for example, the average all-cause hospitalization risk for the diabetes sample (35.9%) is higher than the rate reported in a study of primary care patients (21.1%).[45] The results of the current study are indicative of the adherence-related effects that may be expected for higher-cost patients with more advanced disease. Cost offsets may not be as prominent for healthier adults. Further research would be required to determine the applicability of the reported findings to other populations.

Each study sample included some patients who had more than 1 of the diseases under study. Including these patients makes the samples more representative, because combinations of these conditions (eg, diabetes and hypertension) are common. Excluding these patients would limit the external validity of the results. However, a consequence of including these patients is that the 4 study samples are not strictly independent. The samples provide 4 intersecting (but not fully independent) views of healthcare utilization in this benefit plan population.

There are some inherent risks to the use of medical claims data when measuring utilization and cost. In some cases, ICD-9 codes on medical claims may not accurately or completely reflect the patient's diagnosis. In the current study, medical chart data were not available to validate the coding on the medical claims.

The regression models used multiple covariates to control for the effects of comorbidity on utilization and cost. In most of the models, comorbidity was a significant predictor of utilization and cost. It is possible that unmeasured aspects of comorbidity risk could have biased the reported associations between adherence and cost. For example, if low-adherence patients tend to be sicker, then the costs at low adherence levels would be inflated if comorbidity is not adequately controlled. However, in this study population, there was a *positive* correlation between adherence and comorbidity (as measured by CDI scores)—the sicker patients tended to be more adherent. In this case, if comorbidity is not adequately controlled, it is more likely that the costs at *high* adherence levels will be overestimated. To the degree there is unmeasured comorbidity risk in this study, the models are likely to underestimate the cost reductions associated with high adherence.

CONCLUSION

Although the therapeutic benefits of pharmacotherapy are well understood, the potential economic returns are often missed in the public debate over rising prescription drug costs. Increased drug utilization can provide a net economic return when it is driven by improved adherence with guidelines-based therapy. Our results demonstrate that a net return may be obtained for 3 chronic conditions that account for a large share of long-term medication use—diabetes, hypertension, and hypercholesterolemia. Although drug costs are a relatively small fraction of total healthcare costs for these conditions, they have high leverage—a small increase in drug costs (associated with improved adherence) can produce a much larger reduction in medical costs. As more of these medications become available in generic form, their leverage will become even stronger; it will be possible to achieve the same therapeutic value and medical cost offset at a significantly lower drug cost. Because these benefits derive from improved adherence, greater attention should be devoted to educating patients on the value of their drug therapy and motivating behavior changes that improve adherence.

ACKNOWLEDGMENTS

The authors thank Boris Fainstein, Joan Haynes, and Rich Mountjoy for their assistance with the design and conduct of the study; Qingshan Qian and Jianying Yao for their assistance with the data analysis; and Lon Castle and Les Paul for their assistance with revision of the manuscript.

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APPENDIX Diagnostic Indicators and Drug Classes Used for Patient Identification and Claims Analysis

Condition	Patient Identification*	Disease Subtype Indicators*	Analysis of Medical Cost/Utilization*	Drug Classes
Diabetes	250.xx, 357.2, 362.0x, 366.41, 648.0	250.1–250.9	250.xx, 357.2, 362.0x, 366.41, 648.0	Insulins Oral hypoglycemics
Hypertension	401.xx–405.xx	401.x–405.x	401.xx–405.xx, 272.x, 410.xx–417.xx, 425.x, 428.xx, 429.0–429.3, 433.xx–438.xx, 440.x, 444.xx	Angiotensin-converting enzyme (ACE) inhibitors Angiotensin II receptor blockers Alpha blockers, beta blockers Calcium channel blockers Vasodilators Sympatholytic hypotensives Diuretics
Hypercholesterolemia	272.x	272.1–272.9	272.x, 401.xx–405.xx, 410.xx–417.xx, 425.x, 428.xx, 429.0–429.3, 433.xx–438.xx, 440.x, 444.xx	HMG CoA reductase inhibitors (statins) Fibrates Niacin preparations Bile salt sequestrants
CHF	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx	402.x, 404.x, 428.0, 428.1, 428.9	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx	ACE inhibitors Diuretics Digitalis glycosides Carvedilol

*ICD-9 codes (International Classification of Diseases—9th Revision).[30]
Where indicated, "x" takes any valid value.

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H-16001 "Other studies (The New England Journal of Medicine) reported that less severe reactions—which can go unnoticed or be discounted as effects of aging, have indirectly resulted in numerous injuries. One study estimated that each year, 32,000 elderly persons suffer hip fractures in falls caused by adverse drug reactions, such as the loss of coordination. Another study concluded that 16,000 car accidents that result in injuries each year can be attributed to adverse drug reactions that elderly drivers experience"

Sarah F. Jaggar, Director United States General Accounting Office testimony before the Senate Special Committee on Aging, March 1996

H16002 "Patients forget to take their medications, creatively alter their medications, engage in unendorsed polypharmacy, mix their medications and take medications in combinations that may have dire synergistic interaction effects, such as dizziness and confusion. "

H16003 "For the elderly patient, medication issues and or abuses may also result in accidents, such as a fall that causes a hip fracture. Furthermore, an elderly patient could forget that he or she had already taken the prescribed amount of medication and unwittingly overdose.

Harold Gottlieb, PhD. Drug Benefit Trends 12(6):57-62, 2000. "Medication Nonadherence: Finding Solutions to a Costly Medical Problem"

H16004 "Adverse drug reactions in the elderly, such as drowsiness, loss of coordination, and confusion, may result in serious injury secondary to falls or automobile accidents. Less economically catastrophic adverse drug reactions,

such as loss of functional ability and memory impairment, create equally debillating outcomes."

H16005 "One researcher found that 25% of the elderly patients discharged from a hospital had six or more prescriptions."

From the Office of Inspector General report OIG Medication Regimens: Causes of Noncompliance OEI-04-89-89121

H16006 "The average older person used 4.5 prescription medications and 2 over-the-counter medications on a daily basis. As the number of medications consumed increases, so to does the risk of medication-related problems.

H16007 "Thus, this combination of naturally occurring physiological changes, multiple disease states, receipt of multiple medications, other factors and the prescription of potentially inappropriate medication use puts the elderly at high risk for the development of medication related problems."

Medscape Pharmacists, 2001 "Promotion of a Safe Medication Environment: Focus on the Elderly and Residents of Long-term Care Facilities.

H16008 "Up to 23% of nursing home admissions may be due to elderly patient's inability to self-administer medications. "

From the Office of Inspector General report OIG Medication Regimens: Causes of Noncompliance OEI-04-89-89121

H16009 "Adverse drug reactions in the elderly, such as drowsiness, loss of coordination, and confusion may result in serious injury secondary to falls or automobile accidents. Less economically catastrophic adverse drug reactions, such as loss of functional ability and memory impairment, create equally debilitating outcomes"

"Promotion of a Safe Medication Environment: Focus on the Elderly and Residents of Long-Term Care Facilities. Thomas P. Lombardi, BS, PharmD, FASHP and Jeffery D.

H16010 "In New York state, skilled nursing facilities currently charge over #188 per day on average or $69,000 per year or more. In the New York City Metropolitan Area, which includes the 5 boroughs of New York City, Long Island and Westchester County, the average skilled nursing facility charge is about $222 per day or $81,000 per year. It is estimated that persons in nursing homes stay for 2-1/2 years on average."

H16011 "Home health care is also expensive. In New York, three home health care visits per week by a registered nurse can cost over $12,950 per year. Even custodial home care visits at three per week can cost of $8,960 per year."

H16012 "Nursing home costs have risen 20% in the last three years to a national average of $46,000."

From "Long Term Commentary" http://www.efmoody.com/longterm/commentary.html

H16013 “Drug holidays (from blood pressure medications) are far more common than not. It’s in these patients that we can intervene, Dr. Rudd Said. .....They seem to understand the importance of taking their medications, but sometimes they just don’t.”

American Society of Hypertension
Dr. Peter Rudd, M.D.
Professor of Medicine-Stanford University School of Medicine
Medical Tribune, Internist and Cardiologist Edition 38(12): 1997

H16014: Whereas, Many patients, especially the elderly, are on chronic, multi-drug regimens: and Whereas, Prescription medication nonadherence, often due to lack of patient recollection of vital information. Is a serious problem especially among the elderly and those on multiple drug therapy, and can lead to serious medical complications and significantly poorer clinical outcomes: and.....

The American Medical Association House of Delegates: Resolution 501 1-97

New Technology for Medication Adherence

Electronically Managed Medication Dispensing System

Increasing medication compliance can improve quality of life for older adults.

Kathleen Coen Buckwalter, PhD, RN, FAAN, Bonnie J. Wakefield, PhD, RN, Barbara Hanna, RN, PHN, BSN, CCM, and Julie Lehmann, RN, PHN, BSN

Lack of compliance with prescribed medication regimens is a well-known and well-documented problem among elderly individuals, especially those who live alone or who have some degree of cognitive or functional impairment. Noncompliance results in decreased quality of life, increased health-care costs related to acute and long-term care admissions, and the need to enhance home care support. Hayes, Montague, McKibbin, Brouwers, and Kamani (2001) note only 50% of older adults adhere to medication treatment, with a variety of reasons attributed to non-adherence including poor instructions, disagreement with the treatment prescribed, inability to pay, and adverse effects.

Pillboxes and blister packaging have been set forth as a means to help organize medications with some success in increasing rates of compliance (Ware, Holford, Davison, & Harris, 1991; Wong & Norman, 1987). However, these approaches require a level of manual dexterity that may be lacking in older adults. There is also growing evidence that community-dwelling older adults can increase their compliance with prescribed medications as a result of targeted interventions (e.g., phone calls, electronic devices) encouraging them to take their medication as prescribed (Fulmer et. al., 1999). However, insufficient numbers of rigorous studies examining these compliance aids have been conducted to date.

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THE MD.2 AUTOMATED MEDICATION DISPENSING SYSTEM

An innovative new technology, called the MD.2 Automated Medication Dispensing System (Interactive Medical Developments [IMD], Webster City, IA), recently has been developed to address some of the issues for medication noncompliance. The MD.2 was developed by Dr. Anil Sahai because many of his patients were able to handle most activities of daily living, but were prematurely admitted to acute or long-term care facilities because they were unable to properly manage their medications.

The MD.2 medication-dispensing technology allows caregivers to organize medications into easily opened plastic cups. Each cup holds one or more medications and represents one dispensing period (e.g., morning medications).

Caregivers use a simple and straightforward process to help with installation. User data are collected and include patient's name, address, and phone number; unit serial number; caregiver names and the order in which to call them; medication dispensing times by day of the week; and the standard message, if any, to announce to the user. This information can be entered via the Internet or by faxing or calling the IMD Support Center where it is entered into a database.

At the time of installation, the caregiver or medical professional has the MD.2 unit call the support center and the information is downloaded. Based on this information, the unit verbally prompts the caregiver through the loading of the cups. After loading, the unit is kept locked so the patient does not have access to the medications. Depending on the frequency of doses, the system can dispense medications for a 10- to 30-day period

(the unit holds 60 cups).

Using a series of verbal and auditory reminders (e.g., a flashing light, voice reminders, and a loud beeping noise for a 60- to 90-minute period), the MD.2 will alert patients that it is time for the medication, allowing them to press an easy-to-use button to dispense the pre-filled medication cup. The MD.2 also will remind patients to take the medication with food, check their blood sugar, or announce other pre-programmed messages.

If patients do not dispense the medication after 90 minutes, the MD.2 will lock away the cup so they cannot overdose or double dose. The MD.2 will then begin calling caregivers. Based on the input notification order, the unit will call up to four caregivers or medical professionals to alert them of the non-dispense. It will verbally announce it is the MD.2 and give the user's name, phone number, and the fact that the medication was not dispensed. The caregiver must respond by entering a "1" on their phone or the MD.2 will hang up and call the next caregiver. If none of the caregivers respond by entering a "1," the unit will call the IMD Support Center and they will continue trying to alert the caregivers.

All dispensing history and alarm notices are up-loaded at the end of the day to the Web-enabled support center so that caregivers or other medical professionals can review the dispensing data to monitor patients' status. All user history is stored, and the previous 35 days are available for viewing via secure Internet connection by caregivers and medical professionals. User confidentiality is maintained via the unit serial number and the user's telephone number, which serve as identification numbers for security purposes.

The technology is especially useful with older patients, individuals with brain injuries, or other outpatients who have difficulty managing their medications. Current medication management tools consist of devices such as: weekly pillboxes, which only organize medications; reminder devices such as beeping medication caps or wristwatches, which remind but don't organize; and electronic dispensers, which organize, remind, and safeguard. However, none of these methods have the full functionality of the MD.2 to organize, remind, dispense, monitor, safeguard, and report on medication management. The MD.2 is designed to bridge the gap when simpler reminders do not work and proper medication adherence is critical to avoid a more costly level of care.

Price of the MD.2 varies by distributor. However, average monthly rental costs approximately $90 per month.

EVALUATION OF THE MD.2

Two preliminary studies have been conducted with the MD.2, the first under the auspices of the Johnson County (Iowa) Visiting Nurses Association (VNA) and the second by the California Health Professionals Plus/Home Health Care Management company (CHP Plus).

Visiting Nurses Association Pilot Study

Study Description. In August 2000, the Johnson County VNA installed MD.2 machines in the homes of 12 patients with known or suspected problems with medication non-compliance. Patients were referred to the project either by a nurse or physician. Six patients had a primary medical diagnosis, five of whom also had a secondary psychiatric diagnosis; the remaining six patients had a primary psychiatric diagnosis. Nine patients were women, and three were men. Patient age ranged from 33 to 86.

Medication dosing frequency was twice daily for six patients and three times daily for six patients. The number of medications per patient ranged from 4 to 16, with an average of 8 medications per patient per day.

Outcomes evaluated included the frequency of home health aide visits, dispensing rate statistics, and incidents of request for technical support assistance from the IMD Support Center. Data for the latter two outcomes were collected from reports of the IMD Support Center.

To assess the frequency and content of nursing care and home health aide visits, patient records were reviewed for 3 months prior to and 12 months after installation of the MD.2 or discharge from home care, whichever came first. The number, route, and frequency of prescribed medications also were obtained from the record.

The visiting nurses were given a 2-hour training session by IMD employees. The nurses then installed, maintained, and loaded the units. Patient training was minimal because they only have to push the large red button, when prompted, and then take the medication. During the course of the pilot study, MD2 units remained in the home an average of 5.1 months (range, 2 months to longer than 7 months).

Study Findings. It took an average of 2 to 4 weeks for patients to become comfortable with the MD.2 routine, voice/instructions, and presence in the home. As with any new technology, some of the VNA nurses were more open to using it than others.

For the first outcome, the frequency of home health aide visits, the number of patient home visits did not decrease because other medical problems required attention. However, the nurses' notes reflected home visit time was spent on other issues in the nursing care plan rather than medication compliance.

For the second outcome, dispensing rate statistics, the frequency of missed doses was higher immediately after the MD.2 was placed and

then decreased steadily the longer the patient used the MD.2. An overall dispensing rate of 98.26% was determined: of 3,737 doses monitored, there were 65 "missed doses" where the patient did not access their medications within the 60- to 90-minute window allotted by the MD.2.

The third outcome was incidents of request for technical support assistance from the IMD Support Center. For the 3,737 doses, there were 10 requests for technical support. Seven requests related to maintenance and schedule issues, and three requests were for assistance in removing a "double cup" loaded improperly (i.e., two medication cups nested together with one cap).

Home Health Care Management Study

Study Description. Through a grant from the State of California, Department of Aging Long Term Care Innovative Grant Program, Home Health Care Management tested the MD.2 by comparing it to patients who used medi-sets (plastic medication boxes). The first 6 months of the program compared 89 community-dwelling older or disabled adults who used the MD.2 with 45 older or disabled adults who used the medi-sets. Patients were assigned to either the MD2 or Medi-Set group based on criteria that assessed cognitive and physical functioning.

Study Results. After 6 months of program data, the outcomes favored the MD.2 in terms of reduced hospitalization rates and emergency room visits and fewer number of medications being taken (Table 1). Home Health Care Management staff believed some of the greatest successes of the MD.2 were with individuals receiving warfarin therapy, those with mental health issues, and those with early to mid-stage Alzheimer's disease. The MD.2 was also very effective for patients in independent living facilities.

TABLE 1

COMPARISON OF MD.2 AND MEDI-SET FOR HOME HEALTH CARE MANAGEMENT PATIENTS*

	MD.2	*Medi-Set*
Hospitalizations per patient	.09	.42
Emergency department visits per patient	.18	.42
Prescriptions per patient	7.62	8.65

**After 6 months of program data*

In addition, the MD.2 group reduced the total number of prescriptions being taken to 7.62 compared with 8.65 in the group using the medi-sets. One possible reason for this difference could be the regular and accurate implementation of the prescribed medication regimen that resulted in the stabilization of patients' condition. This stabilization could have then resulted in a decreased demand for compensatory medications. Regular and accurate medication implementation was demonstrated by the fact that those using the MD.2 missed fewer medications than those using the medi-sets (Table 2).

Anecdotal Data and Future Research

Anecdotal data also have been gathered from participants nationally who have used the MD.2. Success has been reported among adults with a variety of chronic diseases, including those with mid-stage Alzheimer's disease who live independently, brain-damaged individuals, individuals with bipolar disease and other psychiatric disorders, insulin-dependent diabetes, congestive heart failure, and acquired immunodeficiency syndrome. In some cases, individuals who were previously confined to a group home setting were able to live independently.

Future research is planned to establish the effectiveness of the MD.2 on outcomes with potential cost benefit to Medicaid and all other payor sources. Planned research for the future will address the following issues:

- Developing a profile of individuals most likely to benefit from use of the MD.2.
- Costs associated with the

TABLE 2

COMPARISON OF MISSED MEDICATION DOSES FOR HOME HEALTH CARE MANAGEMENT PATIENTS USING MD.2 AND MEDI-SETS

	MD.2	*Medi-Set*
Missed doses per patient per 2-month evaluation period	.62	3.39
Total missed doses per patient during 6-month period	2.9	7.31

device including training and installation.

- Estimates of cost effectiveness as opposed to other forms of care (i.e., visiting nurses, assisted living).
- Determining the impact of the MD.2 on the number of hospitalizations and emergency room visits.

Other studies will compare the length of time in home care and measure changes in caregivers' stressors, endurance potential, burden, and well-being between those using the MD.2 and those with their usual medication routine. Cognitive and functional characteristics, and how they influence compliance rates among frail older adults also will be examined.

ENHANCEMENTS TO THE MD.2

The original product has been enhanced. The MD.2+ offers the original functionality of the MD.2 with a built in Personal Response System. The Personal Response System allows patients to wear a small, lightweight, waterproof pendant or bracelet that can be pressed in the event of a fall or other medical emergency. The MD.2+ will then dial out to a 24-hour emergency call center and, through a two-way speaker, the nature of the emergency will be determined and appropriate help will be dispatched. The most recent development is an MD.2 that announces all of its messages in Spanish.

CONCLUSION

Medication management encompasses a set of psychomotor and cognitive activities that are required to take medications as prescribed. Noncompliance with medications increases health-care spending and the need for home care support, and can lead to avoidable hospitalizations and placement in long-term care facilities. Many community-dwelling frail older adults have both cognitive and functional deficits that make it difficult for them to properly manage their medications.. The MD.2 shows great promise in alleviating many of these problems and enhancing compliance through an innovative system of reminders and caregiver support.

More information can be obtained by accessing IMD's Website at www.imd2.com, by sending an e-mail to ddrew@imd2.com, or by calling 1-877-563-2632.

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Enhancing Prescription Medicine Adherence:
A National Action Plan

National Council on Patient Information and Education

August 2007

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Printed in the United States of America.

Preface

In the United States and around the world, there is compelling evidence that patients are not taking their medicines as prescribed, resulting in significant consequences. Lack of medication adherence is *America's other drug problem* and leads to unnecessary disease progression, disease complications, reduced functional abilities, a lower quality of life, and even death.

Contributing to *America's other drug problem* are numerous behavioral, social, economic, medical, and policy-related factors that must be addressed if medication adherence rates are to improve. This includes lack of awareness among clinicians about basic adherence management principles, poor communication between patients and clinicians, operational aspects of pharmacy and medical practice, and professional barriers. Moreover, adherence improvement is affected by federal policies that provide insufficient funding for adherence-related research and federal and state laws and regulations that impact the availability of compliance assistance programs. All of these problems contribute to a rising tide of poor medication adherence and all must be addressed.

The ramifications of poor prescription medicine adherence affect virtually every aspect of the health care system. Addressing this persistent and pervasive problem cannot wait. Today, extensive research data exist that point to actions that can be taken now to improve adherence education and medication management. Accordingly, the National Council on Patient Information and Education (NCPIE) -- a non-profit coalition of more than 100 organizations that are working to stimulate and improve communication on the appropriate use of medicines -- convened a group of advisors from leading professional societies, voluntary health organizations, and patient advocacy groups to assess the extent and nature of poor medicine adherence, its health and economic costs, and its underlying factors. These advisors also examined the current state of research funding and educational initiatives around patient adherence to determine where major gaps still exist.

What follows is the result of this review, which focuses specifically on identifying those action steps that can significantly impact medication adherence and can be readily implemented. As such, this report serves as a **blueprint for action** by all stakeholders. To achieve the awareness, behavior changes, and additional resources for research and education that will improve patient medication adherence requires an ongoing partnership through which policymakers, regulators, the public health community, clinicians, the pharmaceutical industry, and patient advocates can share research, resources, and good ideas, while working toward a common goal. It is intended that this report will be a catalyst for this necessary and important collaborative effort.

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Executive Summary

At the same time that medical science has made possible new therapies for treating AIDS, cancer, and other once fatal diseases, poor adherence with medication regimens has reached crisis proportions in the United States and around the world.

On a worldwide basis, the World Health Organization (WHO) projects that only about 50 percent of patients typically take their medicines as prescribed. In the U.S., non-adherence affects Americans of all ages, both genders and is just as likely to involve higher-income, well-educated people as those at lower socioeconomic levels. Furthermore, since lack of medication adherence leads to unnecessary disease progression, disease complications, reduced functional abilities, a lower quality of life, and even premature death, poor adherence has been estimated to cost approximately $177 billion annually in total direct and indirect health care costs.

Although the challenge of poor medication adherence has been discussed and debated for at least three decades, these problems have generally been overlooked as a serious public health issue and, as a result, have received little direct, systematic, or sustained intervention. As a consequence, Americans have inadequate knowledge about the significance of medication adherence as a critical element of their improved health. Further, adherence rates suffer from the fragmented approach by which hospitals, health care providers, and other parts of the health delivery system intervene with patients and caregivers to encourage adherence. Consequently, many leading medical societies are now advocating a multidisciplinary approach through coordinated action by health professionals, researchers, health planners and policymakers.

Over a decade ago, the National Council on Patient Information and Education (NCPIE) recognized the need for such a coordinated approach to improved medication adherence and issued a report -- *Prescription Medicine Compliance: A Review of the Baseline Knowledge* -- which defined the key factors contributing to poor adherence. Since that time, the National Institutes of Health (NIH) and a number of voluntary health organizations in the U.S. have weighed in with new findings on the importance of adherence for successful treatment. Further elevating the need for action is the WHO, which has called for an initiative to improve worldwide rates of adherence to therapies commonly used in treating chronic conditions, including asthma, diabetes, and hypertension.

Unfortunately, however, these calls for action have yet to be heeded and rates of medicine adherence have not improved. Thus, action is needed now to reduce the adverse health and economic consequences associated with this pervasive problem. While no single strategy will guarantee that patients will fill their prescriptions and take their medicines as prescribed, elevating adherence as a priority issue and promoting best practices, behaviors, and technologies may significantly improve medication adherence in the U.S.

Towards this end, NCPIE convened a panel of experts to create consensus on ten national priorities that may have the greatest impact on improving the state of patient adherence in the U.S. These recommendations serve as a catalyst for action across the continuum of care -- from diagnosis through treatment and follow-up patient care and monitoring. Ultimately involving the support and active participation of many stakeholders -- the federal government, state and local government agencies, professional societies and health care practitioners, health educators, and patient advocates -- this platform calls for action in the following areas:

1. **Elevate patient adherence as a critical health care issue.**
   Medication non-adherence is a problem that applies to all chronic disease states;

affects all demographic and socio-economic strata; diminishes the ability to treat diabetes, heart disease, cancer, asthma, and many other diseases; and results in suffering, sub-optimal utilization of health care resources, and even death. Despite this impact, patient adherence is not on the radar screen of policy makers and many health professionals, which has meant inconsistent government policies and a lack of resources for research, education, and professional development. Until health care policy makers, practitioners and other stakeholders recognize the extent of non-adherence, its cost, and its contribution to negative health outcomes, this problem will not be solved.

2. **Agree on a common adherence terminology that will unite all stakeholders.**
Today, a number of common terms -- compliance, adherence, persistence, and concordance -- are used to define the act of seeking medical attention, filling prescriptions and taking medicines appropriately. Because these terms reflect different views about the relationship between the patient and the health care provider, confusion about the language used to describe a patient's medication-taking behavior impedes an informed discussion about compliance issues. Therefore, the public health community should endeavor to reach agreement on standard terminology that will unite stakeholders around the common goal of improving the self-administration of treatments to promote better health outcomes.

3. **Create a public/private partnership to mount a unified national education campaign to make patient adherence a national health priority.**
To motivate patients and practitioners to take steps to improve medication adherence, compelling, actionable messages must be communicated as part of a unified and sustained public education campaign. A foremost priority is creating the means by which government agencies, professional societies, non-profit consumer groups, and other affected stakeholders can work together to reach public and professional audiences on a sustained basis. Even as NCPIE and various government agencies, professional societies, and voluntary health organizations work to provide information about medication adherence, there needs to be a national clearinghouse, serving as the catalyst and convener so that all stakeholders can speak with one voice about the need for improving patient adherence. NCPIE, a professional society, or academic institution could manage this clearinghouse effectively.

4. **Establish a multidisciplinary approach to adherence education and management.**
There is a growing recognition that a multidisciplinary approach to medication taking behavior is necessary for patient adherence to be sustained. This has led NCPIE to promote a new model -- the "Medicine Education Team" -- in which the patient and all members of the health care team work together to treat the patient's condition, while recognizing the patient's key role at the center of the process. Looking to the future, this approach has potential to improve adherence rates significantly by changing the interaction between patients and clinicians and by engaging all parties throughout the continuum of care.

5. **Immediately implement professional training and increase the funding for professional education on patient medication adherence.**
Today's practitioners need hands-on information about adherence management to use in real-world settings. This need comes at a time when a solid base of research already exists about the steps physicians and other prescribers, pharmacists, nurses, and other health care practitioners can take to help patients improve their medication taking behavior.

Professional societies and recognized medical sub-specialty organizations should immediately apply these research findings into professional education through continuing education courses as well as lecture series on patient adherence issues.

6. **Address the barriers to patient adherence for patients with low health literacy.**
Low health literacy and limited English proficiency are major barriers to adherence and deserve special consideration. Thus, an important target for patient-tailored interventions is the 90 million Americans who have difficulty reading, understanding and acting upon health information. Accordingly, advocates recommend widespread adoption of existing tools, such as the Rapid Estimate of Adult Literacy in Medicine Revised (REALM-R), validated pictograms designed to convey medicine instructions and specific patient education programs that promote and validate effective oral communication between health care providers and patients supported by provision of adjunctive, useful information in its most useful format to address the patient's individual capabilities.

7. **Create the means to share information about best practices in adherence education and management.**
Today, stakeholders have access to more than 30 years of research measuring the outcomes and value of adherence interventions. Building on this foundation, a critical next step is for the federal government -- through the Adherence Research Network -- to begin collecting data on best practices in the assessment of patient readiness, medication management and adherence interventions, incentives that produce quality outcomes from adherence interventions, and measurement tools so that this information can be quantified and shared across specialties and health care facilities. Just as federal and state registries collect and share necessary data on different disease states, a shared knowledge base regarding systems change, new technologies, and model programs for evaluating and educating patients about adherence will significantly improve the standard of adherence education and management.

8. **Develop a curriculum on medication adherence for use in medical schools and allied health care institutions.**
Lack of awareness among clinicians about basic adherence management principles and their effective application remains a major reason that adherence has not advanced in this country. Changing this situation will require institutionalizing curricula at medical, nursing, pharmacy, and dental schools as well as courses for faculty members that focus on adherence advancement and execution of medication-related problem solving. Moreover, once these courses are developed, it will be important for academic centers to elevate patient adherence as a core competency by mandating that course work in this area be a requirement for graduation.

9. **Seek regulatory changes to remove road-blocks for adherence assistance programs.**
Improved adherence to medication regimens is predicated in part on supportive government policies. Unfortunately, a number of federal and state laws and policies now limit the availability of adherence assistance programs. Accordingly, limitations to patient communication about medicine adherence in federal and state laws must be identified for lawmakers and regulators to resolve. Key issues to be addressed include clarifying that education and refill reminder communications fall within the scope of the federal anti-kickback statute, and ensuring that federal and state laws related to patient privacy and the use of prescription data are in balance such that they do not unduly limit the ability of pharmacies to communicate with patients about the

importance of adhering to their prescribed therapy.

10. **Increase the federal budget and stimulate rigorous research on medication adherence.**
Although the National Institutes of Health created the Adherence Research Network to identify research opportunities at its 18 Institutes and Centers, the Network has been inactive since 2002. Moreover, in 2000, when the Network was funding adherence research, the actual NIH dollars earmarked for testing interventions to improve medication-taking behavior was only $3 million in a budget of nearly $18 billion. Thus, it will be important for stakeholders to advocate for the Adherence Research Network to be re-invigorated and for NIH to significantly increase the proportion of its research funding to test adherence interventions and measure their effectiveness. Even if NIH triples its 2000 commitment, the small amount spent on patient adherence will still signal that the issue is a critical area for new research efforts.

*****

Everyone in the health care system – from patients and caregivers to health care providers, patient advocates and payors – has a significant role to play in improving prescription medicine adherence. Thus, an agenda that removes the barriers and advances education and information sharing is a critical step to improving the health status of all Americans. Clearly, the time for action is now.

Introduction

There is much to celebrate about the improved health status of many Americans. Smoking rates have dropped significantly, infant mortality has declined and there have been major advancements in treatments for serious diseases that once devastated the lives of millions. This includes more than 300 new drugs, biologics and vaccines approved by the U.S. Food and Drug Administration (FDA) since 1993 to prevent and treat over 150 medical conditions.[1]

While we recognize such progress, now is the time to be even more mindful of the public health problems we have yet to solve. One of these persistent challenges is improving patient "compliance" (or "adherence") – defined as the extent to which patients take medications as prescribed by their health care providers.[2] At the same time that medical science has made possible new therapies for treating AIDS, cancer, and other once fatal diseases, poor adherence with medication regimens has reached crisis proportions in the United States and around the world. According to the World Health Organization (WHO), only about 50 percent of patients typically take their medicines as prescribed.[3] For this reason, WHO calls poor adherence rates "a worldwide problem of striking magnitude"[3] and has published an evidence-based guide for health care providers, health care managers, and policymakers to improve strategies of medication adherence.[2]

Looking specifically at lack of medication adherence in the U.S., a recent survey reported that nearly three out of every four American consumers report not always taking their prescription medicine as directed.[4] Commissioned by the National Community Pharmacists Association (NCPA), this survey also found a major disconnect between consumers' beliefs and their behaviors when it comes to taking medicines correctly. Some of the findings of the survey include:

+ Almost half of those polled (49 percent) said they had forgotten to take a prescribed medicine;
+ Nearly one-third (31 percent) had not filled a prescription they were given;
+ Nearly three out of 10 (29 percent) had stopped taking a medicine before the supply ran out; and
+ Almost one-quarter (24 percent) had taken less than the recommended dosage.

While disturbing, these statistics only begin to demonstrate the magnitude and scope of poor adherence in the U.S. Lack of adherence affects Americans of all ages and both genders, but is of particular concern among those aged 65 and over who, because they have more long-term, chronic illnesses, now buy 30 percent of all prescription medicines[5] and often combine multiple medications over the course of a day. Regardless of age and sex, poor medication adherence is also just as likely to involve higher-income, well-educated people as those at lower socioeconomic levels.[2] As a result, poor medication adherence has been estimated to cost approximately $177 billion annually in total direct and indirect health care costs.[6]

Adherence rates are typically higher in patients with acute conditions, as compared to those with chronic conditions, with adherence dropping most dramatically after the first six months of therapy.[2] The problem is especially grave for such patients with chronic conditions requiring long-term or lifelong therapy, because poor medication adherence leads to unnecessary disease progression, disease complications, reduced functional abilities, a lower quality of life, and premature death.[3] Lack of adherence also increases the risk of developing a resistance to needed therapies (e.g., with antibiotic therapy), more intense relapses, and withdrawal (e.g., with thyroid hormone replacement therapy)

and rebound effects (e.g., with hypertension and depression therapy) when medication is interrupted.[3] Because of this impact, adherence has been called "the key mediator between medical practice and patient outcomes."[7]

A TIME FOR ACTION

Although the challenge of poor medication adherence has been discussed and debated for at least three decades, these problems have generally been overlooked as a major health care priority. Compounding the situation, adherence problems have been exacerbated by the fragmented approach by which hospitals, health care providers, and other parts of the health delivery system intervene with patients and caregivers to encourage adherence. Consequently, many leading medical societies are now advocating a multidisciplinary approach through coordinated action by health professionals, researchers, health planners and policymakers.

Over a decade ago, the National Council on Patient Information and Education (NCPIE) recognized the need for such a coordinated approach to improved medication adherence and issued a report -- *Prescription Medicine Compliance: A Review of the Baseline Knowledge*[8] -- which defined the key factors contributing to poor adherence. The report further outlined strategies that could be implemented by health care professionals, patients and caregivers and health care systems, including these key strategies recommended for health care providers:

+ Using a verbal discussion reinforced with appropriately designed written materials to help the patient understand the medical condition, the need for the treatment, and the value of the treatment;
+ Offering verbal counseling from both the prescribing health care provider and the pharmacist that the prescription should be filled and taken as prescribed. While written instruction sheets can reinforce these instructions, they should never be used as a substitute for counseling;
+ Providing useful written information in "patient language" that clearly explains how the patient can correctly manage his/her medications. This information includes details on how to administer the medication, the exact time the medicine should be taken and why, how long to take the medicine, recognition and management steps for common side effects, special precautions, and how to monitor the progress of the therapy;
+ Making patients aware of the various medication adherence aids and devices available, such as dosing reminders, pill boxes and refill reminder programs;
+ Monitoring patient adherence with every visit to the prescribing health care provider or pharmacist; and
+ Instructing patients and caregivers on home monitoring activities (such as home blood pressure monitoring) and home monitoring records that should be maintained for use during future medical and pharmacy visits.

Since the NCPIE report was published, the National Institutes of Health (NIH) and a number of voluntary health organizations focusing on the major chronic diseases affecting Americans today -- asthma, cancer, cardiovascular disease, diabetes and mental illness -- have weighed in with new findings on the importance of adherence for successful treatment. The consensus of these groups is that interventions that improve patient adherence improve health status and reduce health care costs. As stated in *The Multilevel Compliance Challenge*, a paper by the American Heart Association:

> "Maximum use of strategies to enhance compliance must be made. Application of these strategies is particularly important now, when there is great pressure to decrease costs and improve quality and patient outcomes."[9]

Further elevating the need for action is the World Health Organization (WHO), which has called for an initiative to improve worldwide rates of adherence to therapies commonly used in treating chronic conditions, including asthma, diabetes, and hypertension. In a 2003 report entitled *Adherence*

to Long-Term Therapies: Evidence for Action, WHO defined poor medication adherence as a critical issue for global public health, and identified five broad dimensions affecting adherence that need to be addressed by health managers and policymakers:[3]

1. social and economic factors;
2. health system and health care team-related factors;
3. therapy-related factors;
4. condition-related factors; and
5. patient-related factors.

To bring about needed change, the WHO report called for a multidisciplinary approach toward adherence that includes patient-tailored interventions and training in adherence management for health professionals. This approach was also addressed in a 2005 review article by researchers Lars Osterberg, M.D., and Terrence Blaschke, M.D. published in the *New England Journal of Medicine* where the authors identified 12 major predictors associated with poor adherence -- from the side effects of treatment to the patient's belief in the benefit of the medicine.[2] (See Table 1; page 29) Noting that race, sex, and socioeconomic status have not been consistently associated with levels of adherence,[2] the authors conclude that poor adherence should always be considered when a patient's condition is not responding to therapy. Accordingly, the authors recommend that physicians ask a series of non-judgmental questions of their patients designed to facilitate the identification of poor adherence and enlist ancillary health care providers, such as pharmacists, behavioral specialists, and nursing staff to improve adherence.[2]

Another major development since the publication of NCPIE's report is new technology that makes available a number of useful mechanisms for fostering adherence. For example, patients can receive pharmaceutical information and refill reminders via letter, fax, telephone, e-mail and pager messages. There are also electronic reminder devices, which can be programmed for multiple daily alarms and may permit the user to record brief dosing instructions. Moreover, a number of medication organizers now incorporate electronic alarms to alert patients when doses are due.

Despite such developments, adherence rates have not changed significantly since NCPIE issued its recommendations over a decade ago, demonstrating that an intensified, sustained focus on adherence improvement among all stakeholders is essential to reduce the adverse health and economic consequences associated with this pervasive problem. While no single strategy will guarantee that patients will fill their prescriptions and take their medicines as prescribed, elevating adherence as a priority issue and promoting best practices, behaviors, and technologies may significantly improve medication adherence in the U.S.

This report, therefore, is intended as a renewed nationwide call to action. Based on an analysis of research to date, it examines the current state of patient adherence and trends that may lead to improved medication use. This report also offers realistic goals for improving medication adherence through patient information and education, health professional intervention, and supportive government policies.

Prescription Medicine Adherence:
A Fresh Look at a Persistent and Complex Problem

Even as the issue of taking medicines as prescribed is getting increased attention within the public health community, the multi-faceted nature of poor adherence has significantly clouded the debate. The following is a look at the current state of patient adherence and the factors contributing to this complex problem.

LACK OF A STANDARD DEFINITION AND CONSISTENT TERMINOLOGY LIMITS CONSENSUS

Even though there is a growing recognition about the need for improvements in medication adherence, progress has been hampered by a lack of consistent terminology. Today, a number of common terms are used to define the act of seeking medical attention, filling prescriptions, and taking medicines appropriately. All have their supporters and detractors and all reflect different views about the relationship between the patient and the health care provider.

In its 1995 report, NCPIE defined adherence as following a medicine treatment plan developed and agreed on by the patient and his/her health professional(s). Originally, NCPIE used the term "compliance" because historically, it is the term most widely used in medical indices. First appearing in the medical literature in the 1950's, the term "compliance" came into popular use following the 1976 publication of the proceedings of the first major academic symposium on the subject.[10] As originally defined, "compliance" was intended to describe "the extent to which patients' behaviors coincide with the health care providers' medical or health advice."

Yet to many researchers, "compliance" connotes a passive role for the patient and appears to blame and stigmatizes the patient's independent judgment as deviant behavior. Thus, many stakeholders prefer the term "adherence," which implies a more collaborative relationship between patients and clinicians and is more respectful of the role that patients can play in their own treatment decisions. Thus, the NCPIE definition proposed in 1995 was intended to encompass the concept of adherence, including two-way communication, patient-centered treatment planning, and agreement upon the medication and dosing requirements.

The term "persistence" has also entered the lexicon and is intended to address the treatment continuum, beginning with having the prescription filled and continuing with taking and refilling the medicine for as long as necessary. However, in the view of some researchers, the term "adherence" is more comprehensive and reflects both taking the medicine as directed (compliance) and continuing to take the medication for the duration required (persistence).

Another term now being used is "concordance," which is intended to convey an active partnership between the patient and the health care professional. Developed by the Royal Pharmaceutical Society of Great Britain, the concept suggests that the clinician and patient find areas of health belief that are shared and then build on these beliefs to improve patient outcomes.[11] However, this term has also been challenged as being more inspirational than what is possible in promoting better medication taking by patients.

Despite the increased use of "persistence," and "concordance," many researchers now use the terms "compliance" and "adherence" interchangeably. However, since "concordance" is being increasingly used in Europe, an important priority for the global public health community is to agree on a standard definition that will unite all stakeholders around the common goal of improving the self-administration of treatments to promote better health outcomes. For the purposes of this report, NCPIE has adopted

the term "adherence" because the term supports a patient-centered approach to improving how patients seek information, fill their prescriptions and take their medicines as prescribed.

THE EXTENT OF THE PROBLEM

Agreeing on a standard definition for patient adherence also requires an up-to-date assessment of the problem, which today rivals many disease states in terms of prevalence, human suffering, and health care costs. From a public health perspective, poor adherence is nothing short of a crisis.

Although the problem varies by condition and the types of drugs prescribed, it is significant, not only in the U.S. but around the world. According to research findings:

+ Between 12 percent and 20 percent of patients take other people's medicines;[11]
+ In developed countries like the U.S., adherence among patients with chronic conditions averages only 50 percent;[3]
+ Other studies show that about one-third of patients fully comply with recommended treatment while another third sometimes comply and one-third never comply;[12]
+ The World Health Organization reports that only about 43 percent of patients in developed nations take their medicines as prescribed to treat asthma and between 40 percent and 70 percent follow the doctor's orders to treat depression;[3]
+ Although hypertension increases the risk of ischemic heart disease three- to four-fold and increases the overall cardiovascular risk by two- to three-fold, just 51 percent of patients take their prescribed doses of drugs to manage this condition;[13]
+ Among 17,000 U.S. patients prescribed beta blocker drugs following a heart attack, a major study conducted by Duke University Medical Center reported that only 45 percent regularly took these medications during the first year after leaving the hospital, with the biggest drop in adherence occurring during the initial months after hospital discharge;[13]
+ Less than 2 percent of adults with diabetes perform the full level of care, which includes self-monitoring of blood glucose and dietary restrictions as well as medication use, that is recommended by the American Diabetes Association;[14]
+ Although adherence with short-term therapy is generally considered to be higher than for long-term treatments, rapid declines occur even in the first ten days of use;[15] and
+ Even among health care professionals, self-reported adherence with prescribed therapies averaged only 79 percent in one study.[16]

Researchers have found that even the potential for serious harm may not be enough to motivate patients to take their medicines appropriately. In one study, only 42 percent of glaucoma patients met minimal criteria for adherence after having been told they would go blind if they did not comply. Among patients who already had gone blind in one eye, adherence rates rose only to 58 percent.[17] Another study of renal transplant patients facing organ rejection or even death from poor adherence with immunosuppressant therapy found that 18 percent of patients were not taking their medicine as prescribed.[18]

SPECIAL POPULATIONS AT RISK

Of special concern to the public health community is poor adherence among people aged 65 and over, who tend to have more long-term, chronic illnesses--such as arthritis, diabetes, high blood pressure, and heart disease-- and therefore, take more different medications as they age. According to one study, people aged 75 years and older take an average of 7.9 drugs per day.[11] Other studies have shown that between 40 percent and 75 percent of older people do not take their medications at the right time or in the right amount[19] due to such complicating factors as having multiple health problems requiring treatment,

needing multiple medications, being seen by multiple prescribers, and having physical and cognitive challenges that may impact medication use.

The impact of poor adherence is also a serious problem among the medically underserved -- those Americans of all ethnic backgrounds who are poor, lack health insurance, or otherwise have inadequate access to high-quality health care. According to the third National Healthcare Disparities Report (NHDR) issued in 2005 by the Agency for Healthcare Research and Quality (AHRQ), health care disparities by race and ethnicity remain prevalent in the U.S. and are significantly correlated with health literacy -- the ability of an individual to access, understand and use health-related information and services to make appropriate health decisions -- among the underserved. The Office of the U.S. Surgeon General estimates that more than 90 million Americans cannot understand basic health information,[20] which costs the health system billions of dollars each year due to misdirected or misunderstood medical advice.

Children and teenagers are also an at-risk group, especially when it comes to adherence to treatments for asthma, one of the most common chronic diseases of childhood.[21] Research shows that adherence to prescribed pulmonary medication may be as low as 30 percent in adolescents,[3] leading to uncontrolled asthma. A number of factors related to children's experiences taking medicines during their formative years affect future rates of compliance. These factors include parents not adequately monitoring their children's use of medicines, poor parental adherence to treatment regimens, and lack of school education about medicine use.

PAYING THE PRICE FOR POOR ADHERENCE

Who is paying the price for the epidemic of poor medication adherence? We all are -- and the costs are substantial. Researchers have calculated that non-adherence costs the U.S. health care system about $100 billion annually,[22, 23, 24] including approximately $47 billion each year for drug-related hospitalizations.[25] Moreover, not taking medicines as prescribed has been associated with as many as 40 percent of admissions to nursing homes[26] and with an additional $2,000 a year per patient in medical costs for visits to physicians' offices.[26] The total direct and indirect costs to U.S. society from prescription drug non-adherence are about $177 billion annually.[27]

Employers also pay a high price for employees' non-adherence to prescribed medical treatments, both in terms of reduced productivity and absenteeism, and in higher costs for private or managed care health insurance benefits. With prescription drugs representing the fastest-growing cost component for most health plans (climbing at more than 17 percent annually),[28] employers are increasingly requiring that covered members and their families assume a greater percent of their cost.

Although the economic cost associated with poor adherence is already staggeringly high, the World Health Organization predicts that this problem will only grow as the burden of chronic diseases increases worldwide.[3] As policymakers consider ways to address the escalating costs of health care in the U.S., it is critical that the agenda include the pressing issue of improving patient adherence with medication regimens. Mounting evidence shows that better adherence leads to improved clinical outcomes and reduced costs.[29] Based on a meta-analysis of 63 studies involving more than 19,000 patients, higher adherence was found to reduce the risk for a poor treatment outcome by 26 percent.[30] Other data associate patient self-management and adherence programs with a reduction in the number of patients being hospitalized, days in the hospital, and outpatient visits. The data suggest a cost to savings ratio of approximately 1:10 in some cases, with the results continuing over several years.[31]

As Americans age, an increasing number are prescribed multiple medications for multiple chronic conditions. As a result, new strategies to enhance prescription medicine adherence are needed. While new interventions are not cost-free, improving adherence is likely to increase the cost effectiveness of health interventions, thereby reducing the burden of chronic illness. The investment of time and resources to improve patient adherence will likely more than pay for itself through improved health status and reduced utilization and costs.

What Is Behind Poor Adherence:
Factors That Contribute to the Problem

Poor adherence encompasses much more than patients not taking their medicines as directed. Numerous behavioral, social, economic, medical, and policy-related factors contribute to the problem and must be addressed if adherence rates are to improve.[3]

To understand the interplay of these issues, the research community has categorized the factors underlying non-adherence as medication-related, patient-related, prescriber-related, and pharmacy-related. Additionally, federal and state government policies can also serve as impediments to adherence improvement. The following describes these factors and the challenges they represent.

MEDICATION-RELATED FACTORS

For many patients, one of the biggest stumbling blocks to taking their medicines is the complexity of the regimen. Studies find that patients on once-daily regimens are much more likely to comply than patients who are required to take their medicine(s) multiple times each day.[32]

Conversely, the number of medications a person takes has a negative impact on adherence. In any given week, four out of five U.S. adults will use prescription medicines, over-the-counter (OTC) drugs, or dietary and herbal supplements and nearly one-third will take five or more different medications.[33] Of special concern are adults aged 65 and older, who take more prescription and OTC medicines than any other age group.[34] According to a 2001 survey of older Americans conducted by the American Society of Health-System Pharmacists (ASHP), 82 percent of patients over age 65 take at least one prescription medicine, more than half (54 percent) take three or four prescription medicines, and as many as a third (33 percent) take eight or more prescription medicines to treat their health conditions.[35] Adherence also decreases when patients are asked to master a specific technique in order to take their medication, such as using devices to test blood levels as part of a treatment protocol, using inhalers, or self-administering injections.[36]

Compounding the problem, many patients -- and especially older adults -- are being seen by more than one physician or other prescriber, and each may be prescribing medications for a specific condition. Unless there is a primary care provider who coordinates these medication regimens, the number of different medicines the patient takes each day may limit adherence while also increasing the risk of medication errors and harmful drug interactions.

Beyond the complexity of the regimen, concern about medication side effects remains a powerful barrier to patient adherence. In a 2005 survey of 2,507 adults conducted by Harris Interactive, nearly half of the respondents (45 percent) reported not taking their medicines due to concerns about side effects.[37] Conversely, when medications such as antidepressants and corticosteroids are slow to produce intended effects, patients may believe the medication is not working and discontinue use.[38]

Addressing these medication-related factors will require better communication between the patient and his/her prescriber about what to expect from treatment and about the patient's medication challenges (including the number of medicines being taken, worries about side effects and how to administer and monitor the medicine). Through high-quality, two-way discussions, clinicians will be able to identify and discontinue unnecessary medications, simplify dosing regimens, and address other medication-related issues that make adherence difficult.

PATIENT-RELATED FACTORS

Patients ultimately are in control of whether, how safely and how appropriately they take their

medicines. For example, a common reason why patients don't take their medicines is simply forgetfulness.[39] Another significant barrier is the inability to understand and act on instructions for taking the medication. In fact, a study found that 60 percent or more of patients being followed could not correctly report what their physicians told them about medication use 10 to 80 minutes after receiving the information.[40]

While problems such as these are significant, public health officials are increasingly concerned about patients and especially those with chronic conditions requiring long-term therapy, such as asthma, diabetes, and hypertension, who make a conscious choice not to fill the prescription, not to take their medicine as prescribed, or to discontinue therapy. Influencing these decisions are a number of factors related to the patient's experiences, perceptions, and understanding about his or her disease. These include:[41]

1. Perceptions about the nature and severity of their illness;
2. Denial of illness and the need to take medicines;
3. The assumption that once the symptoms improve or the person "feels better," he or she can discontinue use of the medication;
4. Limited appreciation about the value of medicines when properly used;
5. Beliefs about the effectiveness of the treatment;
6. Acceptance of taking medications for preventive purposes and for symptomless conditions (e.g. statins to lower blood cholesterol levels);
7. Worries about the social stigma associated with taking medicines;
8. Fear of side effects or concern about becoming drug dependent;
9. Fear of needles and the need for self-injections;
10. Lack of confidence in the ability to follow the medication regimen;
11. Media influence regarding safety or risk issues associated with particular medicines; and
12. Lack of positive motivations and incentives to make necessary changes in behavior.

Along with these attitudes and beliefs, the duration of the course of therapy also contributes to whether and how patients take their medicines.[36] Adherence rates have been found to decline over time when patients are treated for chronic conditions.[29]

Moreover, for many Americans, the high cost of medications is a barrier to medication use.[36] In a 2004 study of nearly 14,000 Medicare enrollees, 29 percent of disabled people and 13 percent of seniors reported skipping doses or not filling a prescription because of cost.[42] Limited access to health care services, lack of financial resources, and burdensome work schedules are also associated with poor adherence to medication regimens.[2]

Compounding these problems is the impact of low health literacy and limited English language proficiency, which greatly affect the ability of patients to read, understand, and act on health information about medication use. According to published studies, 45 percent of the adult population (90 million people) have literacy skills at or below the eighth grade reading level, making it difficult for these individuals to read health information, understand basic medical instructions and adhere to medication regimens.[43] In one study involving patients over age 60 who were treated at two public hospitals, 81 percent could not read or understand basic materials, such as prescription labels.[43] A 2006 study, published in the *Annals of Internal Medicine* found that low-literacy patients have difficulty understanding basic information regarding medication dosage. While over 70 percent of the respondents correctly stated instructions about taking two pills twice a day, only one-third (34.7 percent) could demonstrate the correct number of pills to be taken daily.[44]

Further, studies have found that people with low health literacy or limited English language proficiency are often ashamed to get help with medical instructions,[45] which increases the likelihood that they will not be able to follow their treatment regimens. As a result, the U.S. Surgeon General, the National Quality Forum, and other stakeholders have called for immediate action to improve adherence among these sizeable vulnerable populations.

PRESCRIBER-RELATED FACTORS

In 1995, NCPIE identified the lack of awareness of basic compliance management principles among some clinicians as a major causal factor for prescription non-adherence. More than a decade later, this appears to remain the case. According to a 2004 telephone survey conducted by the Food and Drug Administration (FDA), only 66 percent of consumers polled reported receiving instructions from their physician about how often to take a new medication and only 64 percent were told how much to take.[46] The survey also examined the receipt of medicine information at the pharmacy. Here, the figures dropped considerably, to 31 percent (how often to take) and 29 percent (how much to take) respectively.[46]

Why is this the case? One reason is that clinicians tend to overestimate the extent of their patients' ability to adhere to a medication regimen and the patient's actual adherence level. In one study of 10 family physicians who had known many of their patients for more than five years, researchers found that only 10 percent of the physicians' estimates of adherence with digoxin therapy were accurate when compared with information from a pill count and serum digoxin concentration measurements.[29] Earlier studies reported that health professionals overstate the adherence of their patients by as much as 50 percent.[47]

At the same time, the WHO report attributes lack of adequate medication counseling to the outdated belief that adherence is solely the patient's responsibility.[3] Practical issues such as lack of time and lack of financial reimbursement for education and counseling also represent persistent barriers to health care provider adherence interventions.[48]

Besides these practical issues is the factor of trust between the clinician and the patient. According to a study recently reported in the *Archives of Internal Medicine*, when physician trust levels are low, patients are more likely to forego the use of medications.[49] This study suggests that clinicians need to encourage adherence through behaviors designed to improve patient trust. Further, a meta-analysis of 21 studies assessing the quality of physician-patient communication found that the quality of communication both in the history-taking segment of the visit and during discussion of the management plan significantly improved patient health outcomes.[50]

Finally, there is the pervasive problem of poor communication between the clinician and the patient. Because this lack of effective communication can lead to medication errors and non-adherence, the Institute of Medicine (IOM) in its landmark 1999 report – *To Err is Human; Building a Safer Health System* – called on clinicians to educate their patients about the medications they are taking, why they are taking them, what the medications look like, what time patients should take their medicines, potential side effects, what to do if a patient experiences side effects, and what regular testing is necessary.[51] Osterberg and Blaschke also present a range of communications-based strategies for improving medication adherence in their review article, *Adherence to Medication*, published in the August 4, 2005 issue of the *New England Journal of Medicine*.[2] (See Table 2; page 30 of this report).

PHARMACY-RELATED FACTORS

Because pharmacists have direct and frequent contact both with prescribers and patients, research suggests that community-based pharmacists can play a unique role in promoting medication adherence.[3, 16] For example, a study examining the interaction of 78 ambulatory care clinical pharmacists with 523 patients treated at selected Veterans Affairs medical centers over the course of a year found that pharmacists were responsible

for adjusting patients' drug regimens as well as identifying and preventing drug-related problems.[52]

Also demonstrating the ability of community-based pharmacists to increase medication adherence is the recent Federal Study of Adherence to Medications in the Elderly (FAME) conducted among military health care beneficiaries aged 65 years or older who were prescribed at least four chronic medications a day. Designed to assess the efficacy of a comprehensive pharmacy care program, this multi-phase study examined the impact of patient education and the use of an adherence aid (medications custom packaged in blister packs), finding that the program increased medication adherence and persistence, whereas discontinuation of the program was associated with decreased medication adherence and persistence.[53] Findings from the FAME study call for greater emphasis within health care delivery systems and policy organizations on the development and promotion of clinical programs to enhance medication adherence particularly among the at-risk elderly population.

Despite these research findings, however, four categories of pharmacy-related barriers to improved patient adherence remain and must be addressed. Broadly defined, these categories are: the attitudes of patients and pharmacists, the knowledge level of pharmacists, the operational aspects of the pharmacy practice, and professional barriers.[41]

In its 1995 report, NCPIE identified many attitudinal barriers that contribute to the poor adherence, including the perceptions of patients, caregivers, and other health care providers about the expertise of pharmacists and the pharmacist's willingness to tailor education and counseling to the needs of the patient. Moreover, pharmacists' own views about their role in medication adherence can be a factor. Many pharmacists are accustomed to a paternalistic relationship where the pharmacist tells the patient what to do and the patient is expected to follow those instructions.[26] Further complicating the situation for pharmacists is identifying potential adherence problems when medication regimens can be complex and then applying complex technical information to practice situations.[26]

Beyond these issues, NCPIE has noted functional and professional barriers that can significantly impact the ability of pharmacists to engage in adherence education and counseling. Functional barriers can include space limitations, time constraints, the lack of resources, and the lack of management support to counsel patients on medication adherence.[55] Moreover, thousands of pharmacies must divert time and cannot efficiently fill prescriptions because information needed to obtain reimbursement frequently does not appear on a patient's drug benefit card. As a consequence, thousands of hours are occupied calling employers or insurance companies to obtain this information.[56] Reimbursement for counseling patients has not kept pace with the pharmacy profession's attempts to obtain this payment, although the Medicare prescription drug benefit plan affords opportunities due to requirements for medication therapy management programs (MTMP) for specific enrollees.

Professional barriers also arise from a lack of consensus within the pharmacy community about the role of pharmacists in health care delivery. To gain this consensus, national pharmacy organizations have endorsed the concept of "pharmaceutical care,"[57] a maturation of pharmacy as a clinical profession, with pharmacists cooperating directly with other professionals and the patient in designing, implementing and monitoring a therapeutic plan. This approach requires a knowledgeable frontline staff supported by managers, other pharmacists and effective work systems.

GOVERNMENT IMPEDIMENTS

The pharmaceutical care model advanced by the pharmacy community is predicated on supportive government policies. However, a number of federal and state laws, as currently interpreted, may actually impede the availability of adherence assistance programs.

One such impediment is the federal anti-kickback statute containing rules that cover businesses reimbursed by Medicare, Medicaid or other federally funded health care programs. This statute is so

broadly written that many types of health care practices and business relationships designed to increase patient adherence may theoretically be subject to criminal prosecution under the statute.

To help address this problem, the Office of the Inspector General (OIG) within the Department of Health and Human Services (HHS) issued regulations granting "safe harbor" protections to certain types of health care practices and business arrangements.[1] However, because OIG's regulations don't specifically cover patient education, medication refill reminder programs and other pharmacy-based adherence messaging programs, the result has been a reduced use of adherence messaging programs. In an abundance of caution, some refill reminder programs now exclude any patients who participate in any federal health care program (e.g., Medicare, Medicaid, TRICARE).[2]

Another impediment to pharmacy adherence assistance programs involves federal and state medical privacy requirements. At the federal level, there is the "Privacy Rule,"[3] a set of federal medical privacy regulations issued to implement the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Although these rules permit health care providers to carry out "treatment" functions, including refill reminders and other adherence messaging programs, without first obtaining the patient's written permission,[4] some privacy advocates object to these provisions.

With these concerns in mind, the National Consumers League (NCL) created voluntary performance-based Best Practice Principles that build on the requirements contained in the HIPAA privacy rule.(58) Developed by a Working Group of representatives from public interest groups, health professional societies, the consumer/privacy movement, pharmacy industry trade groups, pharmacy vendors, retail chains, and the pharmaceutical industry, the Best Practices Principles are intended to bridge the gap between the protections afforded by HIPAA and fair information practices that define the degree of control that consumers should have over the ways their health information is used. Accordingly, the Best Practices Principles include:(58)

+ Ensuring that a pharmacy's Notice of Privacy Practices can be easily understood;
+ Providing patients with a description of pharmacy messaging programs;
+ Providing an opportunity to opt out of the pharmacy messaging programs;
+ Ensuring that opt-out mechanisms function properly;
+ Identifying sponsorship;
+ Disclosing limitations of materials as a source of health care information;
+ Providing information that is clear and reliable;
+ Endeavoring to use discretion in communicating about sensitive subjects;
+ Ensuring that persistence and adherence messages are written in a manner consistent with available data about the characteristics of effective messaging; and
+ Engaging in messaging about alternative and/or adjunctive therapies only when there is a clear potential benefit to patients.

Even with these voluntary principles, however, HIPAA does not preempt state law, which is why a number of states have enacted, or are considering, legislation to restrict the ability of pharmacies to conduct adherence messaging programs. As with the federal anti-kickback statute, the unintended consequence of some of these state laws is uncertainty about which types of medical information require patient authorization and which do not. For example,

[1] 42 C.F.R. Part 1001.

[2] To the extent that the antikickback statute discourages refill reminders and other compliance programs, its effect is somewhat at odds with the Medicare Modernization Act, which required that, every Part D benefit plan implement medication management therapy programs (MTMPs). MTMPs are designed to optimize the therapeutic outcome of drug treatment for certain beneficiaries through education and management programs. Improved medication compliance and adherence is a key part of a successful MTMP.

[3] Pub. L. No. 104-191.

[4] 45 C.F.R. § 164.506(a) and (c).

the California Confidentiality of Medical Information Act (CMIA) provides (in relevant part):

> Except to the extent expressly authorized by the patient . . . no provider of health care . . . shall intentionally share, sell, use for marketing, or otherwise use any medical information *for any purpose not necessary to provide health care services* to the patient.[5]

When read literally, the CMIA seems to prohibit adherence-messaging programs without specific authorization, when in fact, the Act views these programs as "necessary to provide health care services" and exempts this requirement. The CMIA also exempts the authorization requirement for adherence communications that address a "chronic and seriously debilitating or life-threatening condition" if certain conditions are satisfied.[6] But since there is uncertainty as to how state regulators could interpret these provisions, many pharmacies and pharmaceutical manufacturers have opted not to run adherence programs in California, or run them on a limited basis. The consequence is that adherence communications for medications for diabetes, osteoporosis, asthma, hypertension and heart attack and stroke prevention now being provided in other states are, in some cases, being withheld from Californians. The same situation could result if a number of state bodies enact legislation that broadly prohibit the use of prescription drug information for commercial purposes, including pharmacy-based programs funded through third parties.

LIMITED FEDERAL SUPPORT FOR ADHERENCE RESEARCH

Besides federal and state laws and policies that impact the availability of adherence assistance programs, insufficient federal funding for adherence research is another impediment to improving medication use. Although created the Adherence Research Network to identify research opportunities at its 18 Institutes and Centers, the Network has been inactive since 2002. Moreover, in 2000, when the Network was funding adherence research, the actual NIH dollars earmarked for testing interventions to improve medication-taking behavior was only $3 million in a budget of nearly $18 billion.[59] The overall NIH budget in 2000 was $17.8 billion.

Such paucity in adherence research funding has implications for public policy, as policymakers look to researchers to help determine priorities for the medical community. While NIH dollars are being spent on patient adherence as it applies to treating specific disease states, very little is actually going into testing interventions and measuring their effectiveness. Thus, a key goal will be to re-invigorate the Adherence Research Network while increasing substantially the level of NIH funding for research to test adherence interventions and measure their effectiveness.

Kripalani, Yao, and Haynes (Interventions to Enhance Medication Adherence in Chronic Medical Conditions) point out key limitations and challenges for future adherence research, noting that because most of the available literature does not separate out the effects of the individual components of multifaceted interventions, it is not possible to draw definitive conclusions about which features of combined interventions are most beneficial.[60] Additional research, the authors note, is needed to clarify which features are most responsible for changes in adherence and clinical outcomes, with the caveat that individual components may not prove powerful enough to show important effects.

Future studies should also examine the effect of varying the intensity of interventions to determine dose response relationships. Such findings would have important implications for health systems considering the implementation of patient adherence programs on a large scale. Investigations should be conducted with clinically meaningful outcomes as the primary end points and be sufficiently powered to detect a difference in these measures. Most important, future research should seek to understand the determinants of adherence behavior and to develop and test innovative ways to help people adhere to prescribed medication regimens, rather than persisting with existing approaches.[60]

[1] Cal. Civ. Code § 56.10(d), as amended by A.B. 715.

[2] Cal. Civ. Code § 56.05(f)(3).

Strategies for Improving Patient Adherence

How do we change behavior? How can we motivate patients with chronic illnesses to take steps that will keep their diseases from progressing? How can we engage health professionals to intervene with patients and their caregivers about the need to take medicines as directed -- sometimes for life? And how can we elevate the subject of prescription medicine adherence, an issue to which Americans have been largely indifferent, to one that is both compelling and actionable by all affected stakeholders?

These are the challenges facing the U.S. health system at a time when lack of patient adherence to medication regimens, especially for the treatment of chronic conditions, leads to unnecessary disease progression, disease complications, reduced functional abilities, a lower quality of life, and even death. To address this serious problem, a range of strategies must be used to target the underlying causes of poor adherence and to make the relevance of taking medicines as prescribed meaningful to all stakeholders -- patients, caregivers, clinicians, payors, public health advocates, and policymakers. But this does not mean starting from scratch: extensive research exists that provides insights into effective approaches to improve adherence to therapeutic regimens.

RECOGNIZING THE DISEASE CHARACTERISTICS OF NONCOMPLIANCE

The 1994 report *Noncompliance With Medications: An Economic Tragedy With Important Implications for Health Care Reform* introduced the concept that non-adherence is a disease because the problem shares many features of a medical disorder, including:[22]

+ Non-adherence can lead to increased morbidity and mortality;
+ The problem can be assessed and monitored;
+ Effective interventions have been identified;
+ Triage is needed to identify those patients at greatest risk of non-adherence; and
+ Non-adherence is a public health problem for which prevention is an important goal.

In light of these similarities, approaching non-adherence as a disease could be an important step towards increasing the extent to which patients take their medications as prescribed by their health care provider(s). With implications for research, health policy, and the day-to-day practice of medicine and pharmacy, widespread recognition of the disease characteristics of non-compliance would put the issue into a new perspective that would help gain the attention, focus and sustained commitment that this problem deserves.

INCREASING PUBLIC AWARENESS THROUGH EDUCATION

To motivate patients to adhere to their medication regimens, the American public must first recognize the role each person plays in taking their medications as prescribed or in making sure that a loved one does so. Simply put, the American public needs increased education about medication adherence that captures their attention, increases their understanding, and enhances their motivation to take their prescribed medication in the recommended way.

To achieve these goals, specialists in medication use advocate mounting a sustained, national public education campaign to provide patients and caregivers with meaningful information about adherence that they can incorporate into their daily lives. Ultimately, enlisting the support and participation of many stakeholders -- including the public health community, physicians and other

prescribers, nurses, pharmacists, the pharmaceutical industry, government, private payors, and consumer organizations – such a campaign must elevate adherence as a health priority and utilize multiple information channels to engage the public on a sustained basis. Only by making the public aware of the role individuals play in the management of their own health conditions will we empower people to ask questions about their medicines, fill their prescriptions, and follow their treatment regimens as recommended.

PATIENT INFORMATION STRATEGIES

As noted by the American Heart Association, the rationale for enhancing adherence is based on the premise that the patient will get well or stay well if the physician, other health care providers, and the health care organization make appropriate recommendations, providing the patient has the requisite knowledge, motivation, skills, and resources to follow the recommendations. Specifically, the American Society of Consultant Pharmacists states that patients need to know:[61]

+ What condition the medicine was prescribed to treat.
+ What the medicine is, why it is needed and how it works in the body.
+ Why the medicine was selected.
+ The dosage schedule and related instructions about how to take the medicine (before eating, with food, etc).
+ Whether the medicine will work safely with other medicines being taken (both prescription and nonprescription medicines).
+ What to do if doses are missed or delayed.
+ The common adverse effects that may occur and what to do about them.
+ How to monitor whether the medicine is having its intended effect (are lab tests or blood work necessary; if so, how often).
+ Serious adverse effects to look out for and what to do if they occur.
+ What action to take when the prescription is about to run out.

In the outpatient setting, the primary opportunities for providing this information to the patient occur in discussions when the prescriber writes the prescription and when the patient fills the prescription at the pharmacy. Visiting nurses in the home setting also have an opportunity for such dialogue with patients. During these discussions, research has found that relaying the most important information first, repeating key points, and having patients restate key instructions increase patient understanding.[62] Moreover, data show that providing patients with information about possible adverse effects does not appear to decrease adherence.[63]

Besides providing basic information about how to take the medication correctly, an important reason for clinicians to educate patients about their medication regimens is to address common misperceptions that lead to non-adherence. This may include the perception that the medication can be stopped when the condition improves or that the medicine is only needed when there are symptoms. Moreover, studies demonstrate the benefits of improved adherence when patients are encouraged to ask questions and share information. This process is built upon the Health Belief Model, one of the most widely used conceptual frameworks in health behavior, which suggests that people's beliefs guide their understanding of and response to their diseases.[26]

However, since studies find patients forget more than half of the information from a verbal explanation immediately after they hear it,[17] health care providers should welcome patients who bring a partner or caregiver as a "second set of ears," and should ask patients to repeat instructions and encourage note taking during the oral discussion. Complementing these actions, providing written information about the medication has been shown to improve patients' knowledge and decrease medication errors. A 2007 study conducted by researchers at the Arnold &Marie Schwartz

College of Pharmacy and Health Sciences, Long Island University, found that approximately two-thirds of surveyed patients reported reading the non-manufacturer developed consumer medicine information (CMI) leaflets about new medications provided by pharmacies.[64] Accordingly, the study recommends that pharmacists should encourage patients to read the CMI leaflet and promote it as a useful resource, although this information should be used in conjunction with, but not as a substitute for, oral discussions.[40]

In the case of teaching complex medication-taking techniques, such as using a metered dose inhaler or administering an injection, oral and written information will not suffice. Here, patients need a health care provider to walk them through the process in easy steps and to observe while the patient repeats the procedures. The health care provider is then able to answer questions, point out any problems with the patient's technique and work with the patient to repeat the procedure until the problems are resolved.

While all these strategies are helpful in promoting patient adherence, how the information is conveyed also matters greatly to how patients ultimately respond. For example, a 2006 study conducted for the American College of Physicians (ACP) Foundation and reported in the *Annals of Internal Medicine*[65] found that a major barrier to patient adherence is patient understanding of prescription drug labels, including the format, content, and use of medical jargon. Because this problem is especially acute among those with lower literacy (eighth grade level or below) and patients taking multiple prescription drugs, the ACP Foundation has launched a Prescription Medication Labeling project to address the problems associated with poor health communication.

A key strategy of the Prescription Medication Labeling project is the use of patient-centered counseling, an approach that focuses not only on the content of the information but also on the tone used by health professionals. As detailed in the 1995 NCPIE report, patient adherence improves when professionals:[36]

+ Are warm and caring and respect the patient's concerns,
+ Talk to patients directly about the need for adherence,
+ Probe patients about their medicine taking habits and health beliefs,
+ Obtain agreement from the patient on the specifics of the regimen, including the medical treatment goals,
+ Communicate the benefits and risks of treatment in an understandable way that fosters the perception that the patient has made an informed choice about his or her care, and
+ Probe for and help resolve patient concerns upfront so they do not become hidden reasons for non-adherence.

BEHAVIORAL REINFORCEMENT AND PATIENT SUPPORT

Especially in chronic disease management, where medication is required on a continuing basis, adherence with medication regimens involves a change in behavior on the part of the patient.[66] In some cases, patients may need to take specific medications every day at a set time. Adherence also requires that patients remember to get their prescriptions refilled and to incorporate their medication taking into their daily schedules and lifestyle.

Because these actions require diligence, adherence can be viewed as a continuum, with most patients starting as very diligent and declining over time. Adherence has also been shown to decline between visits to the physician/clinic.[3] That is why regular interaction between patients and health providers is so important for improving medication use.

Recognizing these challenges, adherence researchers stress the importance of tailoring the medication regimen to the patient's daily schedule and lifestyle, such as:

- Decreasing the number of daily doses to once or twice a day;[17, 36]
- Eliminating unnecessary or redundant medications or using combination products when possible;
- Changing the route of administration, such as using oral medications or transdermal patches; and
- Decreasing the overall cost of the medication regimen if affordability is a barrier to compliance.

Additionally, long-term adherence requires behavioral reinforcement and patient support strategies throughout the continuum of care. Providing cues to patients -- through medication packaging that helps patients chart and remember to take each dose and through tools such as medication organizers and reminder charts -- have been shown to improve adherence. A personal medication chart encourages the patient to keep a list of all the prescription and over-the-counter medications used, including recording how much to take, when and how to use the medicine, why to use the medicine, and the name of the prescriber.

Another approach that has produced measurable outcomes is direct-to-patient adherence programs, such as arranging supportive home visits by health care providers or encouraging the patient to establish a buddy system with a friend who also takes daily medication. In a meta-analysis of 153 studies assessing the effectiveness of different adherence interventions, those that combined educational and behavioral approaches were more successful than single-focused interventions.[67]

Along with these strategies, specialists in the field are advocating for broader awareness and adoption of new technologies that make it possible to engage patients more effectively about medication adherence. For example, prescribers can use email to communicate directly with patients who are encouraged to ask questions electronically. Pharmacies can use adherence-messaging programs to reach patients using letters, newsletters, brochures, telephone calls, e-mails, faxes and even pagers. These programs can be triggered by automated pharmacy dispensing records, based on estimates of when the patient may run out of the medication. These communications not only remind the patient to refill the prescription but also emphasize the importance of following their health care provider's instructions and keeping follow-up visits.

Other technological innovations that have the potential to improve medication adherence include electronic reminder devices and automated medication dispensers. For example, electronic pillboxes are available that can be programmed to light up when a dose is due. Also in development is new technology that allows a microchip to be embedded in the packaging to monitor the dates and times when the package is opened, allowing pharmacies to scan the information and plot out patients' medication taking patterns.

STRATEGIES DIRECTED AT HEALTH PROFESSIONALS

Although ultimately patients must make the decision to fill their prescriptions and take their medicines as prescribed, improved adherence requires the successful interplay between the patient and those involved in managing his/her care -- the physician, physician assistant, nurse or nurse practitioner, and pharmacist. This partnership is the principle behind patient-centered medicine,[68] where clinicians cooperate directly with the patient in designing, implementing and monitoring a therapeutic plan.

Shifting to a patient-centered approach, however, requires that health care providers have the knowledge to educate and counsel about medication adherence. As a result, specialists advocate starting with increased training of prescribers, nurses and pharmacists to improve their adherence-related skills.[68] Currently, courses in patient education and adherence promotion are incorporated into the curriculum of many nursing and pharmacy schools, but there are major gaps, especially in the training of medical students. It is not surprising then that even among health care

professionals, studies find that lack of medication adherence is a problem.[16]

To fill this troubling education gap will require developing a curriculum that will allow medical, nursing and pharmacy students to conceptualize and execute responsible medication-related problem-solving on behalf of individual patients. Curricula should be designed to produce graduates with sufficient knowledge and skills to provide patients with adherence education and counseling competency. Expanding the core competencies of clinicians also requires a significant investment in expanding professional education through courses provided by recognized medical sub-specialty and allied health organizations as well as lecture series on patient adherence.

At the same time, improving the ability of patients to adhere to their therapy regimens necessitates an expanded role for pharmacists, who are among the most accessible members of the health care team once medication therapy is initiated.[3] There is also growing evidence that pharmacy-based interventions are effective in improving drug therapy results. For example, in a study where pharmacists provided adherence counseling to patients with high blood cholesterol, medication adherence improved from a national average of 40 percent to 90 percent.[69]

To capitalize on the role of pharmacists as the nexus for conducting adherence interventions, the pharmacy community has been working to implement collaborative drug therapy management (CDTM) through which pharmacists and physicians voluntarily enter into agreements to jointly manage a patient's drug therapy.[70] Currently, 40 states have specific laws that allow CDTM and others are developing or reviewing proposed legislation to enable CDTM for improved disease and drug therapy management.[56]

At the same time, more initiatives like the "Asheville Project," the longest-running test using pharmacist interventions to improve patient adherence with diabetes and asthma regimens, are needed to improve health outcomes.[71] Featuring patient counseling, the Asheville Project provides pharmacists with intensive training in managing the target disease and then pays them for monthly consultations with patients, during which they encourage those patients to adhere to the recommended lifestyle changes and prescribed medication regimen. Currently, the American Pharmacists Association (APhA) Foundation has launched the Diabetes Ten City Challenge modeled after the Asheville Project to improve medication adherence among people with diabetes.[72] This demonstrates that matching patients with specially trained pharmacists is a useful strategy to help patients learn how to manage their disease more effectively while lowering the costs of health care.

Pharmacists should also take advantage of advances within the practice that make patient adherence efforts more effective. This includes designating areas within the pharmacy that are conducive to patient counseling and undertaking such activities as monitoring blood pressure, blood glucose levels and other patient screening activities. Further, adherence technologies now make it possible for pharmacists to conduct direct-to-patient counseling programs tailored to the needs of patients who have been prescribed medication in virtually every therapeutic class. These programs can be implemented in various forms, including education and reminder letters, e-mail messages, newsletters, brochures, and phone calls.

THE NEED FOR A MULTIDISCIPLINARY APPROACH TO IMPROVE ADHERENCE

If the goal of medication adherence is to improve the outcome for each patient through the correct use of prescribed medicines, then what is ultimately needed is a multidisciplinary approach to adherence management whereby the patient and all members of the health care team work together to cure the patient's illness, provide symptom relief, or arrest the disease process. This approach is intended to convey a respect for the goals of both the patient and the health professional, and envisions patients and clinicians engaging in a productive discussion about medication regimens.

The idea of a multidisciplinary team is the concept behind the term "concordance" advanced by the Royal Pharmaceutical Society of Great Britain[11] and other European bodies, and behind the term "pharmaceutical care,"[57] which has gained traction within the U.S. Regardless of the term, the underlying premise is what NCPIE calls the "Medication Education Team," a model of open communication and shared responsibilities in which physicians and other prescribers, nurses, pharmacists and other providers communicate with patients at every "teachable medicine moment," making communication a two-way street, listening to the patients as well as talking to them about their medicine use. Since the 1980s, NCPIE has advocated for the formation of a "Medicine Education Team" for every patient, so each individual is fully informed about each medicine he/she is taking, has the instructions for taking these medicines properly, and knows the medication risks to avoid.

Recognizing that many interventions have been shown to be effective in improving adherence rates, the World Health Organization (WHO) report specifically calls on health professionals, researchers, health planners and policymakers to implement a multidisciplinary approach to adherence education and management.[3] This has led to the creation of a special Task Force on Medicines Partnership in the United Kingdom.[73] In the United States, pharmacy researchers are also examining ways to demonstrate the benefits of pharmacy-based adherence intervention services. What is needed now is for leading physician, nursing, and pharmacy organizations to embrace NCPIE's concept of the Medicine Education Team, resulting in its widespread adoption in clinical settings.

THE NEED FOR SUPPORTIVE GOVERNMENT POLICIES

At a time when the number of prescriptions dispensed in the U.S. is expected to grow to 4.5 billion by 2010,[74] enabling pharmacists to use the most modern technologies to conduct adherence assistance programs would seem obvious. However, as noted previously, there are a variety of impediments, including limitations by a number of federal and state laws. An immediate need is to resolve ambiguities about whether sponsored programs fall within the scope of the federal anti-kickback statute, and to ensure that federal and state medical privacy laws make clear that pharmacies may communicate with patients about the importance of adherence to prescribed courses of therapy, as long as such compliance programs address privacy-related concerns.

THE NEED FOR RESEARCH SUPPORT AND RESEARCH RIGOR

With the astonishing advances in medical therapeutics during the past two decades, one would think that studies about the nature of non-adherence and the effectiveness of strategies to help patients overcome it would flourish. On the contrary, the literature concerning interventions to improve adherence with medications remains far from robust. Compared with the many thousands of trials for individual drugs and treatments, only a few relatively rigorous trials of adherence interventions exist and these studies provide limited information about how medication adherence can be improved consistently using the resources usually available in the clinical settings.[75]

At the same time, there has been inadequate funding from the NIH for research on the causes of non-adherence and the interventions needed to improve adherence across types of health-care professions, settings, interventions, and persons of varying educational, economic, and ethnic backgrounds. Policymakers must re-examine how research on patient adherence is addressed within NIH with the goal of significantly increasing funding for research on interventions to improve adherence. While the creation of the Adherence Research Network is a good start, now is the time to invest in adherence research to identify behaviorally sound multi-focal interventions across diseases and in different service delivery environments.

Advancing Adherence:
A National Action Agenda

10 PRIORITIES FOR ACTION

Mounting evidence shows that poor medication adherence is pervasive and costly. The problem affects all ages, both genders and people of all socioeconomic levels. Non-adherence is particularly important for patients with chronic conditions as it leads to unnecessary disease complications, reduced functional abilities, a lower quality of life and too often, premature death.

Because of the nature and extent of this challenge, NCPIE has described non-adherence as America's "*other drug problem.*" NCPIE, along with NIH, WHO, and numerous voluntary health and professional societies around the world, has contributed a new understanding about the importance of adherence for successful treatment. The consensus of all stakeholders is that interventions that improve patient adherence enhance health status and reduce health care costs.

But this consensus is only the beginning of what is needed to address the problem of patient nonadherence. Adherence problems have been generally overlooked as a serious public health issue and, as a result, have received little direct, systematic, or sustained intervention. Moreover, Americans have inadequate knowledge about the significance of medication adherence as a critical element of their improved health. Thus, a major, sustained public education effort is required to educate people before they become ill, to prepare them to respond positively to adherence information when faced with a condition requiring medication.

Because the stakes are so high, NCPIE has become a convener and catalyst for promoting a dialogue on new ways to advance patient medication adherence across the continuum of care -- from diagnosis through treatment and follow-up patient care and monitoring. Accordingly, NCPIE convened a panel of experts to create consensus on ten national priorities that may have the greatest impact on improving the state of patient adherence in the U.S. Ultimately involving the support and active participation of many stakeholders -- the federal government, state and local government agencies, professional societies and health care practitioners, health educators, and patient advocates -- this platform calls for action in the following areas:

1. **Elevate patient adherence as a critical health care issue.**
   Medication non-adherence is a problem that applies to all chronic disease states; affects all demographic and socio-economic strata; diminishes the ability to treat diabetes, heart disease, cancer, asthma, and many other diseases; and results in suffering, death, and sub-optimal utilization of health care resources. Despite this impact, patient adherence is not on the radar screen of policy makers and many health professionals, which has meant inconsistent government policies and a lack of resources for research, education, and professional development. Until health care policy makers, practitioners and other stakeholders recognize the extent of non-adherence, its cost, and its contribution to negative health outcomes, this problem will not be solved.

2. **Agree on a common adherence terminology that will unite all stakeholders.**
   Today, a number of common terms -- compliance, adherence, persistence, and concordance -- are used to define the act of seeking medical attention, filling prescriptions and taking medicines appropriately. Because these terms reflect different views about the relationship between the patient and the health care provider, confusion about the language

used to describe a patient's medication-taking behavior impedes an informed discussion about compliance issues. Therefore, the public health community should endeavor to reach agreement on standard terminology that will unite stakeholders around the common goal of improving the self-administration of treatments to promote better health outcomes.

3. **Create a public/private partnership to mount a unified national education campaign to make patient adherence a national health priority.**
To motivate patients and practitioners to take steps to improve medication adherence, there must be compelling and actionable messages as part of a unified and sustained public education campaign. A foremost priority is creating the means by which government agencies, professional societies, non-profit consumer groups, voluntary health organizations and industry sectors can work together to reach public and professional audiences on a sustained basis. Although NCPIE and a number of government agencies, professional societies and voluntary health organizations are promoting information about medication adherence, there also needs to be a national clearinghouse, serving as the catalyst and convener so that all stakeholders can speak with one voice about the need for improving patient adherence. NCPIE, a professional society, or an academic institution could manage this clearinghouse effectively.

4. **Establish a multidisciplinary approach to compliance education and management.**
There is a growing recognition that a multidisciplinary approach to medication taking behavior is necessary for patient adherence to be sustained. This has led NCPIE to promote -- the "Medication Education Team" -- in which the patient and all members of the patient's health care team work together to treat the patient's condition, while recognizing the patient's key role at the center of the process. Looking to the future, this model has the potential to improve adherence rates significantly by changing the interaction between patients and clinicians and by engaging all parties throughout the continuum of care.

5. **Immediately implement professional training and increase the funding for professional education on patient medication adherence.**
Today's practitioners need hands-on information about adherence management to use in real-world settings. This need comes at a time when a solid base of research already exists about the steps physicians and other prescribers, pharmacists, and other health care practitioners can take to help patients improve their medication taking behavior. Professional societies and recognized medical sub-specialty organizations should immediately apply these research findings into professional education through continuing education courses as well as lecture series on patient adherence issues.

6. **Address the barriers to patient adherence for patients with low health literacy.**
Low health literacy and limited English proficiency are major barriers to adherence and deserve special consideration. Thus, an important target for patient-tailored interventions are the 90 million Americans who have difficulty reading, understanding and acting upon health information. Accordingly, advocates recommend widespread adoption of existing tools, such as the Rapid Estimate of Adult Literacy in Medicine Revised (REALM-R), validated pictograms designed to convey medication instructions, and specific patient education programs that promote and validate effective oral communication between health care providers and patients supported by the provision of adjunctive useful information in its most useful

format to address the patient's individual capabilities.

7. **Create the means to share information about best practices in adherence education and management.**
Today, stakeholders have access to more than 30 years of research measuring the outcomes and value of adherence interventions. Building on this foundation, a critical next step is for the federal government -- through the Adherence Research Network -- to begin collecting data on best practices in the assessment of patient readiness, medication management and adherence interventions, incentives that produce quality outcomes from adherence interventions, and measurement tools so that this information can be quantified and shared across specialties and health care facilities. Just as federal and state registries collect and share necessary data on different disease states, a shared knowledge base regarding systems change, new technologies, and model programs for evaluating and educating patients about adherence will significantly improve the standard of compliance education and management.

8. **Develop a curriculum on medication adherence for use in medical schools and allied health care institutions.**
Lack of awareness among clinicians about basic adherence management principles remains a major reason that adherence has not advanced in this country. To change this situation will require institutionalizing a curriculum at medical, nursing, pharmacy and dental schools as well as courses for faculty members that focus on the adherence advancement and execution of medication-related problem solving. Moreover, once these courses are developed, it will be important for academic centers to elevate patient adherence as a core competency by mandating that course work in this area be a requirement for graduation.

9. **Seek regulatory changes to remove road-blocks for adherence assistance programs.**
Improved adherence to medication regimens is predicated on supportive government policies. Unfortunately, a number of federal and state laws and policies now limit the availability of adherence assistance programs. Accordingly, language in these federal and state laws that limits communications to patients about medication adherence must be identified for lawmakers and regulators to resolve. Key issues to be addressed include clarifying that education and refill reminder communications fall within the scope of the federal anti-kickback statute, and ensuring that federal and state laws related to patient privacy and the use of prescription data do not unduly limit the ability of pharmacies to communicate with patients about the importance of adhering to their prescribed courses of therapy.

10. **Increase the federal budget and stimulate rigorous research on medication adherence.**
Although the National Institutes of Health has put in place the Adherence Research Network to identify research opportunities at its 18 Institutes and Centers, the actual NIH dollars earmarked for testing interventions to improve medication taking behavior was only $3 million in a budget of nearly $18 billion in 2000, the latest date available. Thus, it will be important for stakeholders to advocate for NIH to significantly increase the proportion of its research funding to test adherence interventions and measure their effectiveness. Even if NIH triples its 2000 commitment, the small amount spent on patient adherence will still signal that the issue is a critical area for new research efforts.

THE TIME IS NOW

Creating a public policy agenda that elevates patient non-adherence as a priority concern is essential to reduce the adverse health outcomes and economic consequences associated with this pervasive problem. Improving how and when patients take their medicines is a complex challenge, requiring changes in the knowledge, attitudes, and skills of patients, health professionals, and policy-makers alike. While no single strategy will guarantee that patients fill their prescriptions and take their medicines as prescribed, it is hoped that the priorities identified in this report will serve as a catalyst for action and offer realistic goals for improving the standard of medication adherence through research, education, and policy changes.

Now is the time to improve patient care, recognizing the importance of medication adherence, and providing the resources and attention that are required.

Table 1

MAJOR PREDICTORS OF POOR ADHERENCE TO MEDICATION ACCORDING TO STUDIES OF PREDICTORS

Predictor:	**Presence of psychological problems, particularly depression**
Study:	vanServelien et al., Ammassari et al., Stilley et al.
Predictor:	**Presence of cognitive impairment**
Study:	Stilley et al., Kino et al.
Predictor:	**Treatment of asymptomatic disease**
Study:	Sewitch et al.
Predictor:	**Inadequate follow-up or discharge planning.**
Study:	Sewitch et al., Lacro et al.
Predictor:	**Side effects of medication**
Study:	van Servellen et al.
Predictor:	**Patient's lack of belief in benefit of treatment**
Study:	Okuno et al., Lacro et al.
Predictor:	**Patient's lack of insight into the illness**
Study:	Lacro et al., Perkins
Predictor:	**Poor provider-patient relationship**
Study:	Okuno et al., Lacro et al.
Predictor:	**Presence of barriers to care or medications**
Study:	van Servellen et al., Perkins
Predictor:	**Missed appointments**
Study:	Servellen et al., Farley et al.
Predictor:	**Complexity of treatment**
Study:	Ammassari et al
Predictor:	**Cost of medication, copayment, or both**
Study:	Balkrishnan, Ellis et al.

(Source: N Engl J Med 353:5 www.nejm.org August 4, 2005, page 491)

Table 2

STRATEGIES FOR IMPROVING ADHERENCE TO A MEDICATION REGIMEN*

+ Identify poor adherence
  - Look for markers of nonadherence: missed appoint¬ments ("no-shows")
  - Lack of response to medi¬cation, missed refills
  - Ask about barriers to adherence without being con¬frontational
+ Emphasize the value of the regimen and the effect of adherence
+ Elicit patient's feelings about his or her ability to follow the regimen, and if necessary, design supports to promote adherence
+ Provide simple, clear instructions and simplify the reg¬imen as much as possible
+ Encourage the use of a medication-taking system
+ Listen to the patient, and customize the regimen in accordance with the patient's wishes
+ Obtain the help from family members, friends, and community services when needed
+ Reinforce desirable behavior and results when appropriate
+ Consider more "forgiving"** medications when adherence appears unlikely
  - Medications with long half-lives
  - Depot (extended-release) medications
  - Transdermal medications

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* Information in this table was adapted from Osterberg and Rudd (Osterberg, LG, Rudd, P. Medication Adherence for Antihypertensive Therapy. In: Oparil S, Weber MA, eds. Hypertension: a comparison to Brenner and Rector's The Kidney. 2nd ed. Philadelphia: Elsevier Mosby, 2005:848

** Forgiving medications are drugs whose efficacy will not be affected by delayed or missed doses.

(Source: N Engl J Med 353:5 www.nejm.org August 4, 2005, page 493)

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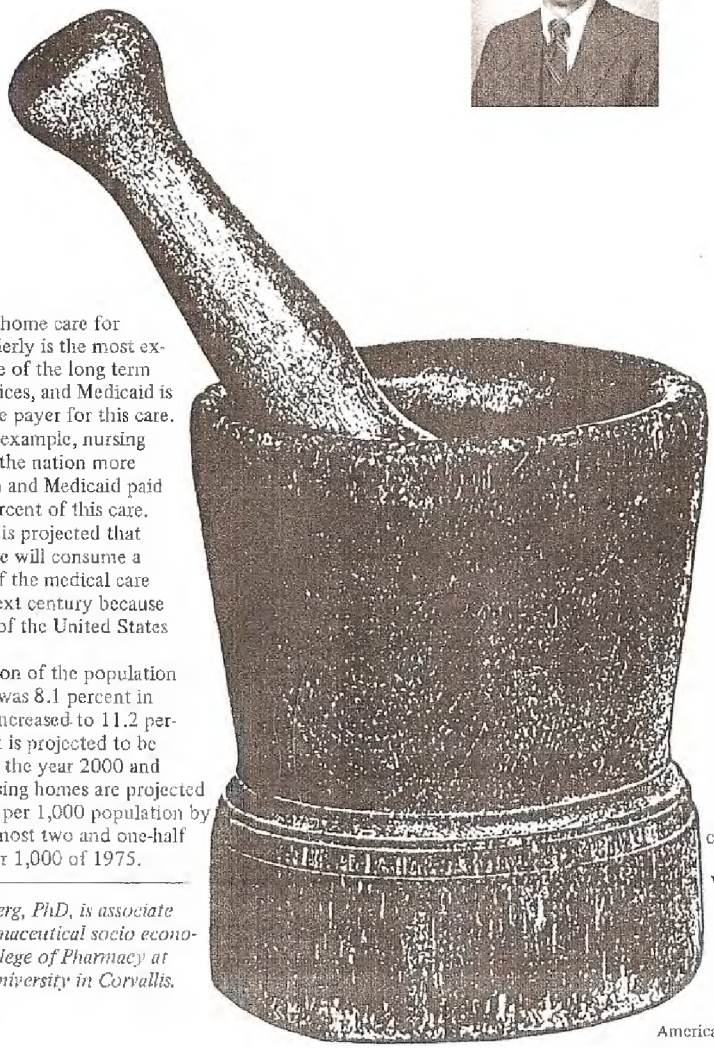
Drugs as a Reason for Nursing Home Admissions

Lee R. Strandberg



Nursing home care for the elderly is the most expensive of the long term health care services, and Medicaid is the largest single payer for this care.

In 1981, for example, nursing home care cost the nation more than $24 billion and Medicaid paid for about 45 percent of this care. Additionally, it is projected that institutional care will consume a growing share of the medical care budget in the next century because the population of the United States is aging.

The proportion of the population age 65 or older was 8.1 percent in 1950 and had increased to 11.2 percent by 1980. It is projected to be 12.2 percent by the year 2000 and residents in nursing homes are projected to number 12.8 per 1,000 population by 2050. This is almost two and one-half times the 5.4 per 1,000 of 1975.

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Drugs and the Elderly

An increasing body of information indicates that inappropriate drug therapy represents a significant problem for older persons. A major reason for the susceptibility of the elderly to drug-related problems is the difference in the amounts and types of drugs consumed, compared to the non-elderly population.

While those 65 and older comprise 11 percent of the U.S. population, they purchase approximately 25 percent of all prescription and non-prescription drugs sold. The elderly tend to require more medications than younger persons for the proper management of acute disease, as well as the increased occurrences of chronic disease patterns.

Of those elderly surveyed by Venner, there were over five chronic disorders per person, most commonly arthritis, high blood pressure, allergies, and cardiovascular disease. Older persons are generally

less physically tolerant of most drugs. They are less capable of metabolizing drugs, and more susceptible to side effects and interactional effects. As a result, they often require a dosage appropriate for geriatric physiology.

Various studies have sought to determine the number of medications taken by older persons. Estimates of prescription drug use by elderly persons residing in their own homes range from an average of 2 to 4 prescription drugs per person, though many receive similar numbers and types of medications as those in nursing homes.

Eberhardt found prescription medication usage among residents of a geriatric apartment complex to be 3.9 drugs per person, the highest figure of these studies. Two studies of elderly community residents showed mean numbers of prescription drugs per person to be 3.4 for those 65 and older, and 2.0 for those 60 and older.

About two-thirds of all elderly surveyed by Venner used at least one prescription drug. A larger random sample of elderly in Ontario was surveyed by Cape, with a mean of 1.6 prescription drugs per person.

In addition to prescription drugs, the elderly use high numbers of over-the-counter drugs, with the average number per person ranging from 1.8 to 3.0. Including prescription, over-the-counter, and social drugs (such as alcohol), 55 percent of elderly persons surveyed use three to five drugs, and 22 percent consume six or more drugs.

Many older patients continue to take drugs while not under regular medical supervision; studies show that from 15 to 24 percent of those elderly surveyed had not visited a physician during the previous 12 months. Other elders visit several different physicians during the year.

It is not unusual for more than one physician to prescribe medications for the older person, especially when there are multiple disease conditions. To the extent that physicians are unaware of the patient's existing drug therapy, the patient may end up with therapeutically incompatible drugs or synergistic drugs, or he may take two drugs with identical ingredients.

The older person is frequently unsure of the purpose, proper dosage and schedule of administration for prescribed medications, and may be unaware that certain medications are affected by food, caffeine, alcoholic beverages, or common over-the-counter drugs such as aspirin or antacids. In addition, older persons may be reluctant to ask their doctors for detailed instructions and information concerning their drug therapy regimen.

In one study of 55 persons 65 and older, none had received adequate information or instructions for the safe use of prescription medications. The inadequacies of physician instructions included the lack of: warnings about the addictive potential of the drug, withdrawal procedures, warnings against concurrent use of specific other drugs, proper identification of the medication, specific directions about taking with or between meals, and specific times to take the medication.

In this study, 25 percent of respondents said that they were not taking their medications as labeled, often because of verbal instructions from the physician changing the directions for use, or because they felt they needed fewer doses.

An assumption is often made that the patient living at home will follow the prescribed therapeutic regimen. Studies have shown that from 25 to 90 percent of outpatients make errors in self-administration of their medications.

Two studies of the elderly, one of persons living in the community, and the other of a self-administration test in a hospital setting, indicated that 25 percent of these persons made errors in using their medications.

Of two hospital outpatient studies, 59 percent and 57.9 percent of elderly outpatients made errors, compared to 42.8 percent of the total outpatient population making errors. Errors may be higher for some populations, as two studies of hospital outpatients showed 90 percent of all participants making some medications errors.

Schwartz determined that 59 percent of elderly outpatients made some error in self-administration, while 26 percent made errors which might have been potentially serious effects on the patient's health.

Among this group, patients averaged 2.3 serious errors a piece, defined as taking a medication not prescribed for the patient, not taking a prescribed medication, taking incorrect doses, taking medication at the wrong times, or without understanding of the medication's purpose.

The only factors which seem to consistently correlate with the tendency to make errors are the patient's age and the number of medications taken, though living alone also tends to increase the likelihood of errors for elderly patients.

Latiolias and Berry identified increased age as a factor in error making, with 57.9 percent of those 60 years or older misusing their medications, compared to 42.8 percent of those under 60.

Over twice as many elderly misused their medications as used them correctly. In addition, it seems that the "older old" have increased problems. Schwartz determined that while 57 percent of elderly from age 60 to 74 made medication errors, 68 percent of those 75 or older made errors.

The total number of prescriptions used also influenced the ability of patients to comply with the drug regimen. Latiolias and Berry determined that the prescription per patient ratio for those misusing their drugs was 2.7, as compared to 1.8 for those using their drugs correctly.

Malahy found a significant correlation between total number of medications taken and number of errors made.

The types of errors most frequently made by outpatients vary from one study to another. Most often cited are errors of overdosage, from taking more than the prescribed dosage or taking the

same drug from two or more bottles, and omission of doses.

Other common errors are taking the drugs at the wrong time, or in the wrong sequence, taking discontinued medications, or using another person's prescription medications.

Interviews of 383 community seniors in Michigan showed that one-fourth of the elderly use four or more prescription drugs. One-third of those interviewed had discontinued the medication early, varied the dosage, or not filled the prescription. Twenty percent had shared medications with others, and over 30 percent were saving old prescriptions.

Pharmacists, nurses and service providers surveyed felt that over 20 percent of their clients overused medications. Over half of the seniors had not discussed interactions of foods or other medications when given a new drug.

Other in-home interviews have revealed that up to 23.6 percent of patients do not know the purpose of the medications they are taking, and that 21 or 22 percent were taking one or more medications which were not currently prescribed.

In addition, persons with difficulty in coping with the environment are also likely to make potentially serious medication errors.

Another viewpoint regarding noncompliance by the elderly has been expressed which relates to assessing the patient's ability to adhere to the medication regimen. The elderly patient often has a number of problems that must be managed with multiple drug therapy. This necessitates an approach geared to more than the simple medical needs of the patient.

What is needed is a careful titration of the patient's ability to adhere to and to tolerate the effects of the proposed therapeutic regimen, coupled with his demographic and lifestyle factors.

The Drug Distribution System

A study funded by the Health Care Financing Administration and conducted by the state of Oregon's Senior Services Division in 1981, found inability to manage medication consumption to be a major cause of nursing home admissions. The agency developed an instrument which assessed geriatric patients' capabilities in a number of areas such as vision, mobility, bathing, continence, etc., in addition to medication management.

The "Placement Information Base" (PIB) assessment tool found that only three percent of the elderly who were living at home alone had a problem with medication management. However, the percentages rise dramatically as the patient moves through the levels of care.

At home with a spouse or others, the figure was 16 percent; in foster homes, it was 43 percent and 90 percent of nursing home residents were at five, the highest level on the PIB scale.

Five on the PIB scale for medication management is, "Does not manage own medications, needs to have some medication administered to him/her by someone else regularly, and daily or more frequently."

Additional analysis of the data indicated that 24 percent of the nursing home residents had no other fours or fives on the remaining 24 PIB factors. It is felt that some of these residents could be living at home if the community drug distribution system used by the elderly were designed to meet their needs.

A Possible Solution

Patient problems such as forgetting to take a dose or taking excessive doses can lead to unnecessary physician, hospital or nursing home admissions. As a possible solution, community pharmacies should dispense medications to selected geriatric patients using a 31 day card system, coupled with drug therapy review and home delivery to those in need of that service.

Candidates for this higher level of service could be identified by family, friends or pharmacists, nurses and physicians using screening criteria such as that put forth by Fedder.

Our country can not afford, economically or humanely, to continue placing large numbers of the elderly into nursing homes. The time has come to look at another cause of this problem and not merely the symptoms such as drug overuse, underuse or compliance.

It is quite possible that the outpatient drug distribution system used by the elderly is one the major reasons they can't remain as outpatients. If the health care system is to continue providing, or at least trying to provide, top notch health care to an aging and aged population, some changes should be made.

It is time to apply the well documented and effective inpatient nursing home pharmacy procedures to the outpatient geriatric population. ■

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MEDICATION NONCOMPLIANCE

$20.00

NONCOMPLIANCE WITH MEDICATIONS

AN ECONOMIC TRAGEDY WITH IMPORTANT IMPLICATIONS FOR HEALTH CARE REFORM

Although pharmaceutical therapy accounts for only about five percent of our total national health care expenditures, **better use of medications by patients can realistically result in clinical savings that amount to more than the original cost of the drugs.**

Accordingly, a major focus of health care reform proposals should be **improving quality control in the prescribing, dispensing** and taking of medicines. **Mobilizing patients' responsibility for their own pharmaceutical care is key** to improving compliance with medication regimens and managing costs systemwide.

A REPORT BY
THE TASK FORCE FOR COMPLIANCE

November 1993
Revised April 1994

Executive Summary

Patients' failure to take prescribed medications correctly is pervasive and often results in any of three negative effects on their health status. Patients may fail to improve, worsen, or relapse, and each effect has a negative economic impact on the entire healthcare system. Recent surveys on the issue of noncompliance have found that patients often fail to have their prescriptions filled and often discontinue their medication too soon. The consequence of these behaviors is a multi-billion dollar burden on the American economy. Costs of hospitalization and physician visits caused by relapse from noncompliance account for $8.5 billion in otherwise unnecessary spending. Research on other effects of noncompliance, such as lost work days, also reveals huge, but largely hidden, costs to multiple systems—including manufacturing costs.

Although pharmaceutical therapy accounts for five percent of the $900 billion spent on U.S. healthcare, noncompliance accounts for up to $100 billion in health care and productivity costs. A concerted effort to increase patient compliance can result in significant savings to the U.S. economy. From this economic perspective, it is important that health care reform proposals include programs designed to improve patient compliance with medications.

Recent research indicates that healthcare delivery and reimbursement systems will benefit when patients receive information on the rationale and importance of drug therapy and effective instruction on its use. As changes in healthcare policy are considered, the patient's responsibility for taking medication appropriately and for treatment outcomes should be addressed.

The March 25, 1992 edition of the *Wall Street Journal* reported the efforts of two pharmaceutical companies (ICI Pharmaceuticals and Searle) to improve the compliance rate of patients taking some of the companies' leading prescription products. These efforts, which include such tactics as regular phone calls to remind patients about refills, newsletters to users, and a toll-free number for patients' inquiries, are costly, but the investment has an enormous potential to improve health care and reduce overall costs. The costs of noncompliance with medication regimens are tremendous and affect all players in the health care system—manufacturers, pharmacies, employers, third-party/managed care programs, society as a whole, and, of course, patients and their families.

Failure to take prescribed medications correctly is pervasive, and may have any of at least three negative medical (and attendant economic) effects. The patient may fail to improve, worsen, or (especially in long-term therapy) relapse. In a recent comprehensive review, for example, Turk and Rudy (1991) found a clear relationship between noncompliance with medications and relapse in patients with arthritis, various types of pain, and severe headache.

A Case in Point

An advertisement appearing in the spring of 1992 shows a physician observing, "When my patients don't return, I assume the therapy is working." On the facing page, one of those patients says: "I couldn't tell my doctor his migraine therapy didn't work." The text of the ad cites data indicating that nearly half of all migraine sufferers have given up on their physicians either because of failure to improve or because of side effects of the medication prescribed. This example illustrates the complexity, subtlety, and importance of the compliance problem. The potential consequences of this particular situation with migraine include:

- Physician misjudgment of the effectiveness of his/her therapy, in this case probably resulting in repeats of this scenario with the next medication prescribed for this patient;

- Loss of confidence by the patient in the effectiveness of medications and perhaps in the skill of the physician;

- Continued migraine attacks with continued erosion of the quality of life of the patient;

- Loss of patient productivity (One estimate, cited in the ad, found that annual lost productivity from migraine attacks fell in the $6 to $17 billion range.);

- Cost of other therapies, including over-the-counter medicines, used by the patient to "try to cope," but to no avail.

This report provides some background on the economics of noncompliance with medication regimens and strategies that can be used to improve compliance.

The Problem

Although medicines comprise only about five percent of our total national health care expenditures, their appropriate use by patients can result in substantial savings by reducing the need for more expensive medical treatment. Unfortunately, medications are not generally taken properly. Patients miss doses, stop taking medication prematurely, misunderstand instructions, and swap medications with friends and relatives. The five most common types of noncompliance are:

1. not having the prescription filled;
2. taking an incorrect dose;
3. taking the medicine at the wrong times;
4. forgetting to take one or more doses; and
5. stopping the medication too soon (Burrell & Levy, 1985).

This behavior has important therapeutic consequences and often results in the failure to control the symptoms and progress of the disease. Noncompliance with medications is especially problematic in chronic diseases that are not associated with any symptoms and in diseases in which the symptoms occur erratically (e.g., mental disorders, cardiovascular diseases, asthma, glaucoma, osteoporosis, and epilepsy).

Noncompliance is common in patients of all ages and across a wide range of diseases. There is generally no correlation with age, sex, socioeconomic status, or level of education.

A recent study of "The Forgetful Patient" by Schering Laboratories (The Schering Report IX, 1987) revealed the following patterns of noncompliance:

- Seven percent of patients did not have their prescriptions filled.

- Fifteen percent of patients admitted to discontinuing their medication too soon.
- Thirty-two percent of patients, told by their doctors to have their prescriptions refilled, failed to do so.

Even those patients who fill and refill their prescriptions appropriately may have lapses in the continuity of their dosing pattern. Many patients take what has been termed "drug holidays"—two-to four-day interruptions in dosing. These holidays are responsible for breakthrough seizures in epileptic patients and for unwanted conception in patients using oral contraceptives (Dirks and Kinsman, 1982).

One in five patients who receives a prescription medication cannot read the label. Some 20 million American adults are illiterate and another 20 million are functionally illiterate to the extent that they cannot comprehend the information. The elderly are particularly likely to have difficulty in reading, in that they tend to have impaired vision and often cannot distinguish the print and certain colors on prescription labels. The elderly are also more likely to have more serious illnesses and must often take multiple medications.

The problem of noncompliance will escalate as the number of elderly persons increases. Currently, one out of every four prescriptions written is for a person who is 65 years of age or older. Diseases of the elderly tend to be chronic, and noncompliance with treatment regimens is more of a problem in chronic as opposed to acute conditions.

Failure to Fill Prescriptions

One important aspect of noncompliance is the failure to fill or refill prescriptions. Nearly 30 years ago, Hammel and Williams (1964) reported that 3.3% of patients never filled newly issued prescriptions. In 1975, Taubman et al., using triplicate prescription forms to track filling behavior, found that approximately 6% of new prescriptions issued were never filled.

The refilling of prescriptions for chronic diseases (e.g., heart conditions, arthritis, asthma) is also a problem. Refilling prescriptions is especially important for the elderly, who, since their diseases tend to be chronic, receive refill authorizations at more than twice the rate of younger persons. Refill noncompliance is also important for other (nonelderly) patients needing chronic medications.

For example, Elixhauser et al. (1990) found, for patients with depression, that less than 70% of authorized lithium prescription refills were obtained between the first and second office visits. The dropoff rate for refilling prescriptions for chronic diseases may reach 75% after one year. Typically, hypertensive patients refill only about 60% of their yearly prescriptions.

A 1988 study of pharmacy services conducted by the Upjohn Company reported that nearly one out of five (19%) consumers interviewed said that at least once in the previous 12 months they had received a prescription and had not filled it. Figure 1 shows the reasons they gave for not filling the prescription. Three-fourths of the time, they either felt they did not need the medicine or did not want it. Similar reasons for not filling prescriptions were given by respondents in a survey by the American Association of Retired Persons (AARP, 1992, Figure 1).

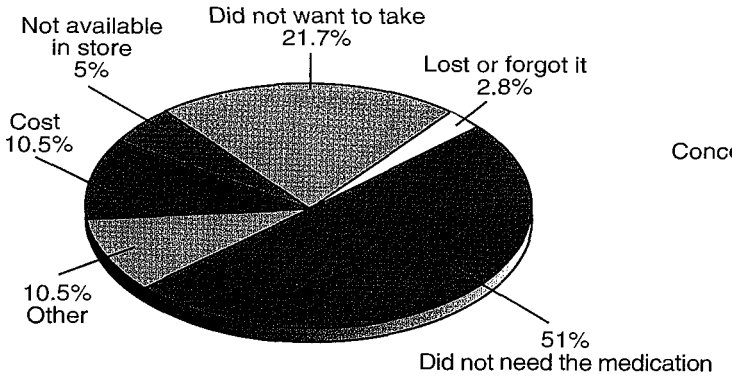
Logic suggests that the cost of the medication might be a factor in failure to fill prescriptions. But in the Upjohn survey only 10.5% of the respondents mentioned cost as a factor in their failure to have a prescription filled. Similarly, in the AARP survey only 14% of elderly respondents who did not fill a prescription cited cost as a reason. Among those who reported that they stopped taking the drug before it ran out or consumed less than the prescribed dose, only 2-4% cited cost as a factor (AARP, 1992). Overall, among the four types of noncompliance reported (failure to fill, failure to take after filling, stopping medication before it ran out, taking less than prescribed dose), cost was given as a reason by only 7% of respondents (AARP, 1992).

Studies of the effect of patient cost sharing have shed some light on the degree to which cost is a deterrent to prescription filling. In these studies patients were required to "copay" out-of-pocket part of the cost of the medication. In one study (Harris et al., 1990), prescriptions filled by employed HMO patients were subjected to two successive, small copayments of $1.50 and $3.00 over a three-year period. This resulted in a 21% reduction in prescription fills, but mostly for drugs used for symptomatic relief (e.g., pain killers, cough and cold preparations, muscle relaxants). Prescription filling rates for drugs with important effects on health status (e.g., for high blood pressure, heart conditions, diabetes) were reduced to a far lesser extent.

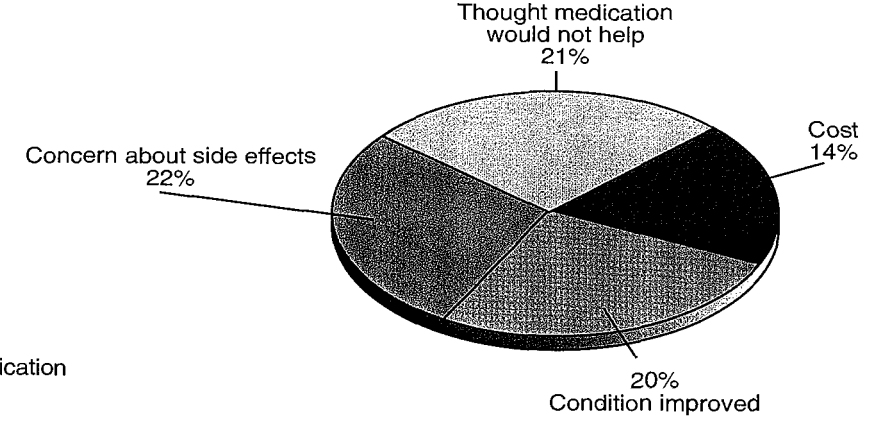
Cost sharing is likely to represent a greater disincentive to fill a prescription for economically disadvantaged persons. Imposition of a small copay ($0.50) on South Carolina Medicaid patients reduced prescription filling rates for important medications, such as cardiovascular and psychotherapeutic drugs (Reeder and Nelson, 1985). But in New Hampshire, a $1.00 copay caused only a minimal reduction in prescription filling by Medicaid patients (Soumerai et al., 1987). These studies suggest that cost may be a significant deterrent to filling prescriptions by our poorest populations.

Figure 1.
Why Prescriptions Are Not Filled

Upjohn Survey



AARP Survey



Note: Multiple responses allowed

Important areas for future research on prescription filling behavior include efforts to determine:

- Relationships between prescription filling and cost for different diseases, severity of disease, and socioeconomic status;
- The extent to which different levels of patient copayment for prescriptions (cost sharing) in third-party programs influences filling rates;
- The effect of triplicate prescription forms for benzodiazepines (tranquilizers) on prescription-filling behavior.

Underuse and Overuse of Medicines

There are literally hundreds of reports describing poor compliance among patients with various medical conditions. Both overmedication and undermedication are common results of poor compliance. Overmedication may lead to increased adverse effects and increased hospitalization (Schernitzki et al., 1980). Undermedication may lead to inadequate treatment of the disease, resulting in complications, an increase in the severity of the disease, and hospitalization or re-hospitalization. The data in Table 1 indicate the relative frequency of overmedication compared to undermedication, collected in several studies. The differences in relative frequencies of over- and undermedication among the three studies cited in Table 1 may reflect differences in sample populations and methodologies. Nevertheless, the data suggest that both overcompliance and undercompliance are common.

Table 1.
Proportion of Overuse to Underuse of Prescribed Medicines

	Latiolias & Berry (1969)	Malahy (1966)	Leroy & Morse (1978) Ages 65+	Ages 0-64
Overuse/ Underuse	1.7	0.36	0.75	0.45

Values over 1.0 indicate overuse exceeds underuse; values under 1.0 indicate underuse exceeds overuse. The data of Latiolias & Barry and Malahy is from outpatient populations; the data of Leroy & Morse is from drug-related hospital admissions of Medicaid patients.

A sampling of medication compliance rates for chronic conditions is shown in Table 2. In all of these studies, the noncompliance behavior studied was *under*compliance, i.e., the process of taking a medication at a level or for a duration less than that intended by the prescriber. *Over*use of prescription medications (sometimes called hypercompliance) has a cost as well. This can take the form of expenditures for prescription medication not really needed or an increased incidence of side effects and adverse reactions. It is equally important to correct both underuse and overuse of medications; **best** use is the goal.

Table 2.
Rates and Possible Consequences of Noncompliance with Medication Regimens for Important Conditions

Condition	*Rate of Noncompliance*	*Possible Consequences*	*Reference*
Epilepsy	30-50%	Relapse	Leppik (1990)
Arthritis	55-71%	Condition worsens	Bloom (1988)
Hypertension	40%	Hospitalization	Clark (1991)
Diabetes	40-50%	Loss of control	Nagasawa et al. (1989)
Contraception (Pill)	8%	Unwanted pregnancy	Jones & Forrest (1992)
Asthma	20%	Attacks, hospitalization (?)	Bauman et al. (1989)
Alcoholism	48-56%	Relapse, hospitalization	Powell et al. (1986)
Organ Transplant	18%	Rejection, death	Rovelli et al. (1989)
Anticoagulants	30%	Bleeding, hospitalization	Joglekar et al. (1988)
Estrogen deficiency	57%	Symptoms, osteoporosis	Hemminki et al. (1991)

Economics of Noncompliance

There is no shortage of opinion on the economic effects of failure to fill or to refill prescriptions. The *Wall Street Journal* article cited above noted a cost of $8.5 billion for increased hospital admissions and physician visits. The problem exists in other countries as well. Lauper (1988), for example, imputes a DM $2-3 billion economic loss due to drugs not taken in the Federal Republic of Germany. The *exact* costs, direct and indirect, of compliance failures cannot be calculated. Some components of the total, however, have been estimated.

The economic value of a medicine is closely related to the ease with which patients can comply with the dosing regimen. A more expensive drug can be more useful than a cheaper drug if compliance is better. Worthen (1979) described the construct of a "usefulness product" in a study of the use of timolol in glaucoma patients. Worthen's premise is simple but basic and can be shown by his example: "... if the drug's effectiveness is 90% (i.e., works 90% of the time) but the patient's compliance is only 50%, we can say that the `usefulness product' of that medication is 45%."

Worthen's procedure can be valuable in drug comparisons. In his own experience, for example, inexpensive epinephrine is 70% effective, but over time, compliance may be as low as 30%, for a usefulness product of 20-30%. Timolol is more expensive and is only 10% more effective than epinephrine, but it had a compliance rate of about 95%. This results in a usefulness product of more than 75%, or 3.5 times that of the less expensive drug.

Economic Effects of Failure to Fill or Refill Prescriptions

The number of prescriptions dispensed annually in the United States is likely to exceed 2 billion by the year 2,000, although that number would be much higher but for the phenomenon of unfilled/unclaimed prescriptions. Recent statistics suggest that sales consist of about an equal number of new versus refill prescriptions, although these proportions vary significantly by therapeutic class. As the population continues to age and chronic diseases become more prevalent, refills will predominate. Thus, failure to refill will become an increasingly important health and economic problem.

Economic Impact on Retail Pharmacy and Pharmaceutical Manufacturers

If only 20% of all written prescriptions were never filled or refilled, the resulting economic effect would be a loss of more than 400 million prescriptions. The economic impact on the retail pharmacy business is considerable:

- At a $20 average prescription charge, the gross revenues lost to pharmacy would be $8 billion.
- Using only a $4 dispensing fee, pharmacies would still be missing $1.6 billion in revenues with no associated cost of goods sold. That is more than $30,000 in fees per pharmacy per year.

Fedder (1990) studied the fate of some 120,000 prescriptions in just **five** pharmacies. He found that 77% of authorized refills were never activated—a projected annual loss of $1.5 million!

The Schering Report (1992), based on 2,000 consumer interviews, estimated that failure to fill prescriptions results in "a shortfall at the pharmacy counter of about 140 million prescriptions worth $2.8 billion." These estimates are based on reports by 8.7% of those interviewed that they failed to have initial prescriptions filled.

All of the losses cited above for pharmacy (aside from the dispensing fee) are also felt by pharmaceutical companies.

Economic Effects of Noncompliance in Clinical Trials

The effects of noncompliance during clinical trials of a drug in development have only recently begun to receive appropriate attention. Noncompliance in this situation has long-range consequences far beyond the few hundred patients who might be involved in the trial. To the degree that noncompliance occurs without a correction factor, it may have effects ranging from failure to gain FDA approval at all to the necessity to increase the recommended dose beyond that which would be required of a fully compliant population. Ironically, an elevated dose may cause a higher incidence of side effects, which may lead to noncompliance.

Urquhart and Chevalley note that "drug trials rarely show the effects of poor compliance, and so reveal average-compliance efficacy." They describe the phenomenon of "patient-initiated drug holidays" of three or more days during chronic therapy. These holidays, which the authors suggest also occur during clinical trials, are believed to result in added medical costs equal to or greater than the procurement costs of the drugs themselves. Of special interest in this paper is the description of the case of cholestyramine (for high cholesterol), which, because of careful planning in clinical trials, was allowed to be relabeled to reflect the efficacy of the drug in cases of full compliance.

Noncompliance Results in Excess Hospital Admissions

Nonfederal hospital costs in the United States now exceed $225 billion. If only 10% of hospital admissions could be traced to noncompliance, the cost would be $25 billion. The following studies provide evidence that the impact of noncompliance on hospital costs is at least this great.

- McEvoy et al. (1984) compared groups of noncompliant and compliant relapsed—and therefore hospitalized—schizophrenic patients. The noncompliant patients

were found to have had a gradual onset of the determinant episode, to have been committed involuntarily, and to remain in the hospital longer.

- In an Israeli study, Levy et al. (1982) identified 2.9% of nearly 1,200 hospital admissions as having been principally caused by noncompliance.

- Kelly and Scott (1990) described a project to improve medication compliance among a group of outpatients with chronic mental disorders. Compliance did improve, and at the end of six months, 33% of the better compliers were in the hospital compared with 45% of a control group whose compliance did not improve.

- Col et al. (1990) reviewed the records of and interviewed 315 consecutive elderly patients admitted to an acute-care hospital. They determined that 11.4% of the admissions could be traced directly to some form of noncompliance. Total cost of these admissions was $77,000 ($2,150 each).

- Green (1988) used a retrospective chart review to compare community mental health center patients having three or more hospitalizations in an 18-month period with a matched group of patients without such hospitalizations. Noncompliance with medications was associated with frequent hospitalization in 92% of the patients.

- Maronde et al. (1989) evaluated the association of underutilization of drugs prescribed for the treatment of hypertension and acute-care hospital readmissions. Controlling for demographic factors and blood pressure, the authors concluded that underutilization of antihypertensive drugs may be associated with hospitalization.

- Sullivan et al. (1990) reviewed several studies and estimated that nearly 2 million admissions annually can be traced to noncompliance.

Noncompliance Increases Nursing Home Costs

Some of the most dramatic data on the costs of noncompliance among the elderly come from Oregon. In this study by Strandberg (1984), functional assessment profiles (ability to take care of oneself) of nursing home residents and of people successfully living at home were compared. The single characteristic that best distinguished individuals who were in a nursing home from those who were not was found to be the inability to manage medications. It was more important than the actual health condition. Indeed, 60% of those placed at extreme risk of nursing home

placement had no equally serious impairment other than their inability to manage their own medication. A more conservative view, removing other impairments that were lower on the risk scale, still left nearly 23% who had no high-risk problem other than the inability to manage medications.

Much more research on this issue is urgently needed, but if even 10% of nursing home admissions are related to compliance problems, this represents an annual cost of at least $5 billion (based on a national figure of $50 billion annually for nursing home care).

Table 3.
The Economics of Noncompliance

Negative Economic Effects of Compliance Behaviors

- Morbidity costs associated with noncompliance
- Additional medical treatment
- Need/use of additional medications
- Hospital/nursing home admissions or readmissions
- Absenteeism or reduced productivity at work
- Mortality costs - including direct costs and indirect costs associated with lost earnings
- Overcompliance leading to overspending
- Lost revenues to drug companies and pharmacies

Positive Economic Effects

- Savings associated with undercompliance with overprescribed medications
- Failure to fill or refill third-party prescriptions resulting in savings to payers

Summary of Economic Losses

Some of the economic effects of noncompliance are listed in Table 3. Most of these economic effects are negative, i.e., they add costs to the health care system. An approximation of the overall economic effects of noncompliance is presented in Table 4. There can only be an approximation

at this point because the pharmacoeconomics of noncompliance is as yet poorly developed. Even with these limitations, the results are compelling.

Table 4.
Annual Economic Costs of Noncompliance

	$ Billion
Revenues from unfilled new and refill prescriptions (Retail)	8
Hospital admissions linked to noncompliance	25
Nursing home admissions linked to noncompliance	5
Lost productivity caused by noncompliance	> 50
Premature deaths caused by noncompliance	?
Health costs in ambulatory patients linked to noncompliance	?
Total Costs	**$100 billion plus**

Source: Berg et al., 1993

Detecting and Improving Poor Compliance

Despite the enormity and complexity of the noncompliance problem, numerous studies have suggested remedies that may be actionable in the real world. Additionally, the high cost of non-compliance is beginning to attract the attention of various stakeholders who wish to improve compliance rates. The following sections describe methods for predicting which patients will be poor compliers, and efforts to improve medication compliance on the part of pharmaceutical companies, health professionals, and managed care organizations.

Diagnosis and treatment of noncompliance must be based on sound basic research delineating the characteristics and causes of this condition, and on demonstrations of effective interventions. The situation is analogous to the process of developing medicines to treat diseases; basic science knowledge in physiology, chemistry, and molecular biology of the disease forms a solid platform of information from which drug development proceeds.

The existing basic science in compliance comes from many disciplines—behavioral sciences, pharmacy, social sciences, community health, public health, psychiatry, specialty medicine, and others. Among all these disciplines, thousands of research articles have been written about

medication compliance. But all of this activity has not resulted in the emergence of a coherent basic knowledge platform. Much of the available research on compliance is poorly done and, more importantly, usually does not address the key clinical and economic issues. Essential research questions for determining the value of specific compliance enhancement programs should include:

- Does the intervention result in improved compliance and also in improved clinical outcomes?
- What are the direct and indirect savings resulting from improved compliance?
- Do the overall savings resulting from the compliance-enhancing program exceed the costs of the program?

Noncompliance as a Behavioral Disease

It is useful to conceptualize noncompliance as a behavioral disease. This disease model may be useful in helping to develop effective interventions. When all illnesses and treatments impacted by noncompliance are considered, noncompliance is arguably one of our society's most expensive diseases, with yearly costs totaling over $100 billion (see Table 4).

Noncompliance with medications has many features of a disease, including:

- Various risk factors have been demonstrated;
- Depending on numerous patient- and disease-related variables, noncompliance is associated with important variations in severity, morbidity, and mortality;
- Triage is necessary to identify those patients in greatest need of treatment for noncompliance;
- Iatrogenic (doctor-caused) noncompliance is an important aspect of this "disease," and validated screens are available to identify physicians who need to improve their communication skills;
- Some cases of noncompliance are "curable," but some are probably not;
- Noncompliance is a public health problem and, accordingly, prevention is a goal.

The noncompliance "disease" can be detected by general screening, using validated demographic, sociographic, and psychographic predictors and questionnaires. The behavior of noncompliant patients and iatrogenic physicians, as identified by these means, can be subjected to detailed examination. Differential diagnosis of noncompliant behavior in patients can be performed by computerized monitoring of refill patterns, and more specifically by analysis of daily pill-taking behavior using microelectronic monitoring devices.

Interventions to treat the "disease" of noncompliance, like that of any other illness, must be tailored to the needs and circumstances of the individual patient, and should be based on underlying causes. Specific interventions with validated effectiveness can be selected. Noncompliance with treatment for chronic disease is itself a chronic disease, and needs sustained or periodic attention.

Importantly, interventions to improve compliance must be subjected to cost-benefit analysis to determine whether, and to what extent, the cost savings resulting from improved compliance exceed the costs of the program. Outcomes studies are required to assess the effect of interventions not only on improving compliance behavior, but also on the overall health of the patient and overall treatment costs.

A scientific approach to the noncompliance "disease" will require well-developed information on each of the dimensions discussed above: risk factors and predictors; differential diagnosis in the individual patient and doctor; effective and specific interventions to improve compliance; and cost benefit analysis and outcomes studies.

Logic suggests that the most efficient approach to the compliance problem is to accurately predict those patients at highest risk and then to use the most specific and effective means to intervene. Choice of intervention should be matched to the type of illness and personality type and social circumstances of the patient.

Predicting Noncompliance

At present a great deal is known about some predictors of noncompliant behavior, but very little is known about others. Many studies have been published, but no consensus has been achieved. As a consequence, interventions have resulted in mixed success. Nevertheless, some general risk factors for noncompliance have emerged.

More than 250 social, economic, medical, and behavioral factors have been found to affect compliance (Fincham and Wertheimer, 1985). Studies to date on determinants of noncompliance have

addressed the following types of variables:

- Demographic, such as gender, age, and income;
- Sociographic, such as family stability, support, and size;
- Psychographic, such as a attitudes, self-image, and locus of control.

Some of these patient characteristics may be disease-specific (e.g., those affecting cognitive ability), and some are subject to change through professional interventions. But all have value in alerting the concerned health professional to the potential for noncompliance. It is not far-fetched to suggest that a "compliance profile" should be a part of every patient's medical and pharmacy record. Before that step is taken, however, much more progress in integrating our knowledge of compliance science and patient behavior will be necessary.

A diversity of factors may be predictive of good or poor compliance. Both patient-related and physician-related predictors of compliance are reported in the literature. One approach to synthesizing the existing research on predictors of noncompliance is to use the technique of "meta-analysis" to reduce the multitude of research results to a usable form. Meta-analysis is defined by one of its primary developers as "the statistical analysis of a large collection of results from individual studies for the purpose of integrating the findings." The following example illustrates the potential of this procedure in pulling together and making some sense of the compliance literature.

Nagasawa et al. (1991) performed a meta-analysis of 26 studies of compliance among diabetic patients. More than 180 different factors correlated with compliance behavior were reduced to the following collective findings:

- Factors related to good compliance: emotional stability, internal and external motivations, perceived benefit of therapy, supportive social and family structure.
- Factors related to poor compliance: perceived barriers to therapy, negative social environment.

Additional meta-analyses are required to assess compliance risk factors for other diseases, for special groups of patients (i.e., elderly, severely ill, ethnic groups, etc.), and for various intervention strategies (see below).

The most important predictor of noncompliance appears to be the interpersonal skills of the physician (Consoli and Safar, 1988; Morse et al., 1991; Manson, 1988). Debra Roter and her colleagues at the School of Hygiene and Public Health of the Johns Hopkins University have developed and tested a tool for assessing doctors' communication styles. The Roter Interaction Analysis System (RIAS) provides physicians with direct feedback and analysis of their individual communication skills based on analysis of audiotapes of actual patient interviews (Inui et al., 1982).

Through the use of the RIAS, strong evidence has been gathered which confirms that a physician's interpersonal skills correlate strongly with, and are predictive of, patient adherence, satisfaction, and recall of information about treatment plans. The RIAS has been found to be highly reliable in predicting both quality of care and patient satisfaction (Inui et al., 1982).

Health Belief Model

A frequently used, intuitively attractive, and validated framework for understanding and predicting compliance behavior has been the Health Belief Model. This simple but powerful concept proposes that being compliant is a function of:

- How serious and how likely are the consequences of noncompliance as perceived by the patient?
- How likely is it that something bad will happen and how bad would it be?
- How beneficial will compliance be and what real or perceived barriers to compliance exist?
- How much better will the patient be if he or she takes the medication and is that worth the cost or risk?

In addition, the model acknowledges the importance of social, psychological, economic, and structural factors in determining compliance. It is, of course, the interaction of all of these variables that results in the behavior of an individual patient.

Using the Health Belief Model, Fincham and Wertheimer (1985) studied the reasons why HMO patients did not pick up their prescriptions. They analyzed factors predictive of compliance and found more than a dozen to be significant. The two most important, however, were 1) the patient's

lack of belief in the benefits of care and 2) lack of information on how to take the medicine. The authors suggest that some measure of potential for non-compliance be included in initial contacts with patients. A short questionnaire, such as the one used in this study, that takes only a few minutes to complete in the physician's office or pharmacy, would enable health professionals to take the steps necessary to encourage compliance.

Predicting Compliance by Asking the Patient

General factors associated with poor compliance that are discovered through research or incorporated into models, have only limited utility in identifying the noncompliant patient (e.g., a patient with a complex medication regimen probably warrants special attention). But if efficiency is to be built into programs to improve compliance, some means of predicting the likelihood of compliance in an individual patient is necessary. Fortunately, some progress has been made in that direction. And, as sometimes happens, the solution may be surprisingly simple —ask the patient whether she or he is a compliant patient.

For example, Moriskey et al. (1986) have reported success in the use of a four-item scale as a predictor of future medication compliance as well as a measure of current compliance. The scale was shown to be reliable and a valid predictor of compliance and blood pressure control. The four questions in the scale could be quickly posed to most patients:

1. Do you ever forget to take your medicine?
2. Are you careless at times about taking your medicine?
3. When you feel better do you sometimes stop taking your medicine?
4. Sometimes if you feel worse when you take the medicine, do you stop taking it?

Hogan et al. (1983) developed a reliable 30-item scale which accurately assigned 89% of a sample of 150 schizophrenic patients to compliant and noncompliant groupings. The authors believe that compliers and noncompliers may differ in their awareness of internal bodily sensations, attitudes, feelings, and emotions. Thus, strategies designed merely to inform may be ineffective with patients who are unaware of these internal cues. The authors felt that the general lack of positive results in promoting compliance may reflect the growing belief among researchers that information which people generate themselves is a more important determinant of behavior than is information provided by others.

Litt (1985) found that adolescent patients' self-assessment of their compliance with contraceptive pills accurately predicted compliance in 75% of the cases. Similar success was achieved using

short vignettes in which patients compared their own behavior with that of hypothetical patients their own age.

Cromer et al. (1989) studied adolescents and their iron therapy, finding only 67% compliant. Among the factors predicting compliance were:

- Patients prediction of his/her own compliance at first visit
- Patient belief in his/her own control of health
- Reminders from family members

In a study of inner-city blacks' compliance with an insulin regimen, Uzoma and Feldman (1989) measured individuals' belief in their own ability to comply and used this measurement to successfully predict compliance. This, in turn, suggested that a program to increase the belief in their own performance would enhance performance.

Interventions to Improve Compliance

For those people who simply forget, telephone, postal, or electronic reminders are likely to be helpful. But given the multiplicity of factors shown to contribute to noncompliance, there must be a correspondingly broad range of interventions. Indeed, many types of intervention have been tried. They range from electronic reminder systems to training sessions aimed at modification of the behavior of physicians and patients. Some successes have been reported, but no 'gold standard' or universally accepted program of compliance enhancement has emerged. It is unlikely that a cure for noncompliance among all patients will be found. Rather, a range of options is needed, each suited to the individual needs of patients with specific risk factors, disease manifestations, and social circumstances.

Compliance Packaging

Various types of compliance packaging have been designed for patient use to facilitate remembering when to take a dose and whether the dose has already been taken. Compliance packaging could become a key tactic in forging a physician-pharmacist-patient communication loop (Smith, 1989). Compliance packaging enables the product to reach the patient with several "built in" compliance features. A compliance package is a prepackaged, ready-to-dispense system that contains one treatment cycle of a medication, compliance aids and patient education materials to help motivate and remind the patient to take the medication correctly.

The Ortho-Novum Dialpak for oral contraceptives was the earliest type of compliance packaging. The complicated dosage schedule of Medrol later led Upjohn to develop the unit-of-use Medrol Dosepak which simplified the dosage schedule. Lilly's Axid Convenience Pak helps remind ulcer patients to take the medication every evening and not to stop therapy when symptoms abate. Allergan's C Cap Compliance Cap can be attached to any of their glaucoma products, to remind patients about the frequency of administration.

The macrodantoin MACPAC (Procter & Gamble) is an integrated system containing seven daily blister-pack cards that can be carried to work, a reminder card between the third and fourth dose cards to encourage the patient not to stop the medication although the symptoms may be disappearing, an information booklet on urinary tract infections, and two dispensing stickers for the pharmacist.

To be maximally effective, a complete compliance package must be developed according to patient education guidelines. Once a quality package is produced, health professionals must support it through counseling and reinforcement (Smith, 1989). The utility and economic viability of compliance packaging systems, however, must ultimately depend on demonstrations of their efficacy and cost effectiveness.

Devices

Several marketplace trends and technical developments are converging to set the stage for the appearance in the near future of a plethora of compliance-improving devices. The first trend is the burgeoning popularity of consumer electronic products. The second trend is the explosive growth in home healthcare devices. These include: home glucose monitoring, now the standard for diabetes management; home blood pressure cuffs for self-monitoring, allowing hypertensive patients increased control over their illness; hand-held smoking cessation computers which allow for programmed withdrawal from smoking; and electronic devices to monitor cholesterol and triglycerides through simple home testing.

These devices are appearing at a time when patients increasingly want to assume greater control over their health care, and when managed care companies are increasingly demanding that patients be treated at home rather than in hospitals. The confluence of these trends, plus growing awareness of the extraordinary costs of noncompliance with medications, is driving the rapid development of compliance device technologies.

Compliance devices are already marketed through specialty catalogues, gift shops, electronics retailers, pharmacies, and direct mail channels. At present, these versions are limited to portable

devices that signal the patient to take medication, and require an elapsed timer being set and reset, or the individual entry of each medication taking time. Bedside versions for nursing homes or invalids are also available, although these instruments are often expensive, and may be difficult to operate. However, clinical trials have shown these devices to have a significant impact on improving compliance and reducing morbidity (McKenney et al., 1992).

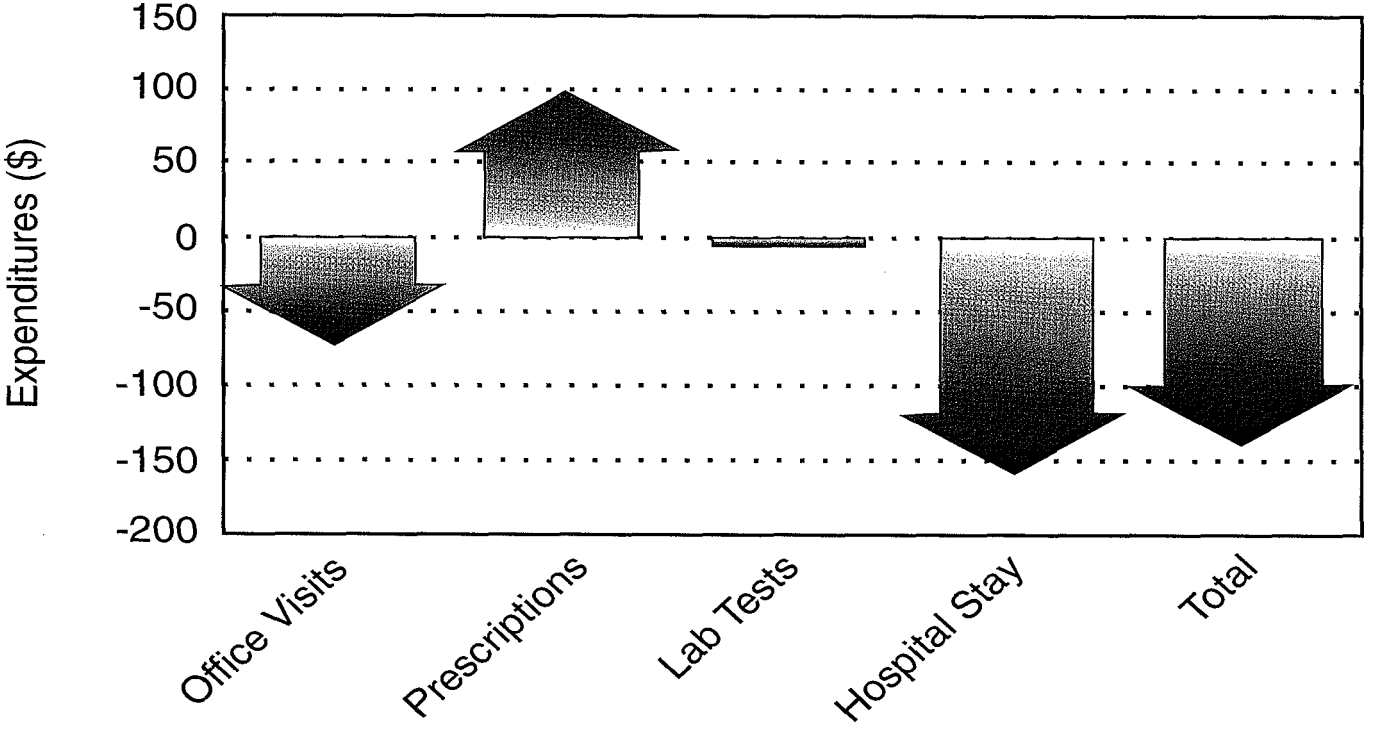
A new generation of compliance technologies now under development will utilize "off the shelf" microelectronic technology now widely used in hand-held computers and calculators. These devices will be portable, offer interactivity with the patient, accommodate multiple medications, and provide a record of patient behavior. Their cost/benefit ratios will have to be demonstrated, but are likely to be favorable. An example is CompuMed, an automated medication dispenser (CompuMed Inc., Meeteetse, WY). The Wyoming Medicaid Agency believes the dispenser is effective, since it is covering the device as a reimbursable expense at over $450, or a rental fee of $46 monthly. At least three other state Medicaid programs cover this device.

Integrated Approaches

Patients for whom the situation is more complicated will require more than just prompting or reminding, and for these patients an integrated approach, featuring multiple interventions, will be needed. An example of such an integrated approach is the program described by Sclar et al. (1992), which has evolved into the Wellspring program of ICI Pharmaceuticals. The program, which includes telephone contact, postal reminders, an educational newsletter, and various samples of health-related items, resulted in a significant increase in the number of days supply of medication acquired by both new and experienced hypertensives (Figure 2).

Windsor et al. (1990) demonstrated the effectiveness of a multi-strategy intervention program in asthmatic adults. The interventions included: one-to-one instruction, a self-help guide, a support group session, and two reinforcement phone calls. The program, which costs about $32 per patient, was associated with a compliance rate increase of more than 40% in inhaler use.

Figure 2.
Education Improves Compliance with Antihypertensive Medicines, Reduces Utilization of HMO Services, and Lowers Overall Costs



Cost Effectiveness of Compliance-Improving Strategies

Comprehensive, integrated programs, like those described by Sclar and Windsor, are the exception rather than the rule. Many more demonstrations of intervention programs in specific diseases, patient populations, and health care settings must be done to convince stakeholders that compliance intervention is worth doing.

What is most needed are demonstrations that compliance enhancement programs save money for healthcare payers. Sclar's study, for example, showed that although the Wellspring program resulted in higher use and costs of medicines, overall costs were lowered due to reduced utilization of other, generally more expensive services such as lab tests, hospital stays, and office visits. Net treatment costs declined by about $100 per patient (Figure 2).

Other studies which calculate the dollar savings or cost effectiveness of educational programs and other compliance-enhancing strategies are shown in Table 5. These studies generally show cost savings resulting from fewer hospitalizations, office and emergency room visits, lab tests, and other services.

These studies vary in size, patient characteristics, methodological rigor, type of intervention, and other important parameters. The magnitude of demonstrated cost savings varies widely among these studies, but all show that money was saved. Some have calculated that more was saved than was spent on program costs. None of the studies report net losses resulting from compliance-enhancing programs.

These findings are encouraging, but further information is required. Additional analysis of these and other cost benefit studies of compliance are required to identify and confirm the most cost effective interventions. The results would also help to design convincing, large-scale demonstrations of cost savings associated with improved compliance.

TABLE 5.
COST SAVINGS OF COMPLIANCE PROGRAMS

Program	*Patients*	*Savings*	*Benefit/Cost*	*Reference*
Pharmacy-based compliance clinic	25	$43,000 in 33 months	12/1	1
Medication-monitoring service for geriatric patients	14	$265-565/ patient/month	7/1-4/1	2
Compliance education for hypertension	--	$100/ patient/year	2.5/1	3
Asthma self-management	683	--	111/1	4
Education of schizophrenics at a day treatment center	18	$10,000	--	5
Asthma self-management in inner city*	58	--	5.9/1	6
Education for congestive heart failure	50	452 hospital patient-days	--	7
Telephone hotline service for diabetics*	6,000	$1.7-3.5 mil emergency and hospital hospital admissions, and office visits for medications	--	8
Computer-assisted telephone refill reminders in a community pharmacy	450	--	1.26/1-1.67/1	9
Hospital-based clinical pharmacy program	355	$208,000	--	10

* Medication management was part of an overall education effort, involving life-style, diet, and general health measures.

1) Cable & Schneider, 1982; 2) Joyner et al., 1983; 3) Eastaugh & Hatcher, 1982; 4) Sperling, 1984; 5) Britt & Stowell, 1983; 6) Roccalla, 1976; 7) Rosenberg, 1971; 8) Miller & Goldstein, 1972; 9) Bryan et al., 1983; 10) Bond & Monson, 1984.

Partners in Identifying Noncompliant Patients and Improving Compliance

Programs with a focus on interventions directed at health care professionals are especially likely to show positive results. There is considerable literature indicating that good compliance is associated with good communication between health professionals and the patient and with a high level of patient satisfaction with the provider and the care received.

Physicians

Considerable research has shown a relationship between compliance and the quality of the doctor-patient relationship. The importance of the doctor-patient interaction as a determinant of good compliance may vary for different illnesses and types of patients, but one component of any effective compliance-enhancing plan is almost certain to involve the physician.

Kaplan et al. (1989) found that specific aspects of physician-patient communication were consistently related to compliance and also to overall health as assessed physiologically (blood pressure, blood sugar), behaviorally (functional status), and subjectively. Uhlmann et al. (1988) concluded that patients whose physicians responded to specific requests over time had fewer insulin reactions and greater compliance with insulin injection regimens.

The evidence is compelling that some improvement in compliance is achieved through improvement in the physician-patient encounter. Inui et al. (1976) found that patients of physicians who were tutored in techniques of communication and education were more compliant with drug regimens and had better control of their blood pressure than patients of untutored physicians. This landmark study concluded that physicians who are provided with strategies for identifying the noncompliant patient and for intervening in that behavior, can improve both compliance and control of hypertension (Inui et al., 1976).

Educational programs and other assistance for physicians to help them better manage the compliance problem can take at least three forms: instruction in the general factors involved in noncompliance; instruction in interpersonal behaviors shown to promote compliance; and assistance in identifying those patients most at risk for noncompliance. This may be as simple as supplying copies of one of the short questionnaires described above.

Since information alone is insufficient to effect a change in compliance behavior, the mere distribution of educational materials to patients, without a meaningful emotional link between patient and

physician, is unlikely to be effective.

Physicians need to be advised that some proportion of their patients are noncompliant and that the medical consequences may be accompanied by a loss of confidence in the physician or dissatisfaction with care.

Pharmacists

The retail pharmacist has significant potential, both as a source of compliance information and as a partner in enhancing compliance. It is essential, however, to demonstrate to pharmacists that increased compliance makes good business sense as well as contributes to better pharmaceutical care. Providing economic incentives is one approach. Development of computer software to assist in identifying noncompliers is another.

A special opportunity is available in the U.S., where some pharmacists are now required to "counsel" Medicaid patients when a prescription is dispensed. Even basic assistance by the pharmacist is likely to be effective. According to the Schering Report XIV (1992), the simple act of the pharmacist, rather than the clerk, handing the medication to the customer improved compliance by 25%!

Managed Care

Because of its strong economic interest in enhanced outcomes, the managed care industry has the potential to become a highly motivated player in efforts to improve medication compliance. Managed care organizations compete in the areas of efficiency and quality, and improving compliance will enhance both.

However, compliance enhancement programs are likely to increase drug utilization (see Sclar et al., 1992); managed care pharmacy directors responsible for line item drug budgets are understandably reluctant to implement programs that will increase their expenses. The challenge is to bring the compliance message to those managed care executives responsible for overall operating costs. Ways must be found to involve chief executives and chief financial officers of these organizations. And to convince these individuals to adopt a given compliance program, studies will be required to show the added value and overall cost savings of the proposed intervention.

The Bottom Line - Patient Responsibility

It is clear that to improve compliance we need to improve the relationship between providers and patients and between patients and pharmaceutical products. Yet it is important to remember that in two studies discussed above—one by the American Association of Retired Persons and one by The Upjohn Company—the primary cause of failure to fill prescriptions was the patients' belief that they had no need for the medication. This finding leads many researchers to the conclusion that we must direct our efforts toward educating patients and assisting them in accepting responsibility for their own treatment.

Leading researchers Debra Roter and Judith Hall conclude that "the most important contribution to patient compliance with drug prescriptions appears to be the patients' understanding of the illness, the rationale and importance of the drug therapy, and the instructions for its use" (Roter and Hall, 1992). This information must be conveyed within the context of a relationship between the doctor and patient characterized by shared responsibility for the patient's health.

In the end, the patient makes the ultimate decision to have a prescription filled, to take the medicine as prescribed, and to refill it as instructed. In their landmark book **Facilitating Treatment Adherence**, authors Donald Meichenbaum and Dennis Turk assure providers that the time and effort spent on helping patients take responsibility for their treatment "will pay handsome rewards." Most importantly, they conclude, "Health care providers can share the responsibility for treatment adherence with patients and significant others in their lives. The teaching of self-management skills to patients represents a major challenge for the health care professions."

Patient choice is emerging as an important theme in the healthcare reform agenda, but patient responsibility has not yet been emphasized. Patient responsibility, especially in taking medications properly, needs to assume its proper place next to patient choice of providers and health plans. The dual engines of choice and responsibility must be harnessed for effective management of health care costs.

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New Technology for Medication Adherence

Electronically Managed Medication Dispensing System

Increasing medication compliance can improve quality of life for older adults.

Kathleen Coen Buckwalter, PhD, RN, FAAN, Bonnie J. Wakefield, PhD, RN, Barbara Hanna, RN, PHN, BSN, CCM, and Julie Lehmann, RN, PHN, BSN

Lack of compliance with prescribed medication regimens is a well-known and well-documented problem among elderly individuals, especially those who live alone or who have some degree of cognitive or functional impairment.

Non-compliance results in decreased quality of life, increased health-care costs related to acute and long-term care admissions, and the need to enhance home care support. Hayes, McDonald, Garg, & Montague (2004) note only 50% of older adults adhere to medication treatment, with a variety of reasons attributed to non-adherence including poor instructions, disagreement with the treatment prescribed, inability to pay, and adverse effects.

Pillboxes and blister packaging have been set forth as a means to help organize medications with some success in increasing rates of compliance (Ware, Holford, Davison, & Harris, 1991; Wong & Norman, 1987). However, these

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approaches require a level of manual dexterity that may be lacking in older adults. There is also growing evidence that community-dwelling older adults can increase their compliance with prescribed medications as a result of targeted interventions (e.g., phone calls, electronic devices) encouraging them to take their medication as prescribed (Fulmer et al., 1999). However, insufficient numbers of rigorous studies examining these compliance aids have been conducted to date.

If patients do not dispense the medication after 90 minutes, the MD.2 will lock away the cup so they cannot overdose or double dose.

THE MD.2 AUTOMATED MEDICATION DISPENSING SYSTEM

An innovative new technology, called the MD.2 Automated Medication Dispensing System (Interactive Medical Developments [IMD], Webster City, IA), recently has been developed to address some of the issues for medication noncompliance. The MD.2 was developed by Dr. Anil Sahai after he observed many of his patients who were able to handle most activities of daily living were prematurely admitted to acute or long-term care facilities because they were unable to properly manage their medications.

The MD.2 medication-dispensing technology allows caregivers to organize medications into easily opened plastic cups. Each cup holds one or more medications and represents one dispensing period (e.g., morning medications).

Caregivers use a simple and straightforward process to help with installation. User data are collected and include patient's name, address, and phone number; unit serial number; caregiver names and the order in which to call them; medication dispensing times by day of the week; and the standard message, if any, to announce to the user. This information can be entered via the Internet or by faxing or calling the IMD Support Center where it is entered into a database.

At the time of installation, the caregiver or medical professional has the MD.2 unit call the support center and the information is downloaded. Based on this information, the unit verbally prompts the caregiver through the loading of the cups. After loading, the unit is kept locked so patients do not have access to the medications. Depending on the frequency of doses, the system can dispense medications for a 10- to 30-day period (the unit holds 60 cups).

Using a series of verbal and auditory reminders (e.g., a flashing light, voice reminders, and a loud beeping noise for a 60- to 90-minute period), the MD.2 will alert patients that it is time for their medication, allowing them to press an easy-to-use button to dispense the pre-filled medication cup. The MD.2 also will remind patients to take the medication with food, check their blood sugar, or announce other pre-programmed messages.

If patients do not dispense the medication after 90 minutes, the MD.2 will lock away the cup so they cannot overdose or double dose. The MD.2 will then begin calling caregivers. Based on the input notification order, the unit will call up to four caregivers or medical professionals to alert them of the non-dispense. It will verbally announce it is the MD.2 and give the user's name, phone number, and the fact that the medication was not dispensed. The caregiver must respond by entering a "1" on their phone or the MD.2 will hang up and call the next caregiver. If none of the caregivers respond by entering a "1," the unit will call the IMD Support Center and the Center's staff will continue trying to alert caregivers.

All dispensing history and alarm notices are up-loaded at the end of the day to the Web-enabled support center so that caregivers or other medical professionals can review the dispensing data to monitor patients' status. All user history is stored, and the previous 35 days are available for viewing via secure Internet connection by caregivers and medical professionals. User confidentiality is maintained via the unit serial number and the user's telephone number, which serve as identification numbers for security purposes.

The technology is especially useful with older patients, individuals with brain injuries, or other outpatients who have difficulty managing their medications. Current medication management tools consist of devices such as: weekly pillboxes, which only organize medications; reminder devices such as beeping medication caps or wristwatches, which remind but don't organize; and electronic dispensers, which organize, remind, and safeguard. However, none of these methods have the full functionality of the MD.2 to organize, remind, dispense, monitor, safeguard, and report on medication management. The MD.2 is designed to bridge the gap when simpler reminders do not work and proper medication adherence is critical to avoid a more costly level of care.

The price of the MD.2 varies by distributor. However, average monthly rental costs approximately $90 per month.

EVALUATION OF THE MD.2

Two preliminary studies have been conducted with the MD.2, the first under the auspices of the Johnson County (Iowa) Visiting Nurses Association (VNA) and

the second by the California Health Professionals Plus/Home Health Care Management company (CHP Plus).

Visiting Nurses Association Pilot Study

Study Description. In August 2000, the Johnson County VNA installed MD.2 machines in the homes of 12 patients with known or suspected problems with medication non-compliance. Patients were referred to the project either by a nurse or physician. Six patients had a primary medical diagnosis, five of whom also had a secondary psychiatric diagnosis; the remaining six patients had a primary psychiatric diagnosis. Nine patients were women, and three were men. Patient age ranged from 33 to 86.

Medication dosing frequency was twice daily for six patients and three times daily for six patients. The number of medications per patient ranged from 4 to 16, with an average of 8 medications per patient per day.

Outcomes evaluated included the frequency of home health aide visits, dispensing rate statistics, and the number of requests for technical support assistance from the IMD Support Center. Data for the latter two outcomes were collected from reports generated by the IMD Support Center.

To assess the frequency and content of nursing care and home health aide visits, patient records were reviewed for 3 months prior to and 12 months after installation of the MD.2 or discharge from home care, whichever came first. The number, route, and frequency of prescribed medications also were obtained from records.

The visiting nurses were given a 2-hour training session by IMD employees. The nurses then installed, maintained, and loaded the units. Patient training was minimal because they only need to push the large red button, when prompted, and then take the medication.

TABLE 1

COMPARISON OF MD.2 AND MEDI-SET FOR HOME HEALTH CARE MANAGEMENT PATIENTS*

	MD.2	*Medi-Set*
Hospitalizations per patient	.09	.42
Emergency department visits per patient	.18	.42
Prescriptions per patient	7.62	8.65

**After 6 months of program data*

TABLE 2

COMPARISON OF MISSED MEDICATION DOSES FOR HOME HEALTH CARE MANAGEMENT PATIENTS USING MD.2 AND MEDI-SET

	MD.2	*Medi-Set*
Missed doses per patient per 2-month evaluation period	.62	3.39
Total missed doses per patient during 6-month period	2.9	7.31

During the course of the pilot study, MD.2 units remained in the home an average of 5.1 months (range, 2 months to longer than 7 months).

Study Findings. It took an average of 2 to 4 weeks for patients to become comfortable with the MD.2 routine, voice/instructions, and presence in the home. As with any new technology, some of the VNA nurses were more open to using it than others.

For the first outcome, the frequency of home health aide visits, the number of patient home visits did not decrease because other medical problems required attention. However, the nurses' notes reflected home visit time was spent on other issues in the nursing care plan rather than medication compliance.

For the second outcome, dispensing rate statistics, the frequency of missed doses was higher immediately after the MD.2 was placed and then decreased steadily the longer patients used the MD.2. An overall dispensing rate of 98.26% was determined: of 3,737 doses monitored, there were 65 "missed doses" where patients did not access their medications within the 60- to 90-minute window allotted by the MD.2.

The third outcome was the number of requests for technical support assistance from the IMD Support Center. For the 3,737 doses, there were 10 requests for technical support. Seven requests related to maintenance and schedule issues, and three requests were for assistance in removing a "double cup" loaded improperly (i.e., two medication cups nested together with one cap).

Home Health Care Management Study

Study Description. Through a grant from the State of California, Department of Aging Long Term Care Innovative Grant Program, Home Health Care Management

tested the MD.2 by comparing it to the use of medi-sets (plastic medication boxes). The first 6 months of the program compared 89 community-dwelling older or disabled adults who used the MD.2 with 45 older or disabled adults who used the medi-sets. Patients were assigned to either the MD.2 or the medi-set group based on criteria that assessed cognitive and physical functioning.

Study Findings. After 6 months of program data, the outcomes favored the MD.2 in terms of reduced hospitalization rates and emergency room visits and fewer number of medications being taken (Table 1). Home Health Care Management staff believed some of the greatest successes of the MD.2 were with patients on warfarin therapy, patients with mental health issues, and patients with early to mid-stage Alzheimer's disease. The MD.2 was also very effective for patients in independent living facilities.

In addition, the MD.2 group reduced the total number of prescriptions being taken to 7.62 compared with 8.65 in the group using the medi-sets. One possible reason for this difference could be the regular and accurate implementation of the prescribed medication regimen that resulted in stabilization of patients' condition. This stabilization could have then resulted in a decreased demand for compensatory medications. Regular and accurate medication implementation was demonstrated by the fact that patients using the MD.2 missed fewer medications than patients using the medi-sets (Table 2).

Anecdotal Data and Future Research

Anecdotal data also have been gathered from participants nationally who have used the MD.2. Success has been reported among adults with a variety of chronic diseases, including those with mid-stage Alzheimer's disease who live independently, brain-damaged individuals, individuals with bipolar disease and other psychiatric disorders, and patients with insulin-dependent diabetes, congestive heart failure, and acquired immunodeficiency syndrome. In some cases, individuals who were previously confined to a group home setting were able to live independently.

Future research is planned to establish the effectiveness of the MD.2 on outcomes with potential cost benefit to Medicaid and all other payor sources. Planned research for the future will address the following issues:

- Developing a profile of individuals most likely to benefit from use of the MD.2.
- Determining costs associated with the device including training and installation.
- Estimating the cost effectiveness of the MD.2 compared to other forms of care (i.e., visiting nurses, assisted living).
- Determining the impact of the MD.2 on the number of hospitalizations and emergency room visits.

Other studies will compare the length of time in home care and measure changes in caregivers' stressors, endurance potential, burden, and well-being between those using the MD.2 and those using their normal medication routine. Cognitive and functional characteristics, and how they influence compliance rates among frail older adults also will be examined.

ENHANCEMENTS TO THE MD.2

The original MD.2 has been enhanced. The MD.2+ offers the original functionality of the MD.2 with a built-in Personal Response System. The Personal Response System allows patients to wear a small, lightweight, waterproof pendant or bracelet that can be pressed in the event of a fall or other medical emergency. The MD.2+ will then dial out to a 24-hour emergency call center and, through a two-way speaker, the nature of the emergency can be determined and appropriate help dispatched. The most recent development is an MD.2 that announces all of its messages in Spanish.

CONCLUSION

Medication management requires psychomotor and cognitive activities to take medications as prescribed. Non-compliance with medications increases health-care spending and the need for home care support, and can lead to avoidable hospitalizations and placement in long-term care facilities. Many community-dwelling older adults have both cognitive and functional deficits that make it difficult for them to properly manage their medications. The MD.2 shows great promise in alleviating many of these problems and enhancing compliance through an innovative system of reminders and caregiver support.

More information can be obtained by accessing IMD's Website at www.imd2.com, by sending an e-mail to haroldp@imd2.com, or by calling 1-877-563-2632.

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Medication adherence and cognition

Medical, personal and economic factors influence level of adherence in older adults

Raymond L. Ownby, MD, PhD, MBA

Medication adherence is increasingly being recognized as a significant issue in treating geriatric patients. A report by the Institute of Medicine[1] identified medication nonadherence as a notable source of medical errors.

Poor adherence has been shown to decrease the effects of prescribed medications or other treatments and to increase the likelihood of poor outcomes.[2] Adherence has been related to intermediate clinical outcomes in several diseases. An increased incidence of adverse events has been linked to nonadherence in the elderly.[3]

Elders' adherence to prescribed medications is a complex phenomenon that depends on an interaction of medical, medication, personal, and economic factors.

► Medical factors that affect adherence include cognitive abilities, as well as overall health status (eg, number of chronic conditions).

► Medication factors related to adherence include the characteristics of the medication (eg, dosing frequency or presence of side effects).

► Personal factors that affect adherence include:

▷ personal beliefs about the condition for which the medication is prescribed (eg, how serious the condition is and how likely the medication is to have a positive effect).

▷ individual cognitive abilities, including memory, overall intellectual ability, organization skills, and health literacy. Health literacy has emerged as an important factor that affects older persons' capacity, for example, to make health care choices.[4]

► Economic factors pertinent to medication adherence include whether patients have insurance or other financial resources to pay for the medication.

► Patients' relationship with their physician as well as the physician's communication style can affect adherence.[5]

► In the older adult with memory problems, we have found that whether patients depend on themselves or a caregiver can have a significant impact on adherence.[6] Not all caregivers take responsibility for a patient's medication, and family members' beliefs about a medication can also affect the patient's adherence.

Evaluation of elders' medication adherence as a factor in treatment success or failure is thus potentially complex, difficult, and time consuming.

Role of cognitive abilities

Few studies have directly investigated the determinants of elders' medication adherence. In an ongoing study using electronic medication adherence monitoring (Medication Event Monitoring System [MEMS]), preliminary results have shown that patients' cognitive skills and health literacy are related to their adherence to medications prescribed for memory impairment (see http://www.patcai.org). The electronic monitoring system records the date and time of each medication dose, and a software application provides a report of the number of doses taken in a specific interval, at the correct time of day, and at the correct interval between doses. All study subjects have been diagnosed with some form of memory impairment and are taking one of the cholinesterase inhibitors (eg, donepezil, rivastigmine, galantamine). These are the only medications for which adherence is being monitored.

Preliminary analyses show that specific cognitive abilities are related to different aspects of adherence.[7] In regression models, patients' delayed recall of a list of words was related to patients having taken the correct number of doses in a 30-day interval, without regard to dosing interval. When adherence was defined more strictly as taking the correct number of doses in approximately the correct interval, more complex cognitive abilities were involved.

While memory continued to be an important predictor of adherence, health

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Disclosures: Dr. Ownby has no actual or apparent conflict of interest with the subject of this article. He has no financial or other material interest conflict with the companies that manufacture the electronic medication adherence monitors described in this article.

literacy (as measured by the Test of Functional Health Literacy[8]), executive abilities (time taken to complete a maze task), and general cognitive status (Alzheimer's Disease Assessment Scale, cognitive subscale[9]) all contributed independently to medication adherence. Whether patients' memory is poor, as well as other abilities—including general ability and health literacy, may thus be related to how well they take their medications.

Patient traits and adherence

Although one might expect that older adults would have lower levels of medication adherence than younger adults, some studies have shown that older adults may have higher levels of adherence, perhaps because they are not as busy with other activities as are younger persons,[10] or because they are more aware of the potential impact that medications may have on their health.[6] However, in a study by Carney et al, depression was significantly associated with worse medication adherence in elders.[11]

In some studies, age has not been directly related to adherence, although poorer cognitive function has. Since increasing age places elders at greater risk for deficits in memory or general cognitive function, the apparent relation between adherence and age may be mediated by cognition rather than age itself. Other patient characteristics, such as socioeconomic status, may be related to adherence.[12]

Patient beliefs and adherence

The Health Belief Model[13] has been a stimulus for numerous studies of medication adherence. Starting with the idea that patients' beliefs about medications will impact how they take these medications, the model predicts that patients' beliefs about their conditions and the conditions' likely outcomes with and without treatment will affect adherence.

In a study of patients at a memory disorders clinic based partly on this model, a complex pattern of connections was found among patient beliefs and adherence as reported by caregivers.[6] Numerous variables were assessed, including cognitive status as an index of dementia severity, number of medications, total number of medication doses per day as an index of regimen complexity, and whether the patient depended on a caregiver or him- or herself to remember to take the medication. Patients' beliefs about the seriousness of their condition were significant predictors of their rat-

Medication adherence in older adults is a poorly understood phenomenon with multiple determining factors. Asking open-ended questions may be the best tool available to determine whether older adults with cognitive impairments are compliant.

Illustration for GERIATRICS by Michael Morgenstern

Table 1 Key risk factors for nonadherence

- Low levels of health literacy
- Poor understanding of the purpose for medication
- Poor understanding of the impact of a medication on health outcomes
- Memory or general cognitive impairment
- Living alone or not having a caregiver
- Regimen complexity
- Communication difficulties between physician and patient
- Lack of insurance or other inability to pay for medication

Source: Created for GERIATRICS by RL Ownby.

ing of its likely outcome without treatment; this rating was, in turn, related to adherence. In this study, older age was related to better adherence, while the presence of side effects was related to lower levels of adherence.

Risk factors for nonadherence

Given the complexity of medication adherence and the difficulties that practicing clinicians face in assessing and addressing it, clinicians should be advised to focus on significant factors in nonadherence (table 1). In our ongoing study of medication nonadherence in patients with a mean age of 82.3 years, analysis of preliminary data reveal two distinct patterns of adherence.[14] A majority (ie, 80% to 90%) of patients have high levels of medication adherence as determined by electronic monitoring. These patients still function at independent levels in activities of daily living, and their memory impairments are mild. They often live with a spouse or another caregiver.

A smaller, but distinct, second group (10% to 20%) of patients has been identified as having low levels of adherence. They may still live independently, but show clear evidence of memory impairment. They typically live alone and report that they rely on themselves and not a mechanical aid (eg, pillbox) to remember to take their medication.

These observations are similar to those of other adherence studies of the elderly.[15,16] A European study with a population-based random sample of persons age 75,[15] for example, showed that evidence of cognitive impairment (MMSE score less than 24) increased the likelihood of nonadherence nine times, and that elders living alone were twice as likely to have medication errors. This study did not explore the effect of the presence of a caregiver, but it showed that the use of a compliance aid (eg, pillbox) increased adherence by nearly 4.5 times. The study showed that many patients had low levels of knowledge about medications and the purpose for which they had been prescribed. In fact, 40% of patients did not know the purpose of the medication, 79% did not know the consequences of not taking medication, and 95% were not aware of the possibility of a toxic drug reaction.

Factors associated with medication nonadherence include regimen complexity, acuity, and economics

Communication patterns, and most likely, the physician-patient relationship they reflect, affect medication adherence.[11] Stewart et al[17] argue that three physician behaviors may be critical for medication adherence:

1) **Provide** a full explanation of the reason for prescribing the medication and provide the expected outcome. Tell the patient WHY you are prescribing this drug and what you expect it will do.

2) **Emphasize** the shared responsibility of the patient and physician in health outcomes. Tell the patient that you have done what would be expected given these symptoms or this condition, and what you expect him or her to do as well.

3) **Explore** factors in the patient's life relevant to obtaining and using the medication as scheduled. Ask the patient if there are any reasons why he or she may not be able to do as you have instructed.

Although time consuming, developing a relationship with individual patients and providing them with this type of information may aid in improving adherence.

Other factors associated with medication nonadherence in the older adult include:

► Regimen complexity. Consider simplifying regimen complexity (eg, reducing the number of times medications are taken daily) to improve adherence.[12]

► Acuity. How well a patient understands the medical condition for which he or she is being treated has an impact on adherence, with decreasing adherence over time in chronic, largely asymptomatic conditions, such as hypertension[18] and dyslipidemias.[16]

► Economics. The importance of economic factors should not be neglected. Patients who have difficulty paying for medication report skipping medications a majority of the time.[19,20]

Assessing adherence

One research finding on the assessment of patient medication adherence is consistent: patient self-report of adherence is unreliable. Therefore, clinicians must be careful to use supplementary information when assessing patients' medication adherence. If self-report is used, MacLaughlin et al[21] argue that open-ended questions are more likely to elicit accurate information than specific ques-

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Table 2 Adherence assessment in older patients

Assessing current adherence behavior

First, evaluate how the patient takes his or her medications

- From pharmacy bottle, other packaging (eg, blister pack)
- Is the patient assisted by a caregiver?
- Does the patient use any organizing device, such as a weekly pill organizer?

Ask that the patient bring all medications to each visit

- Assess number of doses available for each medication in relation to refill date
- Check refill dates to ensure that medications are refilled at appropriate intervals

Self report or pill counts – not recommended because of inaccuracy

- If this strategy is used, ask patients open-ended questions about how they take their medications

Caregiver report – accuracy unclear but may be discrepant from patient report[2]

Source: Created for GERIATRICS by RL Ownby based on information from references 2, 6, 22-24.

Table 3 Assessing functional ability to adhere

Mental status screening: Scores on cognitive screening instruments, such as the Mini-mental State Exam (MMSE) may be related to medication adherence,[6, 15-17] although none of these have provided cutoff scores that might be used in clinical assessment.

MedTake inventory[15] assesses accuracy of patients' knowledge of medication regimen by asking them to describe how they take their own medications and then scoring their response on four dimensions: (1) dose, (2) indication, (3) whether taken with food and water, (4) dosing regimen. For each medication, 25% correct is awarded, and then an overall average percentage is calculated. In one study, the MedTake score was significantly related to MMSE performance.

Hopkins Medication Schedule[16] provides a standard scenario for taking aspirin and an antibiotic. The patient is asked to indicate when doses should be taken in relation to meals and snacks on a paper form. He or she is then asked to fill a pillbox to further demonstrate his or her understanding of how to take the medication. Scores on this measure have been related to memory and executive function.

DRUGS inventory[17] requires patients to identify each of their own medications they should be taking on a specific day, open the appropriate container, take out the correct dose of medication, and indicate the timing of each dose on a recording form.

Informal assessment of patient's ability to put medication in organizer or complete a calendar. This approach might be useful in clinical settings. The clinician can ask the patient to demonstrate how and when he or she takes prescribed medications. Difficulties with this task in the office would imply that difficulties are likely at home.

Source: Created for GERIATRICS by RL Ownby based on information from references 2, 6, 22-24.

continued from page 32

tions with yes or no answers. Rather than asking the patient "Are you taking your medications as prescribed?" it may be preferable to say, "Tell me how you take your medications," or to ask the patient to demonstrate how he or she takes their medications with a pillbox.

The clinician may ask the patient about side effects as a means of assessing adherence, since the presence of side effects may reduce patients' adherence. The clinician can ask open-ended questions, or ask specific questions about common side effects, opening the conversation to possible reasons why a patient does not take a specific medication.

Several systematic methods of assessing a patient's functional ability to adhere are listed in tables 2 and 3.[22-24] In general, these methods provide standardized assessments of medication adherence-related behaviors, such as understanding directions on a prescription label and identifying correct times to take doses.

Electronic medication adherence monitors, although most often used in research contexts, are potentially useful in clinical settings. These monitors record the time and date at which doses of medication are taken. Information can be recorded centrally by telephone or at each visit.

Table 4 Strategies for improving medication adherence in older patients

Patients with low levels of health literacy

- ▶ Offer structured or guided support for medical problem solving by providing information about medication and asking patient to explain consequences of not taking it or how to cope with adverse effects.
- ▶ Provide information to patient orally and in writing at a level understandable to the patient. When in doubt, assess readability level of written information through measures available in standard word processing software (search for "readability" in software help function).

Patients with lack of understanding of the medication's purpose or impact on a disease

- ▶ One-to-one educational intervention that includes questions and answers to ensure patient understanding
- ▶ Provide written information, individually tailored if possible
- ▶ Include the purpose of the medication in the written prescription so that it is printed on the prescription bottle label (eg, "Sig: donepezil, 10 mg: One every day for memory problems").
- ▶ Provide the patient with an easy-to-read summary of the medication or medication changes that includes the purpose.

Patients with memory or general cognitive impairment

- ▶ Provide a pillbox or blister pack
- ▶ Encourage patient to enroll in an automated reminding service when available
- ▶ Coaching the patient on using daily routine as a support for medication adherence (eg, always taking medication at breakfast)

Patients living alone or not having a caregiver

- ▶ Mobilize patient's family to assist in supervision (even if via telephone)
- ▶ Investigate local visiting nurse and social work services

Patients with complex regimen dosing

- ▶ Simplify medication regimen to fewest possible doses each day

Communication difficulties between physician and patient or patient-caregiver dyad

- ▶ Explain why the medication is prescribed and what outcome is expected
- ▶ Emphasize the shared responsibility of the patient and physician in health outcomes
- ▶ Explore factors in the patient's life relevant to obtaining and using the medication as scheduled

Lack of insurance or other inability to pay for medication

- ▶ Provide information on manufacturers' programs to provide medications
- ▶ Assist patients in enrollment in programs
- ▶ Consider switching to generic medications when suitable alternatives are available

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Improving adherence

Several extensive reviews evaluate the effectiveness of methods to improve medication adherence.[25-27] Methods for improving patient adherence are listed in table 4. In general, studies of interventions to improve patient adherence to medication regimens have shown small, but statistically significant, effects. Small changes in adherence may be difficult for clinicians to detect and interventions that produce them may thus appear ineffective.

Further, studies have typically included participants with a wide range of levels of adherence. Since studies have shown that older patients may have high levels of adherence, the effect of an intervention on groups of persons with high and low levels of adherence may be watered down in these studies.

Research studies have shown different rates of adherence in patients with different demographic characteristics (eg, nonwhite[16]), in different diseases, and with different medications. Ultimately, it may be necessary to develop individually tailored interventions that consider patient, disease, and treatment characteristics.

Use of technology-based interventions may be a useful strategy for dealing with poor medication adherence.[28] For example, while tailored information interventions (interventions that target patient adherence by providing information tailored to patients' interests or needs) are known to improve adherence, preparation of tailored medication information for each individual may be excessively time-consuming. Creation of educational materials can be automated through a computer-based application, making the preparation and dissemination of individually-tailored materials part of clinical office practice.[29] Other automated interventions (eg, computer-based telephone reminding), have also been shown to improve adherence.[30]

Conclusion

Although critically important, medication adherence in older adults is a poorly

understood phenomenon with multiple determining factors. Research on interventions to improve adherence has shown modest, but statistically significant, effects. However, results of existing studies make it difficult to determine the most important factors for improving adherence.

It is not clear the extent to which observed effects on adherence are related to already high levels of adherence in some patients. Future efforts to improve adherence may require individually-targeted interventions that consider important patient and disease characteristics. Technological devices may aid in this time- and labor-intensive effort.

Acknowledgments: Preparation of this article was supported by grant K23 AG19745 from the National Institute on Aging to Dr. Ownby. The author also acknowledges the contribution of an anonymous reviewer some of whose comments and suggestions are incorporated in this article.

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By M. Christopher Roebuck, Joshua N. Liberman, Marin Gemmill-Toyama, and Troyen A. Brennan

Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending

DOI: 10.1377/hlthaff.2009.1087
HEALTH AFFAIRS 30,
NO. 1 (2011): 91–99

ABSTRACT **Researchers have routinely found that improved medication adherence—getting people to take medicine prescribed for them—is associated with greatly reduced total health care use and costs. But previous studies do not provide strong evidence of a causal link. This article employs a more robust methodology to examine the relationship. Our results indicate that although improved medication adherence by people with four chronic vascular diseases increased pharmacy costs, it also produced substantial medical savings as a result of reductions in hospitalization and emergency department use. Our findings indicate that programs to improve medication adherence are worth consideration by insurers, government payers, and patients, as long as intervention costs do not exceed the estimated health care cost savings.**

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Almost half of all Americans, approximately 133 million people, live with at least one chronic disease.[1] Because ongoing use of prescription medication is a key component of treatment for chronic conditions, medication adherence—or making sure that patients take the drugs prescribed for them—is a matter of great importance to policy makers, insurance plan sponsors, physicians, and patients.

Patients who adhere to their medication regimens enjoy better health outcomes[2,3] and make less use of urgent care and inpatient hospital services, compared to patients with similar medical conditions who are not adherent.[4,5] Yet despite the evidence of improved outcomes from adherence, the World Health Organization reports average medication compliance rates in developed countries of just 50 percent.[6]

By definition, improvements in medication adherence increase pharmacy spending. Health care reformers and payers are therefore interested in knowing whether or not the higher pharmacy costs are more than offset by reductions in the use of medical services. If so, the financial benefit may justify adopting programs that promote compliance or that remove barriers to adherence.

Given the widespread policy debate over how best to bend the health care cost curve downward, it is surprising that medication adherence by patients with chronic diseases does not feature more prominently in the conversation. However, as we discuss in this article, research into medication compliance suffers from methodological challenges that may call the validity of the results into question.[5,7,8] This could explain the lack of discussion in the health policy arena about the value of medication adherence.

Research in this area focuses on chronic conditions that are highly prevalent, costly, or both. These include asthma, congestive heart failure, depression, diabetes, epilepsy, gastrointestinal disorders, hypertension, osteoporosis, schizophrenia, and dyslipidemia (high levels of "bad" cholesterol).

To date, investigators have routinely found improved adherence to be associated with lower total health care costs.[9–12] Notable exceptions include depression, osteoporosis, and asthma—conditions in which adherence has sometimes

been associated with increases in overall costs, perhaps because of the dominance of brand-name, and thus more expensive, medications in the treatment of these conditions.[13–15] Reductions in hospitalizations and emergency department visits are overwhelmingly reported to be the key drivers of declining health care costs associated with improved medication adherence.

However, these prior studies have a common limitation: the inability to establish a causal link between the key explanatory variable—medication adherence—and the outcomes of interest, such as hospitalizations and total health care costs. This limitation springs from the use of an observational research design, as opposed to a randomized controlled trial.

Observational research can never reveal if individuals in the groups being compared differ in ways that are not observed. If an unobserved and unmeasured trait is related to both the characteristic that differentiates the groups—the explanatory variable—and the outcome being examined, then the trait may bias the results. This problem, known as endogeneity, plagues the published literature on the relationship between medication adherence and health services use and cost. One example of this sort of bias is known as the "healthy user effect": the tendency of people who more closely follow their medication regimens to also engage in such health-enhancing behavior as exercising regularly and eating a healthy diet.[16]

This article examines the relationship between medication adherence and the use and cost of health services in patients who had one or more of the following four chronic vascular conditions: congestive heart failure, hypertension, diabetes, and dyslipidemia. We analyzed a large panel data set and used an advanced econometric technique that addresses the endogeneity problem by mathematically eliminating unmeasured confounding variables if they did not change over time. Our combination of data and methods allowed us to move from possibly uncovering statistical associations to more confidently inferring causal links between medication adherence and the use and cost of health care.

We also investigated whether or not medication adherence had a differential impact on health outcomes depending on patients' sex or age. Specifically, we compared people under age sixty-five with older patients, given that people age sixty-five and older make up a particularly important cohort in light of their eligibility for Medicare. Our findings revealed robust reductions in emergency department visits and inpatient hospital days as a result of medication adherence. Consequently, adherence leads to total health care cost savings. We conclude by commenting on the implications of these findings in the context of health care reform.

Study Data And Methods

STUDY SAMPLE As one of the largest pharmacy benefit managers in the United States, CVS Caremark adjudicates prescription drug claims for its clients: sponsors of health insurance plans. For this study we extracted integrated pharmacy and medical administrative claims data from the CVS Caremark data on people who had continuous health insurance coverage sponsored by one of nine US employers from January 1, 2005, through June 30, 2008.

We used primary, secondary, and tertiary *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM), codes to construct cohorts of patients with the four targeted conditions. We selected patients who had at least two outpatient visits on different dates, or one hospitalization or emergency department visit, with a specified ICD-9-CM code (see Appendix Table A1).[17] We included subjects in more than one disease cohort if they met our inclusion criteria (see Appendix Table A2 for the extent of the overlap).[17]

After we used the first six months of data to properly calculate the adherence measures, as described below, our analytical data set consisted of a panel of 135,008 individuals, each with three consecutive yearly observations (July 1, 2005–June 30, 2006; July 1, 2006–June 30, 2007; and July 1, 2007–June 30, 2008). The final sample included 16,353 patients with congestive heart failure, 112,757 with hypertension, 42,080 with diabetes, and 53,041 with dyslipidemia.

STUDY VARIABLES The empirical analysis included three measures of health services use: annual numbers of inpatient hospital days, emergency department visits, and outpatient physician visits. It also included three measures of health services cost: annual pharmacy, medical, and total health care costs. All six of these dependent variables applied to all medical causes, not just the specific diseases we studied.

We used data on coordination of benefits so that the cost measures would comprise contributions from all payers, including plan sponsors, members, and other insurers such as Medicare. The inclusion of nine different payers decreased the study's sensitivity to potential differences in the employers' pharmacy and medical benefits.

Pharmacy costs consisted of ambulatory prescriptions dispensed by outpatient, community-based, or mail-service pharmacies. We derived

medical costs from medical claims. Total health care costs represented the sum of pharmacy and medical costs.

We measured adherence using the medication possession ratio (MPR). A common metric in pharmacoeconomics and outcomes research, this ratio uses pharmacy claims data to derive the proportion of time that a patient has medication on hand to treat a specific condition.

In our study, for every therapeutic class of drug used to treat each chronic condition (see Appendix Table A1),[17] we calculated a patient's medication possession ratio for each of the three yearly observations as the number of days during the year when the patient had medication, divided by the number of days in the year. For example, a patient who had a supply of medication for a total of 255 days in a given year would have had a medication possession ratio of 0.70 (255 days of possession divided by 365 days).

We consulted pharmacy claims during the first six months of our study (January 1 through June 30, 2005) to "credit" the patient's first medication possession ratio with medication on hand as of the beginning of the first observation year. Subsequent calculations carried leftover medication from year to year. Therefore, MPR values ranged from 0 to 1.

Next, we derived condition-level adherence for each patient-year observation. We calculated this as the average of the medication possession ratios for all therapeutic classes for each chronic disease, weighted by the days' supply in each therapeutic class (see Appendix Table A1).[17] For patients who had been diagnosed with a chronic condition but had not yet received any medication for it, we used a condition-level medication possession ratio of 0.

Finally, we constructed a dichotomous variable for adherence for each of the four vascular conditions. We considered a condition-level medication possession ratio below 0.80—a threshold commonly used by researchers—to be nonadherent, and a ratio of 0.80 or greater to be adherent. Again, we created this variable for each patient-year observation. For a more detailed discussion of the derivation of our adherence measure, see Appendix Section 1.[17]

In addition to the indicators of adherence, we used dichotomous variables for age, depending on whether or not the patient was sixty-five or older (as of the first day of each year), and sex, using pharmacy benefit eligibility records. To control for the presence of other diseases, we derived the Charlson Comorbidity Index for each year.[18–20] We also included time dummy variables to control for concurrent trends in health services use and cost, such as drug price inflation, expansions in the availability of generic drugs, and advances in health care technology.

STATISTICAL ANALYSIS We estimated condition-specific models for each of the six dependent variables, for a total of twenty-four models. The endogeneity of adherence in these models was a key methodological concern in our analysis. Consequently, as previously described, we used linear fixed-effects modeling to handle this potential problem. To examine differential effects of adherence, we also added interactions between adherence and sex and age group to the models.[21] We used the statistical software Stata, version 11.1.

LIMITATIONS Our study had various limitations. First, we did not analyze the timing of adherence effects on health services use and cost. Because many patients in our analytical data set may have been long-term users of their vascular medications, the estimated impacts of adherence could represent cumulative rather than instantaneous effects. In other words, one should not necessarily expect to see immediate reductions in medical costs from improved medication adherence. This is a particularly salient point for insurers with short time horizons.

Second, we advise against adding together estimates of condition-specific effects for patients with more than one vascular disease. Such addition could double-count reductions in health services use and cost resulting from adherence.

Third, the study sample was a relatively large and demographically diverse set of patients insured by their employers, and the group age sixty-five and older included both active employees and retirees. Moreover, we analyzed both existing and new cases of vascular disease. Despite these broad inclusion criteria, our results might not be generalizable to all populations.

Finally, although our econometric method addressed the potential endogeneity of adherence largely ignored in prior studies,[22] fixed-effects modeling is still not as good as a randomized controlled trial in establishing causality.[23]

Results

With regard to sample characteristics, we found that males constituted a somewhat higher proportion of the congestive heart failure (55 percent) and diabetes (53 percent) cohorts than did females, whereas the dyslipidemia (50 percent) and hypertension (51 percent) groups were more evenly balanced by sex. Congestive heart failure patients tended to be older (average: 77 years) than patients with the other three conditions (averages: 65–68 years).

Average medication possession ratios varied across the four conditions: Congestive heart failure patients had the lowest (0.40), and patients

with hypertension had the highest (0.59). Adherence rates ranged from 34 percent to 51 percent.

Congestive heart failure patients spent an average of 11.90 days in the hospital per year, compared to 3.29 days for patients with hypertension, 4.26 days for those with diabetes, and 2.24 days for those with dyslipidemia. Total health care costs per patient per year averaged $39,076 for congestive heart failure, $14,813 for hypertension, $17,955 for diabetes, and $12,688 for dyslipidemia. Pharmacy costs (for all prescriptions filled, not just those for the four chronic vascular conditions) ranged from $2,867 to $3,780 per patient per year (see Appendix Table A3).[17]

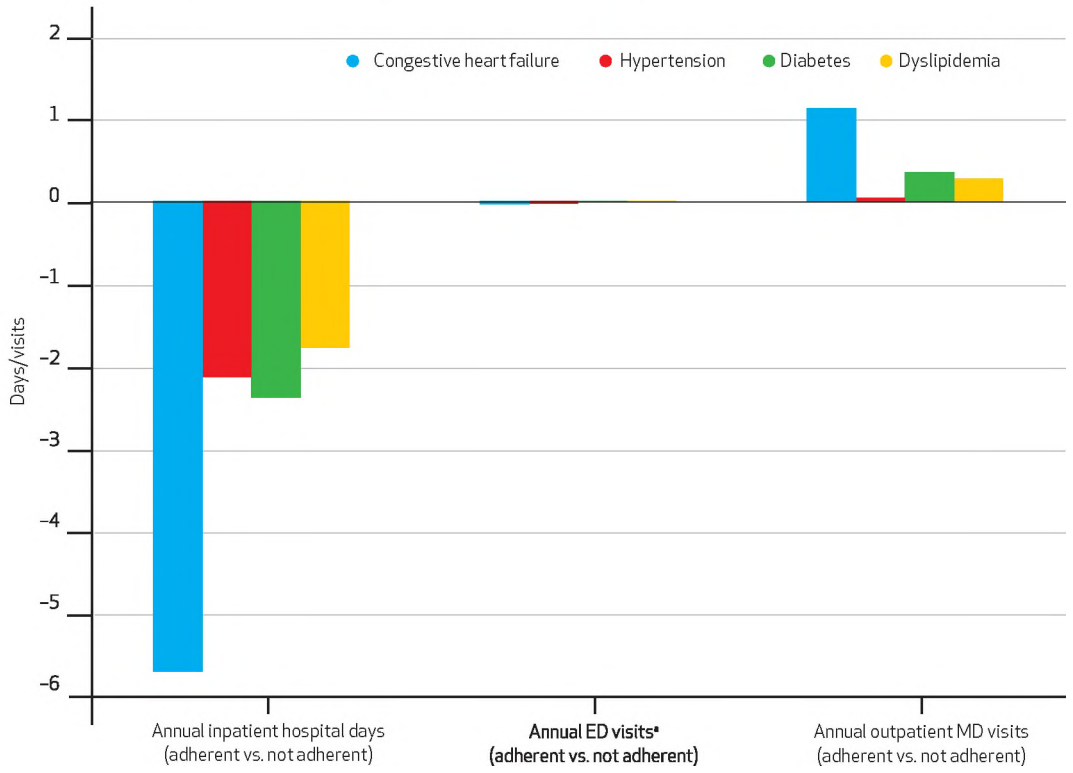
Exhibit 1 presents estimates of the effects of adherence versus nonadherence from the multivariate models of health services use.[24] Across all conditions, adherence was associated with significantly lower annual inpatient hospital days, ranging from 1.18 fewer days for dyslipidemia to 5.72 fewer days for congestive heart failure. Annual emergency department visits were fractionally lower (between 0.01 and 0.04 visits per patient per year) among adherent patients. Finally, adherent patients visited their doctors more often than their nonadherent peers did, with the exception of people with hypertension (not statistically significant).

The effect of adherence on hospitalization was greater (in absolute value) for people age sixty-five and older than for younger patients for all conditions. Adherent patients in the older group had 5.87 (in cases of congestive heart failure), 3.14 (hypertension), 3.41 (diabetes), and 1.88 (dyslipidemia) fewer inpatient hospital days annually (Exhibit 2), compared to 4.74, 0.57, 0.83, and 0.44 fewer days, respectively, for adherent patients in the younger group (data not shown).

Exhibit 3 presents results from the models of health services spending. As we anticipated, adherent patients had higher pharmacy spending than those who were not adherent. The average

EXHIBIT 1

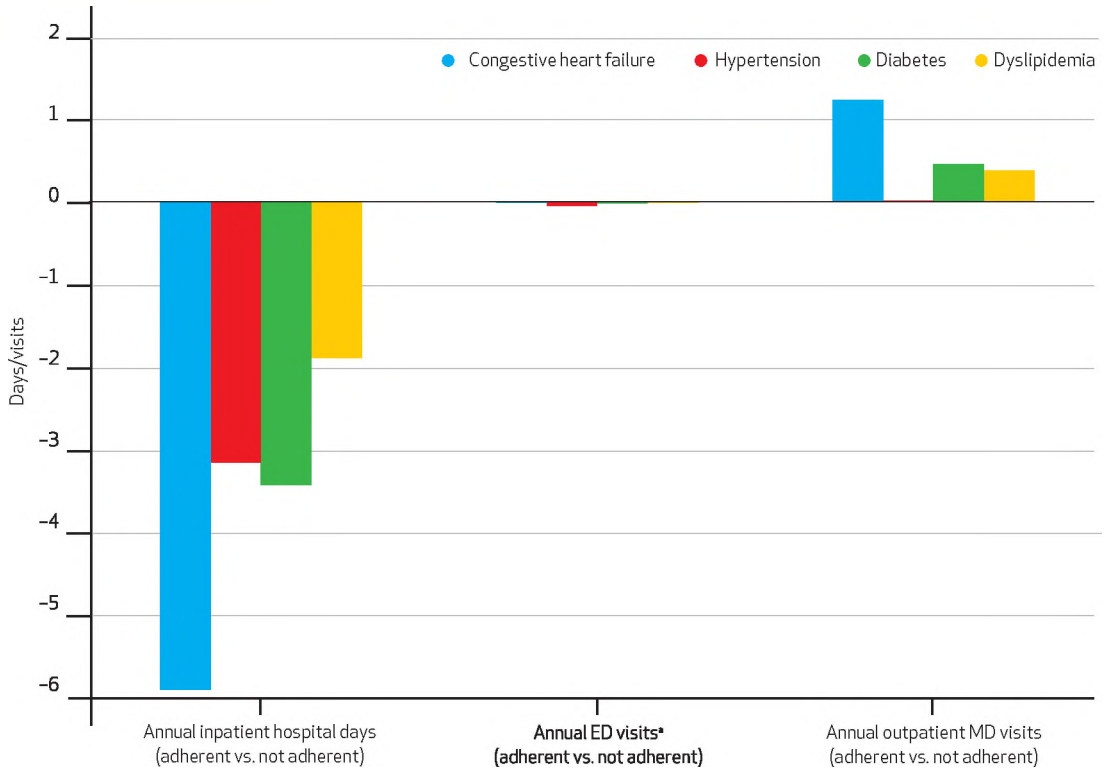
Impact Of Medication Adherence In Chronic Vascular Disease On Health Services Use, 2005–08



SOURCE CVS Caremark integrated pharmacy and medical administrative claims data, January 1, 2005–June 30, 2008. **NOTES** Presented are marginal effect estimates from linear fixed-effects models of health services use. All models included a weighted Charlson Comorbidity Index (see Notes 18–20 in text); two year-indicator variables; dummy variables for age 65 or older, male, and adherent; and interaction terms for adherent with male and age 65 or older. All estimates were significant at $p < 0.01$ except emergency department (ED) visits for congestive heart failure patients ($p < 0.05$) and outpatient physician visits for patients with hypertension (not significant). [a]Values for this segment of the exhibit are as follows. Congestive heart failure: −0.04; hypertension: −0.03; diabetes: −0.02; and dyslipidemia: −0.01.

EXHIBIT 2

Impact Of Medication Adherence In Chronic Vascular Disease On Health Services Use For Patients Age 65 And Older, 2005–08



SOURCE CVS Caremark integrated pharmacy and medical administrative claims data, January 1, 2005–June 30, 2008. **NOTES** Presented are marginal effect estimates from linear fixed-effects models of health services use. All models included a weighted Charlson Comorbidity Index (see Notes 18–20 in text); two year-indicator variables; dummy variables for age 65 or older, male, and adherent; and interaction terms for adherent with male and age 65 or older. All estimates were significant at $p < 0.01$ except emergency department (ED) visits for congestive heart failure patients (not significant), emergency department visits for dyslipidemia patients ($p < 0.10$), and outpatient physician visits for hypertension patients (not significant). [a]Values for this segment of the exhibit are as follows. Congestive heart failure: −0.01; hypertension: −0.05; diabetes: −0.02; and dyslipidemia: −0.01.

annual pharmacy spending of adherent patients was $1,058 more for those with congestive heart failure, with comparable figures of $429 for hypertension, $656 for diabetes, and $601 for dyslipidemia.

In all four conditions, annual medical spending was significantly lower for adherent patients. Adherence reduced average annual medical spending by $8,881 in congestive heart failure, $4,337 in hypertension, $4,413 in diabetes, and $1,860 in dyslipidemia.

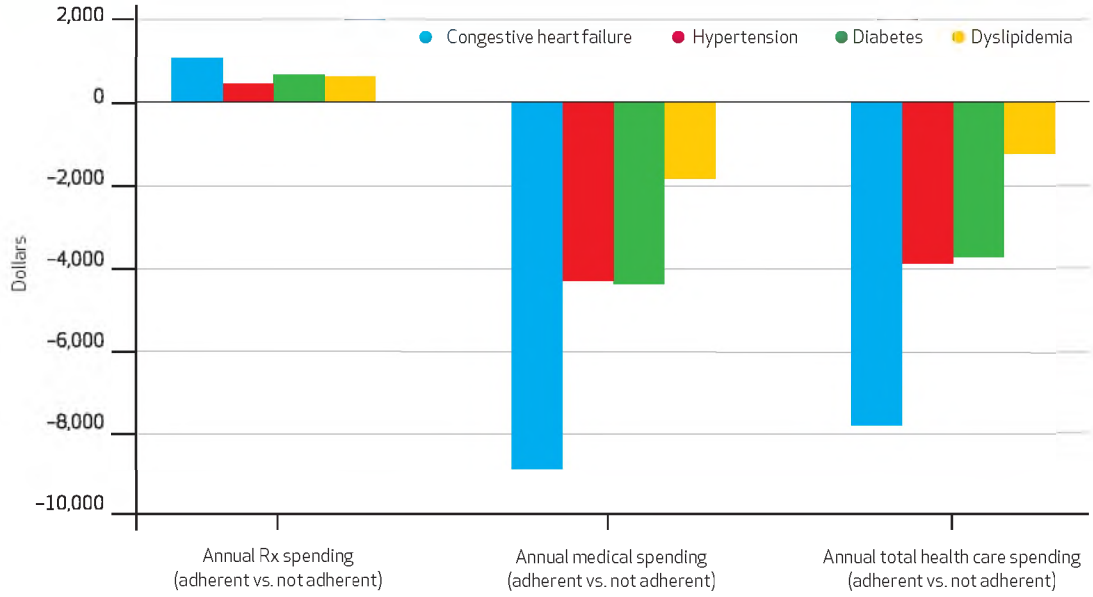
Particularly important from a policy perspective is the impact of medication adherence on total health care spending. Across the board, adherent patients spent significantly less than nonadherent patients. Annual per person savings amounted to $7,823 for congestive heart failure, $3,908 for hypertension, $3,756 for diabetes, and $1,258 for dyslipidemia. Combining the increases in pharmacy spending with the decreases in medical spending, average benefit-cost ratios from adherence for the four vascular conditions we examined were 8.4:1 for congestive heart failure, 10.1:1 for hypertension, 6.7:1 for diabetes, and 3.1:1 for dyslipidemia.

The impact of adherence on total health care spending was similar for patients in both age groups with congestive heart failure, but the effects of adherence in the other three conditions were more pronounced for patients age sixty-five and older. Annual total per person health care savings in the older group were $7,893 for congestive heart failure, $5,824 for hypertension, $5,170 for diabetes, and $1,847 for dyslipidemia (Exhibit 4). Average benefit-cost ratios from adherence for this group were 8.6:1 for congestive heart failure, 13.5:1 for hypertension, 8.6:1 for diabetes, and 3.8:1 for dyslipidemia.

In general, adherence effects did not differ substantially by sex. The exception was in congestive heart failure, where females experienced greater reductions in health services use and

EXHIBIT 3

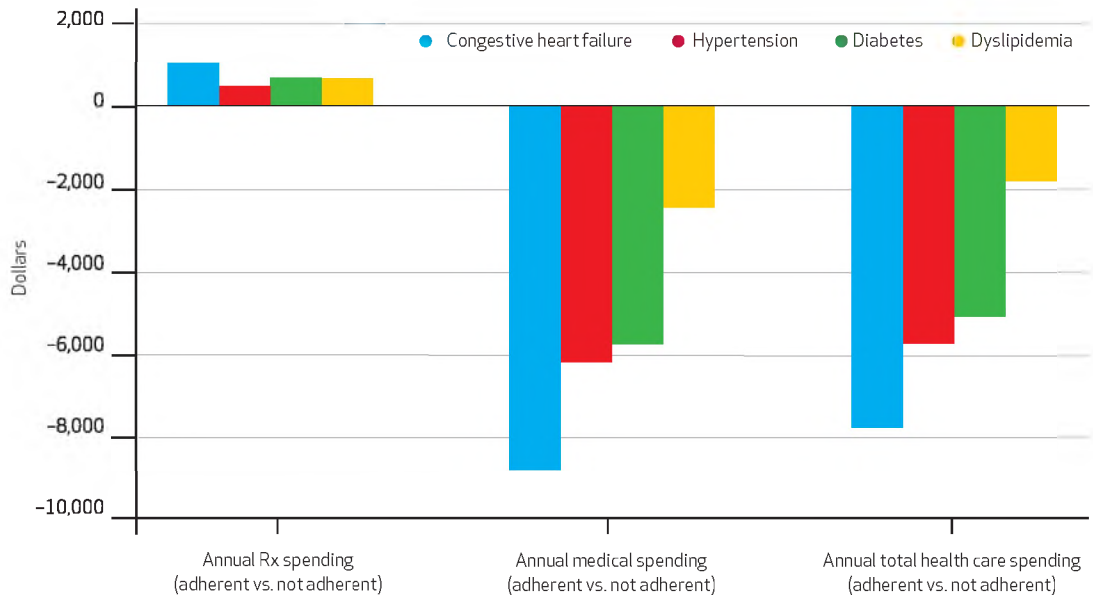
Impact Of Medication Adherence In Chronic Vascular Disease On Health Services Spending, 2005–08



SOURCE CVS Caremark integrated pharmacy and medical administrative claims data, January 1, 2005–June 30, 2008. **NOTES** Presented are marginal effect estimates from linear fixed-effects models of health services cost. All models included a weighted Charlson Comorbidity Index (see Notes 18–20 in text); two year-indicator variables; dummy variables for age 65 or older, male, and adherent; and interaction terms for adherent with male and age 65 or older. All estimates were significant at $p < 0.01$.

EXHIBIT 4

Impact Of Medication Adherence In Chronic Vascular Disease On Health Services Spending For Patients Age 65 And Older, 2005–08



SOURCE CVS Caremark integrated pharmacy and medical administrative claims data, January 1, 2005–June 30, 2008. **NOTES** Presented are marginal effect estimates from linear fixed-effects models of health services cost. All models included a weighted Charlson Comorbidity Index (see Notes 18–20 in text); two year-indicator variables; dummy variables for age 65 or older, male, and adherent; and interaction terms for adherent with male and age 65 or older. All estimates were significant at $p < 0.01$.

spending. All model results are presented in Appendix Tables A5–A11.[17]

Discussion

Our results are evidence that medication adherence reduces total annual health care spending for people with chronic vascular disease. Savings are realized mainly through reduced inpatient hospital days and emergency department visits. Moreover, adherence effects are more pronounced for patients age sixty-five and older.

The issue of medication nonadherence in the elderly was implicitly addressed by the Affordable Care Act of 2010. This legislation progressively reduces, and will eventually close, the existing gap in prescription drug coverage for Medicare beneficiaries (the Part D "doughnut hole"). More generally, the act provides for therapy management and covers certain wellness programs that might improve medication adherence and other aspects of patient compliance with health regimens.[25] Our work suggests that policy makers were prudent in including those provisions in the new law.

Our analysis demonstrates that the additional pharmacy spending incurred from adherence is more than offset by the medical savings realized. The question then becomes whether or not policies and programs that are implemented to improve adherence can do so at costs that do not exceed the expected benefits. Findings from Medicare disease management demonstrations have been mixed: Only 20 percent of evaluated programs have been near or at budget-neutrality.[26]

However, the cost of an adherence intervention is directly related to the mode of delivery. Complex, coordinated care involving physicians, nurses, and case managers may be both successful and costly. Alternatives that require fewer resources—such as electronic monitoring devices and pharmacist-led patient counseling—have shown promise in improving patients' medication adherence at less expense.[27]

To permit rigorous evaluation, policy analysts trained in economics methods should collect data on the costs and benefits of adherence interventions. It is important to note that altering pharmacy benefit designs to improve medication adherence does not necessarily impose additional costs. Value-based insurance designs address cost-related nonadherence by reducing or eliminating patient copayments for medications used to manage chronic conditions. These designs do not add to spending; rather, they shift spending from the enrollee to the plan's sponsor.[28]

Conclusions

In light of the Affordable Care Act's expansion of access to medical care, policy makers must now search for ways to improve health outcomes while reducing spending. Our results indicate that despite higher pharmacy spending, medication adherence by patients with chronic vascular disease provides substantial medical savings, as a result of reductions in hospitalization and emergency department use. Benefit-cost ratios range from 2:1 for adults under age sixty-five with dyslipidemia to more than 13:1 for older patients with hypertension.

Given these findings, plan sponsors, government payers, and patients should consider participating in programs that improve medication adherence, as long as intervention costs do not exceed the estimated health care savings. Value-based insurance design, electronic monitoring devices, and pharmacist-led counseling are among the least costly alternatives. No matter what the intervention, actively encouraging medication adherence for chronic disease should be a top priority. ■

Selected findings from this work were delivered in an oral presentation at the third biennial conference of the American Society of Health Economists at Cornell University, in Ithaca, New York, on June 21, 2010. A related poster presentation was given at the 2010 AcademyHealth Annual Research Meeting, in Boston, Massachusetts, on June 28, 2010. The authors thank participants at those meetings for their interest and suggestions. Invaluable were the critical comments of three anonymous reviewers and the editors. The authors are thankful for those individuals' contribution to this work. The views expressed by the authors do not necessarily represent the views of the Centers for Medicare and Medicaid Services or the US government.

NOTES

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17 To access the Appendix, click on the Appendix link in the box to the right of the article online.

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22 See Appendix Section 2 (see Note 17) for a comparison of our linear fixed-effects models to pooled ordinary least-squares estimation. This exercise largely confirms the endogeneity of adherence and shows that prior studies probably overestimated the absolute value of the impact of adherence on health services use and cost.

23 Fixed-effects modeling does not allow for the control of confounders that vary over time. Thus, for example, if patients who become adherent simultaneously start exercising regularly (assuming that both of these behavioral changes reduce health services use and spending), the estimated impact of adherence would remain biased. Another drawback of the linear fixed-effects modeling approach is that it leaves open the possibility of reverse causality. That is, the reported relationships could indicate an impact of hospitalization on adherence. For example, a hospitalization may shock a patient into becoming adherent. We examined this possibility by estimating the impact of prior adherence on hospitalization and found no effect.

24 Bivariate relationships between adherence and health services use and spending are presented in Appendix Table A4 (see Note 17). The complete set of linear fixed-effects model results are provided in Appendix Tables A5–A10.

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28 Of course, there would certainly be some administrative fixed cost involved in implementing value-based insurance design, and lower copayments might have moral-hazard costs. That is, with low or no out-of-pocket spending required, patients might be induced to fill more prescriptions than necessary, possibly for consumption by other patients with higher copayments.

ABOUT THE AUTHORS: M. CHRISTOPHER ROEBUCK, JOSHUA N. LIBERMAN, MARIN GEMMILL-TOYAMA & TROYEN A. BRENNAN

M. Christopher Roebuck is director of health economics and strategic research at CVS Caremark.

Christopher Roebuck and his collaborators at CVS Caremark, the pharmacy health services provider, found themselves well positioned to address a long-standing question: Do people who properly and consistently use medications to manage chronic illness have markedly lower health care spending? "Research kept showing an association," Roebuck says. "Still, investigators couldn't confidently credit adherence for the lower costs." But Roebuck's team had access to integrated medical and pharmaceutical claims data, and expertise in advanced econometric methods—the tools needed to start settling the matter, and to identify the medical services that adherence reduced.

Medication adherence might not be a new issue, Roebuck explains, but it has yet to receive due consideration. Concerns over possible decreased medication use among patients whose high drug spending placed them in the Medicare Part D doughnut hole "heightened interest in adherence and made it part of the reform conversation," he notes. He and his coauthors hope that their current findings will increase the attention focused on adherence, as well as the full clinical and cost-saving potential of pharmacy management.

Roebuck, a health economist, joined CVS Caremark in 2002 and is now its director of health economics and strategic research. He first used the econometric techniques employed in the study reported on here to explore the economics of substance abuse, while he was a senior research associate at the University of Miami School of Medicine. A doctoral candidate in public policy and economics at the University of Maryland Baltimore County, he holds a master of business administration degree in finance from the University of Miami.

Joshua N. Liberman was vice president of strategic research, analytics, and outcomes at CVS Caremark.

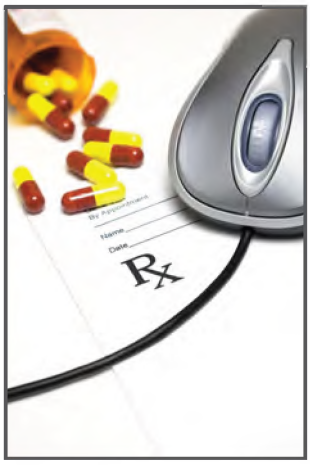
Joshua Liberman completed his twenty-year-long affiliation with CVS Caremark in December 2010. As vice president of strategic research, he directed an outcomes research unit with an emphasis on pharmacy benefit designs, prescription drug use patterns, and pharmacy services. Liberman received a master's degree in health science and a doctorate in epidemiology from the Johns Hopkins Bloomberg School of Public Health.

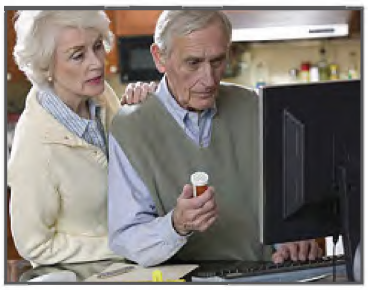
Marin Gemmill-Toyama is a health insurance specialist at the Centers for Medicare and Medicaid Services.

Marin Gemmill-Toyama, a senior research analyst at CVS Caremark until August 2010, is a health insurance specialist at the Centers for Medicare and Medicaid Services (CMS). She holds a doctorate in social policy and a master's degree in international health policy from the London School of Economics, as well as a master's degree in economics from the University of Delaware. She has participated in research projects for the Commonwealth Fund and the World Health Organization.

Troyen A. Brennan is executive vice president and chief medical officer of CVS Caremark.

Troyen Brennan has been executive vice president and chief medical officer of CVS Caremark since 2008. From 2006 to 2008 he was chief medical officer of Aetna. His academic career included appointments as a professor of medicine at Harvard Medical School (1988–2007) and a professor of law and public health at the Harvard School of Public Health (1992–2007). A member of the Institute of Medicine, a diplomate of the American Board of Internal Medicine, and the author of more than 250 original research articles, Brennan holds a master's degree in political economics from Oxford University and a law degree from Yale Law School, as well as a master of public health degree and a medical degree from Yale Medical School.





Center for
Technology and Aging

Technologies for Optimizing Medication Use in Older Adults

Position Paper
October 2009

Table of Contents

List of Abbreviations

A1c ..... Glycated hemoglobin or HbA1c
ADEs ..... Adverse drug events
APHID ..... Automated Patient History Intake Device
CCD ..... Continuity of care document
CCR ..... Continuity of care record
CDA ..... Clinical document architecture
CMS ..... Centers for Medicare & Medicaid Services
EHR ..... Electronic health record
HL-7 ..... Health Level 7 (a medical information interface standard)
IHI ..... Institute for Healthcare Improvement
INR ..... International Normalized Ratio
IOM ..... Institute of Medicine
IV ..... Intravenous (administration of medications)
LTC ..... Long term care
MMSE ..... Mini-mental state examination
MTMP ..... Medication Therapy Management Program
NGO ..... Non-governmental organization
Part D ..... Medicare's prescription drug program
PHR ..... Personal health record
PT ..... Prothrombin time
RFID ..... Radio-frequency identification
The Center .... Center for Technology and Aging
VA ..... United States Department of Veterans Affairs
VHA ..... Veterans Health Administration
VNA ..... Visiting Nurse Association

Executive Summary

Medication use is ubiquitous among older adults, with 90% of older adults using one or more prescription medications per week.[2] While medications are widely appreciated, commonly used, and help many older adults lead longer, healthier, and more productive lives, there is still great room for improvement in medication use.

The paper provides an overview of the medication-use process, and discusses three areas of opportunity for medication optimization for older adults: 1) medication reconciliation, 2) medication adherence, and 3) medication monitoring. Medication-use problems can occur at different phases in the medication-use process. To help pinpoint where medication-use problems occur, what opportunities exist to solve these problems, and which technologies may be beneficial in the process, it is helpful to visualize the medication-use process as a series of five steps or phases: assess, prescribe, dispense, administer, and monitor.[3-5] Medication reconciliation problems mainly present in the Assess and Prescribe phases of the medication-use process, whereas medication adherence problems commonly occur in both the Dispense and Administer phases.

A number of technology-enabled interventions can mitigate medication-use problems, optimize process step efficiency, and improve the health and independence of older adults. In alignment with the mission of the Center for Technology and Aging, this paper will focus on technology-enabled interventions predominantly aimed at improving the health of older adults while promoting independent living in community-based, home, and long-term care settings. Patients and caregivers primarily use these technologies to improve self-management of care and enhance communication of medication information to clinicians. The technologies described in this report should be viewed as a limited sample and not an exhaustive list.

> The New England Healthcare Institute estimates that $290 billion of healthcare expenditures could be avoided if medication adherence were improved.[1]

Medication optimization solutions that reduce the cost and burden of illness among older adults are urgently needed. While medication-use problems are not limited to older adults, older adults are disproportionately affected by such problems. Greater access to proven medication optimization technologies can lead to safer, more effective medication use among older adults.

Introduction

The Center for Technology and Aging is devoted to helping California and the nation more rapidly implement technologies that help older adults lead healthier lives and maintain independence. Of the many potential technology areas, the Center is focusing first on advancing technologies that improve ("optimize") medication use among older adults.[6] In September 2009, the Center launched its Medication Optimization Initiative, which includes the Center's Medication Optimization Diffusion Grants Program.

The Center's Medication Optimization Initiative aims to increase use of technologies that:

- Help improve medication use in older adults (60+ years old) with chronic health conditions
- Enable independent living and the ability to live in the setting of one's choice
- Will lead to improvements in the cost and quality of care
- Reduce the need to move to more intensive, higher-cost care settings
- Reduce the burden on formal and informal caregivers
- Improve medication reconciliation, medication adherence, and/or medication monitoring
- Are used in the home, as well as other long-term and post-acute care settings
- Include medical devices and information and communications technologies

This paper identifies and describes issues and opportunities for the Medication Optimizaton Diffusion Grants Program and related initiatives. The paper provides an overview of the medication-use process, and discusses three areas of opportunity for medication optimization in older adults: 1) medication reconciliation, 2) medication adherence, and 3) medication monitoring. Example technologies that support each area are also described. The Center believes that examples help to transform the abstract into the concrete. However, the technologies mentioned in this report should be viewed as a limited sample and not an exhaustive list.

Many research sources informed and guided this work, including articles published in peer-reviewed journals, research and position papers from government and non-government websites, views expressed in expert panels and informant interviews, and pre-existing research reports from the Health Technology Center and the New England Healthcare Institute. The Center views this position paper as a starting point for discussion, and expects to build on this foundation by collaborating with and learning from stakeholders who bring their extensive knowledge, experience, and innovative ideas to the collaboration process.

Overview of Medication Use in Older Adults

Medication use is ubiquitous among older adults. According to surveys, 90% of older adults use one or more prescription medications per week,[2] 41% of older adults take five or more medications,[7, 8] and 12% use 10 or more medications per week.[2]

Medication-related problems are not limited to older adults. But older adults are disproportionately affected by such problems because so many use medications. Medication-use problems are also exacerbated by conditions that are inherent to aging. Such conditions include the high prevalence of co-morbid illness and polypharmacy use. To further compound the challenge of medication problems among older adults, information about appropriate dosing and the risk of adverse reactions in segments of this population are often unavailable. Frail, older adults with multiple health challenges are often excluded from clinical drug trials—clinicians' primary source of information about the effects of particular medications.

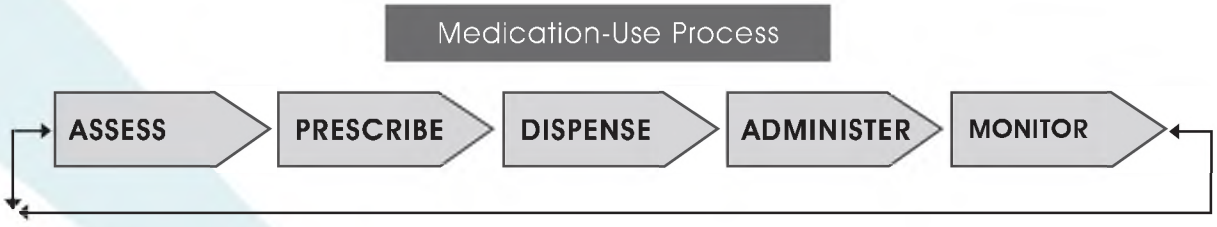
Suboptimal medication use can increase the burden of illness and result in higher costs to families and society:

- Adverse drug events are a leading cause of morbidity and mortality. According to the Institute of Medicine (IOM), more than 2 million serious adverse drug events and about 100,000 deaths occur annually due to medication problems.[4]
- In one study, the risk of hospitalization was twice as high in chronically ill individuals who did not take their medications as directed, compared to chronically ill individuals who did.[9]
- The New England Healthcare Institute estimates that $290 billion of healthcare expenditures could be avoided if medication adherence were improved.[1]

While medications are widely appreciated, commonly used, and help many people lead longer, healthier, and more productive lives, there is still great room for improvement in medication use. Medications are too often underused, overused, or misused.[4, 10]

Medication-use problems can occur at different phases in the medication-use process. To help pinpoint where such medication-use problems occur, what opportunities exist to solve these problems, and which technologies may be useful to support such solutions, it is helpful to visualize the medication-use process as a series of steps or phases.[3-5]

The diagram below describes the medication-use process in five steps: assess, prescribe, dispense, administer, and monitor. Underuse of medications tends to occur at the prescribe and administer phase of the medication-use process. In the prescribe phase, underuse includes the failure to prescribe medications for which there is an evidence base for reduction in morbidity and mortality.[4]



Overview of Medication Use in Older Adults

Underuse in the administer phase can occur because of forgetfulness, which is unintentional, or an intentional decision to stop using a medication because of side effects or other reasons. Underuse in the administer phase often falls under the rubric of "medication nonadherence."

Overuse of medications occurs in the prescribing phase when there is no evidence base for reduction in morbidity and mortality, but a prescription is issued anyway. Overuse is best documented in the use of antibiotics for treatment of colds, upper respiratory infections, and bronchitis.[4] Overuse by individual patients can also occur in the administer phase when forgetfulness leads to double dosing.

Misuse of medications is the inappropriate use of medications. Misuse can include unintentional errors in administration that lead to adverse reactions. Misuse also includes intentional overuse to harm oneself or to satisfy an addiction. In the context of this paper, misuse will refer to suboptimal medication adherence, which includes failure to follow treatment recommendations, i.e., not picking up the right drug once it is dispensed, and not administering it on time, in the right dose, and for the right length of time. Failing to follow instructions, missing doses, taking double doses, and taking medication at the wrong time are all adherence-related misuses. Another important "misuse" of medications that is highlighted in this paper, is inadequate monitoring.

Information and communication are the glue that holds the process together, helping to ensure successful outcomes. The process of assessing patient needs and prescribing, dispensing, administering, and monitoring medications often depends on accurate, complete and timely information. If members of the medication-use social system (patients, physicians, pharmacists, etc.) ignore important information or do not have access to important information, the opportunity to respond to patient needs and optimize the treatment regimen will be lost.

Opportunities for Medication Optimization

Significant opportunities to improve medication use exist in the following three areas: medication reconciliation, medication adherence, and medication monitoring. Interventions in these three opportunity areas can address medication-use problems that are important, widespread, and potentially addressable by technology-enabled innovations. Medication reconciliation problems mainly present in the assess and prescribe phases of the medication-use process, while medication adherence problems commonly occur in the dispense and administer phases.

After providing a high-level snapshot, each opportunity area will be described, along with example technologies that may support each of these opportunities. Note that these opportunities and example technologies serve as a starting point for consideration, and are not meant to represent all possible opportunities and technologies for medication optimization.

Chart 1 provides a high-level view of the medication-use phases, and the goals associated with each. A limited set of example technologies is also shown. These example technologies both support each of the phases and goals and align with the mission and goals of the Center for Technology and Aging. For a broader look at the process steps, goals, and supportive technologies, see Appendix A.

Chart 1. The Medication-Use Process:
Process Step Goals and Example Technologies for Patients and Caregivers

Medication Reconciliation		Medication Adherence		Medication Monitoring
Assess	**Prescribe**	**Dispense**	**Administer**	**Monitor**
Goals • Patient history includes a complete and accurate medication list • Patient needs are accurately conveyed and understood	**Goals** • Medication orders are documented and shared with patients	**Goals** • Medication is made available • Medication picked up by patient • Patient and caregivers understand medication instructions	**Goals** • Individual dose dispensed • Individual dose taken by patient (on time, in the right dose, and for the right length of time)	**Goals** • Routine dosing and tracking of medication • Reports and trending information from medication log generated • Clinician adjusts medication as needed • Prescriptions refilled
Example Technologies • Medication List Software • Personal Health Records	**Example Technologies** • Medication List Software • Personal Health Records	**Example Technologies** • Teleconsultations • Online Patient Education • Cognitive Assessment Tools • Pharmacy Kiosks	**Example Technologies** • Medication Adherence Devices (integrated and standalone, simple and advanced function)	**Example Technologies** • Personal Biometric Testing Device • Wireless Communication Devices • Personal Health Records

Opportunities for Medication Optimization

Medication Reconciliation

Medication reconciliation is the process of creating an accurate list of all medications a patient is taking and comparing that list against new physician orders. The five main steps of the process are: 1) developing a list of current medications; 2) developing a list of medications to be prescribed; 3) comparing the medications on the two lists; 4) making clinical decisions based on the comparison; and 5) communicating the new list to appropriate caregivers and to the patient.[11]

Medication Reconciliation	
Assess	**Prescribe**
Goals • Patient history includes a complete and accurate medication list • Patient needs are accurately conveyed and understood	**Goals** • Medication orders are documented and shared with patients
Example Technologies • Medication List Software • Personal Health Records	**Example Technologies** • Medication List Software • Personal Health Records

Since most medication errors are made at the "interfaces of care," the Joint Commission asserts that medication reconciliation should be done at every transition of care, including changes in setting, service, practitioner, or level of care. A change in a patient's condition is also a critical point when medication reconciliation is needed.[12]

When care transitions occur, the complete and reconciled list of medications should be communicated to the patient's known primary care provider, or the original referring provider, or a known next provider of service. When a patient transitions from a service organization to home, a complete and reconciled list of the patient's medications should be provided directly to the patient (and the patient's family as needed). When appropriate, the list should be explained and the communication should be documented.[13] Patient assessment is also an important component of the medication reconciliation.

A primary goal of medication reconciliation is to avoid adverse drug events (ADEs) and the associated increases in health problems, hospitalizations, and emergency room visits. While not all ADEs are due to medication reconciliation errors, the data below suggest that such errors may play an important role.

- Approximately 20% of patients discharged from the hospital to their home experienced an adverse event in one study. More than 66% of these adverse events were medication related[14]
- Medication discrepancies were the most common drug-related problem at the time of hospital discharge in one study and the cause of half of all preventable adverse drug events 30 days after discharge[15]

Opportunities for Medication Optimization

Medication Reconciliation

- Another study found that half of previously hospitalized patients who were receiving continuing care from their primary care physician experienced at least one medication error within two months of discharge from the hospital[16, 17]

According to the Institute for Health Improvement (IHI), a well-designed medication reconciliation process has the following characteristics:

- Uses a patient-centered approach
- Makes it easy to complete the process for all involved
- Helps people understand the benefits of medication reconciliation
- Minimizes the opportunity for drug interactions and therapeutic duplications by making the patient's list of home medications available when physicians prescribe medications
- Provides the patient with an up-to-date list of medications
- Ensures that other providers who need to know have information about changes in a patient's medication plan[18]

Physicians are often legally responsible for medication reconciliation errors.[17] However, the patient is the one constant in the continuum of care. Hence, patients, family members, or other informal caregivers should be encouraged to carry a current medication list to all medical encounters and settings.[17] As electronic health records (EHRs) remain absent in most care settings and systems, patients (and caregivers) should take an active role in the medication reconciliation process. Even if a care provider has an EHR system, patients need to actively check the accuracy of medication data. In a recent study of medication discrepancies, 70% of medications recorded in patients' electronic medical records were no longer being taken.[19]

Opportunities for Medication Optimization

Medication Reconciliation Technologies

Patients and caregivers can utilize technologies to help mitigate medication reconciliation problems. Using a variety of online programs and technologies, patients or caregivers can provide complete, up-to-date patient medication histories. There are several models for medication lists. Some online medication lists only allow one-time entry of medication information, while others electronically store information for continuous updates. Most lists require patients to enter drug, dose, and other medication information, which can leave room for error. Electronic lists in this form are often only accessible to patients and caregivers. In order for clinicians to access this medication list, patients must bring a printout of the list with them to the medical exam.

Examples of one-time entry medication lists are listed below. See IHI.org and ntocc.org for additional examples.

Name	Organization	Description
My Medication Log	Cardiovascular and Public Health Detailing Programs	A medication log for use in the Cholesterol Action Kit http://www.ihi.org/IHI/Topics/PatientSafety/MedicationSystems/Tools/MyMedicationLog.htm
Universal Medication Form	McLeod Health in Florence, SC	A form where patients can enter medications used, allergies, and immunization records
Health and Safety Passport	California Pacific Medical Center, San Francisco, CA	Patients list their medications, health history, and other relevant information
Med List	A statewide, collaborative initiative in Massachusetts	Medication list to keep track of patient medications and supplements. Also offers tips for using medications wisely.
My Medicine List	American Society of Health-System Pharmacists (ASHP)	A tool where patients can develop and manage their own medication list. The tool can be found on the ASHP Foundation website and on http://www.safemedication.com/meds/medForm.cfm
Pill Card	Agency for Healthcare Research and Quality (AHRQ)	Information on how to develop an easy-to-use "pill card" for patients, parents, or anyone who has a hard time keeping track of their medicines at http://www.ahrq.gov/qual/pillcard/pillcard.htm
My Medicine Record	Food and Drug Administration (FDA)	Patients list prescription medicines, over-the-counter medicines and dietary supplements. http://www.fda.gov/cder/consumerinfo/my_medicine_record.htm

Opportunities for Medication Optimization

Medication Reconciliation Technologies

Movement toward continuous electronic medication lists begins to offer increased clinician access, while interoperability opportunities emerge to pull information from prescription records and integrate with personal health records (PHRs) and EHRs. PHRs are a set of technologies through which patients can access and manage their own health information, regardless of care setting. The contents of PHRs vary, but can include at a minimum diagnosis/problems, medications, allergies, and past medical history. Additionally, PHRs can have a provider/clinician portal, where providers can enter and maintain information. Common across many of these systems are support for the Continuity of Care Record (CCR) as outlined by the American Society for Testing and Materials (www.ccrstandard.com) and/or the Continuity of Care Document (CCD) outlined by HL7 (www.hl7.org). Both standards provide a core data set of the most relevant administrative, demographic, and clinical information facts about a patient's healthcare. There are currently hundreds of different PHR offerings, including services from Google and Microsoft as well as a non-profit/for-profit partnership collaborative: Dossia (www.dossia.org). In addition, many health systems and large clinics have developed their own PHRs that integrate with their EHRs. In the long term, many providers will have access to integrated PHRs and EHRs. Their EHR/PHR's will be able to accept CCR/CCD information from other providers on an automatic or on-demand basis. Most provider organizations will have added portal functions to their PHR to provide improved access, self-service, continuity of chronic care, and remote care.

Walgreen's currently provides pharmacy patients access to their medication history through online tools. Patient drug and dose information input errors can be reduced as prescription information and filling history is automatically pulled into the list. Like other medication lists, patients often fail to share this information with the clinician. Walgreens has recently partnered with Microsoft® HealthVault™, a web-based PHR platform, giving Walgreens pharmacy patients the ability to upload their medication history into HealthVault and share this information with caregivers, clinicians, and others. Medication information will be automatically updated daily in HealthVault, allowing patients to share their most up-to-date health information while avoiding manual entry of data.[20]

Opportunities for Medication Optimization

Medication Reconciliation Technologies

Check-in medication kiosks, piloted at the Veterans Health Administration (VA), have patients and caregivers review and adjust their medication history, pre-populated from their EHR. The VA developed the Automated Patient History Intake Device (APHID) for use in the ambulatory setting, where patients review and update their medication histories before their appointments. APHID pulls medication lists from the VA's electronic health record and has patients review the name, dose, frequency and pictorial representation of the medications. Patients have the opportunity to input information from non - VA clinician visits into the kiosk, which can then be used on subsequent visits. Providers then review the updated medication history during the appointment, looking for possible drug interactions and duplicate therapies. During the pilot of APHID, a study found that older adults thought the kiosk was simple to use (75.4%) and navigate (66.7%), and that the medical information was easy to understand (94.2%). APHID's utilization of EHR and patient input on medication history prior to medical appointments also has the potential to reduce clinician reconciliation work and streamline work processes. While the reconciliation process cannot be completely replaced by technology, kiosks reduce the time clinicians spend entering medication information while engaging patients and caregivers in managing the patient's health.

Opportunities for Medication Optimization

Medication Adherence

The World Health Organization defines adherence as "the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider."[9] Non-adherent patient behaviors occur at two main points in the medication-use process (Dispense and Administer). A significant portion (12%) of patients will not take possession of dispensed medications.[8] Of the patients that do pick up the dispensed prescription, 40% will not administer the medications correctly.[21] Medication adherence problems can also arise in the Monitor phase of the process, as patients may self-adjust their medications inappropriately, or stop altogether because of side effects.

Medication Adherence	
Dispense	**Administer**
Goals • Medication is made available • Medication picked up by patient • Patient and caregivers understand medication instructions	**Goals** • Individual dose dispensed • Individual dose taken by patient
Example Technologies • Teleconsultations • Online Patient Education • Cognitive Assessment Tools • Pharmacy Kiosks	**Example Technologies** • Medication Adherence Devices (integrated and standalone, simple and advanced function)

Suboptimal medication adherence can have negative consequences for individuals, families, and society, as medication non-adherence significantly increases the cost and burden of illness.[8] The New England Healthcare Institute estimates that $290 billion of health care expenditures could be avoided each year if medication adherence were improved.[1]

Medication non-adherence is considered responsible for:

- 33%-69% of medication-related hospital admissions
- 23% of all nursing home admissions
- Increased use of expensive, specialized medical resources
- Unneeded medication changes
- Unexplained treatment failures
- Repeat office visits[8]

Opportunities for Medication Optimization

Medication Adherence

Poor medication adherence has many root causes. Adherence is influenced by prior experiences, cultural factors, personal beliefs, treatment side effects, patient-provider relationships, and financial constraints.[22] Medication adherence can be especially difficult for older adults. Physical, cognitive, and sensory health often decline with age. Mobility difficulties, forgetfulness, and diminished sight and hearing make it more difficult to acquire medications, understand instructions, remember to take medications on time, and read and hear medication-taking instructions. Because medication adherence is considered an instrumental activity of daily living, the ability to manage medications successfully is an important factor in maintaining independence in the older adult population.[23]

Because medication adherence is multi-factorial, many clinicians believe that a multi-faceted approach is most effective at improving adherence. Many also believe that adherence interventions must be customized to the individual's needs. Such interventions include:

- Simplifying the patient's medication regimen, e.g., changing from dosing three times a day to twice a day
- Identifying if the medication has untoward effects, e.g., causes side effects or financial burden
- Better motivating the patient to persist in taking their medications. (This is particularly important in chronic illnesses that are asymptomatic, such as hypertension)
- Providing cues or reminders to take medications as prescribed

According to Logue (2002) there are several ways to measure the outcomes from medication adherence interventions.

- Objective symptom assessment and physical examination, e.g., vital signs, lung and heart auscultation
- Direct indicators, e.g., blood glucose level
- Indirect indicators, e.g., pill counts, filling/refilling of prescriptions, pill diaries
- Subjective reports, e.g., patient or family statements
- Frequency of visits to emergency departments[24]

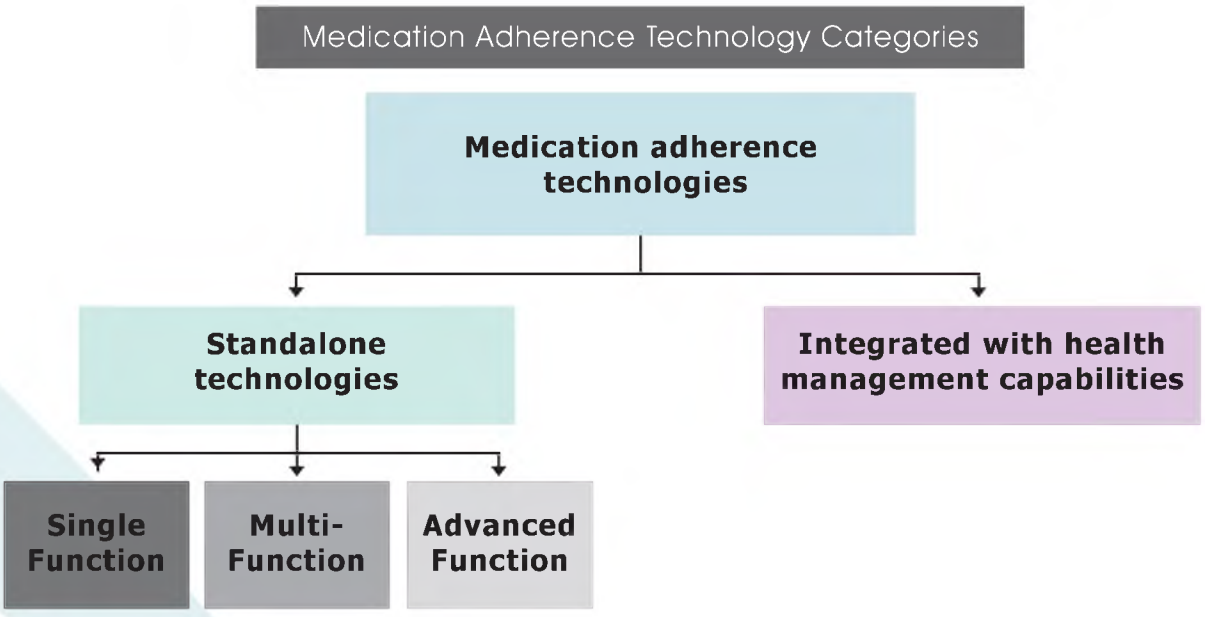
In a recent comparison of methods to assess medication adherence and classify nonadherence, patient self-report, pharmacy refill records, and use of electronic pill container lids all provided similar estimates of overall adherence. But refill records and data from the electronic pill containers were in highest statistical agreement.[21]

Opportunities for Medication Optimization

Medication Adherence Technologies

In dispensing medication to the patient, cognitive assessments can assist in determining a patient's capability for medication adherence. Specific cognitive abilities including memory, literacy, executive abilities and general cognitive status all relate to different aspects of medication adherence.[25] Common cognitive assessment tests like the Mini-Mental State Exam (MMSE) have been shown to correlate with medication adherence, especially in the elderly. Lower scores indicate lower cognitive function making patients less likely to take their medication correctly.[26] Work is currently underway to computerize cognitive assessment tests for online access by patients in the home, physician's office, community-based or long-term care setting.[27] The regular use of computerized cognitive assessments can establish a clear baseline of cognitive function and can set the stage for continuous assessment and/or assessment after injury.[28] Should cognitive assessment scores begin to fall in certain areas, medication regimes and use of more complex adherence dispenser devices can be adjusted accordingly.

Medication adherence technologies have been expanding in both variety and sophistication. Technologies can assist patients and caregivers with obtaining proper medication information, patient education, medication organization, dispensing, dose reminders, and safeguard against an overdose. Such technologies can be classified as standalone or integrated technologies. Standalone technologies tend to be less complicated and can be single-function, multi-function or have advanced functions. Integrated technologies are more complex and integrate medication management with other health management capabilities such as general health monitoring, sensors, or health information storage.



Opportunities for Medication Optimization

Medication Adherence Technologies

A technology can potentially provide one or more functions to an individual patient under a "medication administration continuum," including:[29]

1. Fill: provides patient with information and/or instructions about the drug
2. Remind: reminds patients to take medications – audibly, visually, or both
3. Dispense (e.g., in the home): automatically dispenses medications, usually at certain times/intervals
4. Ingest: detects whether or not a patient has ingested his/her medications
5. Metabolize: detects whether or not a patient has metabolized his/her medication
6. Report: logs date and time when medication is taken and reports to clinician/caregiver
7. Adjust: adjusts medication automatically if needed

Ingest, metabolize, and adjust can be considered "advanced functions" because these capabilities are still largely in development. A technology that performs one function currently available within the medication adherence technology spectrum is a single-function technology while a device that performs two or more functions currently available within the spectrum are referred to as multi-function technology. Advanced function technologies perform one or more of the currently available spectrum functions and can also perform one of the more advanced functions including detection of medication ingestion, metabolism, or adjustment.

Standalone technologies are the simplest and easiest to use; however, they lack the functionality for more comprehensive health management. Examples of standalone technologies include medication information devices, medication reminders, a medication dispenser, or a device that combines informing, reminding, and dispensing. Many standalone technologies are currently available on the market. Additional standalone technologies are being developed, including those with advanced functions. Rex the talking pill bottle is a single-function standalone device that assists visually or cognitively impaired patients with accessing recorded medication information. The pill bottle contains a speaker with recorded information from the pharmacist stating the name of the drug, what it is used for, dose, frequency, duration, side effect warnings, and refill instructions. Kaiser Permanente has implemented this technology in over 140 facilities.

A multi-function standalone technology, Philips Medication Dispensing Service, organizes and dispenses 10-30 days worth of medication (depending on the dose frequency) by individualized doses into plastic cups. Patients are reminded to take their medication based on verbal and auditory reminders. To safeguard against double dosing or missed doses the system will lock away the dispensed medication after 90 minutes if it has not been removed

Opportunities for Medication Optimization

Medication Adherence Technologies

from the device. It will then alert up to four caregivers, including health care professionals, that a dose was missed. Alert and dispensing history are uploaded daily to a web-support system allowing caregivers and clinician review. In a study comparing the Philips Medication Dispensing Service with plastic medication boxes, Philips Medication Dispensing Service was shown to reduce hospitalization rates, emergency room visits, and (where appropriate) decrease the number of medications taken by the patient. Staff at the Johnston County VNA, where the Philips Medication Dispensing Service machines were installed and where the study was conducted, thought the greatest success with the Philips Medication Dispensing Service was seen in patients on warfarin therapy or those who had mental and cognitive health issues.[30]

	Philips Medication Dispensing Service	**Medi-Set Medication Boxes**
Hospitalization per patient	0.09	0.42
Emergency Department visits per patient	0.18	0.42
Prescriptions per patient	7.62	8.65

Advanced function standalone medication technologies using direct measures, such as detecting if a patient ingested his/her medication or whether they have metabolized the medication, are mostly in development and not yet available on the market. A few examples include MagneTrace and Xhale's SMART™. The "ideal" technology would continue to improve the patient's medication adherence, and start to integrate monitoring features like automatically adjusting medication doses.

Developed more recently, integrated medication adherence technologies integrate pill dispenser and reminder systems with general health monitoring or health information storage. For example, InforMedix's Med-eMonitor System is a portable electronic medication-dispensing device, holding one month's supply of up to 25 different medications, with add-on health management features. Once dispensed, the system asks the patient to confirm they have taken the medication while recording the date and time the medication was delivered. Patients are then asked a series of health related questions about their blood pressure, blood glucose level, and signs concerning stroke. If a health problem is reported, or if no response is received over a certain period of time, the system will attempt to contact the patient, caregiver, physician or emergency services as needed. Use of the InforMedix' Med-eMonitor System was associated with improved mean medication adherence rates of over 92% compared to a 40% baseline medication adherence rate.[31] Use of the system was also associated with a reduction in Hemoglobin A1c levels in individuals with Type 2 diabetes—by an average of 18.5% in a 3-month period.

Opportunities for Medication Optimization

Medication Adherence Technologies

Integrated technologies can primarily be medication management devices with add-on health management features or home health devices with add-on medication management features. While these integrated technologies allow for more comprehensive health management, they can be more expensive and complicated than their standalone counterparts, making them more difficult to use. These integrated technologies often use a service-based pricing model (compared to a one-time fee for standalone technologies). Some integrated solutions are currently available on the market, while others are in development.

Patients have highly varied needs for medication adherence technologies. Some patients want a simple, inexpensive technology while others may have a condition requiring an expensive, integrated technology as well as a spectrum of technologies in between. There is a need for a large portfolio of technologies, from simple to complex, in order to meet needs for all patient segments in the most appropriate way.

Opportunities for Medication Optimization

Medication Adherence Technologies

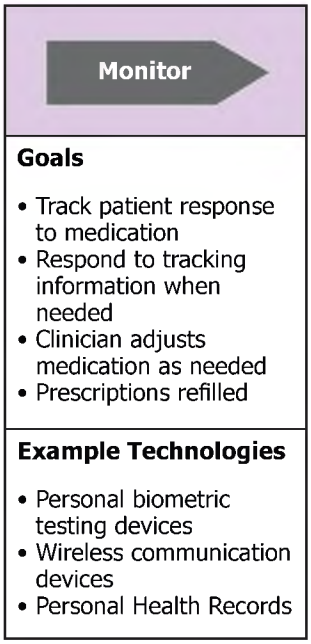
Table 3: Medication Adherence Technologies

Category	Description	Sample Techs	Pros	Cons	Market Stage	Economics	Categories in Medication Adherence Spectrum
Single-Function	Performs one function currently available within the medication adherence technology spectrum	• iGuard • Timex messenger • Rex Pill bottle • Gentle Reminder	Simplest and easiest to use technologies	• Lacks greater functionality for more comprehensive health management	Many technologies out on the market and currently used	• Usually a one-time purchase • Prices can vary widely • Relatively inexpensive	Fill, Remind or Dispense
Multi-Function	Performs two or more functions currently available within the medication adherence technology spectrum	• EMMA • Philips Medication Dispensing System • MedSignals • uBox • Dispense-a-Pill	• Mostly easy to use • Integrates multiple functions for better health management	• May be complex or require greater caregiver involvement • Lacks functionality for more comprehensive management	Many technologies out on the market and currently used	• Usually a one-time purchase • Prices can vary widely (less than $100 to $1000+)	Fill, Remind, Dispense, and Report
Advanced Function	Performs one or more of the currently available spectrum functions and can also perform one of the more advanced functions	• MagneTrace • Xhale's SMART	• Advanced technologies allow actual tracking/ adjustment/ ingestion of medication • Integrates multiple functions	• Considerably more complicated than single/ multi function without clear benefit understanding • In some cases, may lack comprehensive management functionality	Most technologies still in development	• Currently unclear - most technologies still in development • May be relatively expensive	Advanced functions: Ingest, Metabolize, and Adjust
Integrated with Health Management Capabilities	Technologies that integrate medication administration with other health-related management functions (i.e. monitoring, sensors, independent living assistance)	• Med-eMonitor • HealthHero • Home HealthPoint • Zume Life Zuri • Intel HealthGuide	• Combined offering allows for broad patient management • Many devices likely to move towards integration of health tracking/ monitoring	• Relatively complicated, may require caregiver involvement • May require greater tech knowledge	• Some techs currently on market and used • Other techs in development	• Usually upfront cost plus a monthly fee (service-oriented model) • Upfront cost can be relatively high	Fill, Remind, Dispense, and Report

Opportunities for Medication Optimization

Medication Monitoring

In the context of this paper, medication monitoring primarily refers to the process of monitoring a patient's response to a medication. Secondarily, medication monitoring can also reveal whether a patient is taking a medication, or taking an appropriate dosage at the appropriate times. Monitoring information includes biometric data, administrative data (e.g., whether a prescription was filled), subjective reports, and health service utilization data.



Inadequate monitoring is a natural target for quality improvement.[32] According to a study of ambulatory Medicare beneficiaries, adverse drug events occurred at a rate of 50 per 1000 person-years, with a rate of 14 preventable adverse drug events (ADEs) per 1000 person-years. Suboptimal monitoring was involved in 61% of the preventable adverse drug events.[2] Monitoring problems that were associated with ADEs tended to fall into the categories of monitoring too infrequently or not responding adequately to signs, symptoms, or laboratory test indications of drug toxicity.[2]

The following emphasizes monitoring in the case where a patient is at risk for adverse reactions. But medication monitoring can also be used to keep a patient motivated, e.g., measuring blood pressure to affirm that anti-hypertensive medications and a low-sodium diet are working as expected. If diet or a lower dose of medication is not enough to reach targeted goals, medication adjustments based on monitoring information can be made.

Medications that place patients at risk for adverse reactions are especially important to monitor. Warfarin is an exemplar in this case. Warfarin (an oral anticoagulant) is widely used to prevent deep vein thrombosis, and problems associated with atrial fibrillation and prosthetic heart valves.[33] While warfarin's effectiveness for these conditions is widely acknowledged, warfarin use must be closely monitored. Adverse reactions that are serious enough to send someone to the emergency room are common with warfarin. In one study, anticoagulants were second on the list of adverse drug events presenting to the emergency department, with 6.2% attributable to anticoagulants.[34, 35] (Adverse drug events associated with insulin topped the list with an 8% incidence rate.) Bleeding is the most serious and common complication of warfarin use.[36] Most bleeding problems are clinically minor,[36] but fatal hemorrhagic events claim the lives of 1% of patients each year.[32]

Opportunities for Medication Optimization

Medication Monitoring

Age is the main risk factor for bleeding[36] and this is a concern because many older adults are on warfarin therapy. In one study of ambulatory older adults, 7% were using warfarin.[2] Warfarin use among nursing home residents may be as high as 12%, according to some authors.[37] Research suggests that for every 10 year increase in age above 40, the risk of major bleeding increases 46%.[36]

Warfarin can be safely used if therapeutic monitoring is done well. The risk of bleeding can be assessed via a blood test of prothrombin time (PT) International Normalized Ratio (INR). Warfarin dosage can be adjusted down if the patient's INR is too high.[36] However, a dose of warfarin that is too low can place the patient at increased risk of stroke or other thomboembolic event. Hence, frequent monitoring is needed to decide on the optimum dosing level.

Convenient, drop-in prothrombin time testing clinics have been available for decades. At-home or near-home prothrombin testing devices are widely available and Medicare payment coverage is available for beneficiaries who are using warfarin to prevent problems from chronic atrial fibrillation, venous thromboembolism, and heart valves.

Opportunities for Medication Optimization

Medication Monitoring Technologies

Point-of-care testing devices are available to monitor blood pressure, peak flow (for asthma), blood glucose (for diabetes), and a host of other health conditions. Many devices can interface with a personal computer, and increasingly with home monitoring devices. Data can also be uploaded to a clinician's portal or other remote site.

Returning to the example of home monitoring of warfarin, point-of-care testing devices have increased patients' role in the management of their health, reducing visits to warfarin clinics. Many studies have shown effective home and self-management of anticoagulation therapy.[38, 39] Communication tools and devices to streamline medication dose adjustments are also becoming more sophisticated and reliable. In a proof-of-concept study, clinicians successfully used a decision support tool to calculate dose modifications and relayed the changes through an interactive voice response system.[40] An internet-based medication adjustment tool (using an algorithm and clinician supervision) was associated with better patient anticoagulation control (74% time in therapeutic range) compared to an anticoagulation management service (58.6% time in the therapeutic range) for home warfarin monitoring.[40]

Wireless communication devices including cell phones, computers, point of care testing devices and automated dispensing devices enable continuous, real-time data collection and transmission of medication results and biometric data. Currently, mobile phone applications are available that allow users to personally manage their medications, with reporting and trending features. These applications are available from devices like Apple's iPhone and Research in Motion's Blackberry. Development of applications are growing for warfarin monitoring, and glucose and insulin dosage monitoring. Some applications have additional health management information like food intake and exercise. Biosensors, which collect and wirelessly transmit biometric data are in development to measure ingestion and metabolism of medication. Please refer to the advanced function standalone medication adherence technologies for further information on developing technologies in the field.

Point-of-care testing devices to monitor medication are becoming more prevalent and accurate with wireless capabilities. The increased ability to store, view, and trend data by patients, caregivers, and clinicians can improve management of patients' medication programs.

Discussion

The Center for Technology and Aging is committed to encouraging wider use of viable technologies that compare favorably on the following criteria: population applicability, health and economic outcomes, workforce relief, stakeholder readiness, and policy relevance.[6] Many medication optimization technologies have been discussed. Most have potential to benefit a large portion of the older adult population and to benefit from favorable policy developments.

Population Applicability: Because so many older adults use medications, most of the discussed technologies are potentially beneficial to a significant population of older adults who are at-risk for moving to a higher level of care. Technologies may also be instrumental in enabling people with high-burden disabilities and chronic illnesses to better self-manage their health conditions and thereby prevent injuries and complications.

Health and Economic Outcomes: Credibly demonstrating improvements in health and economic outcomes is one of the largest challenges that medication-use technologies face. Randomized, controlled trials are the gold standard for demonstrating such improvements. But most technologies, if tested at all, have been studied with less robust methods, e.g., pre-post observation studies. On the positive side, well-known and well-respected organizations, such as the Veterans Administration and Kaiser Permanente, have increasingly demonstrated "in practice" the benefits of medication optimization technologies.

Workforce Relief: In the medium- to long-term, some technologies may reduce demands on the ever-stretched work force that cares for older adults—by encouraging greater self-managment and other efficiencies. Expanding use of such technologies in the short term, however, may place extra burdens on this home care and health care workforce. Many in-home medication-use technologies, for example, will require someone to train the patient or informal caregiver.

Stakeholder Readiness: Standalone technologies may achieve more rapid adoption because they do not require buy-in from a complex web of stakeholders, nor do they require interoperability. Technologies that interface with multiple medical devices and information technologies may be adopted more slowly. However, more complex, interoperable solutions may be needed, especially where breakdowns in communication are at the heart of the problem (e.g., as in medication reconciliation).

Discussion

Policy Relevance: Many current and emerging policies seem to favor medication optimization solutions. The Centers for Medicare and Medicaid Services (CMS) have taken a leading role in improving medication use for older adults and others that are eligible for Part D Medicare coverage of prescription drugs. For example, CMS is in the process of instituting improvements in Medication Therapy Management Programs (MTMP) that are currently offered by Part D sponsors (CMS contracts with "Part D sponsors" to provide prescription drug coverage for Medicare beneficiaries). To maintain status as a Part D sponsor, organizations must provide MTMP services for selected Medicare clients, i.e., those who have multiple chronic illnesses, use multiple medications, and incur high drug costs. According to a recent CMS call letter, MTMP services will soon have to meet more stringent standards, such as quarterly, targeted medication reviews to assess drug use and monitor any problems.[41]

Non-governmental organizations (NGOs) are also leading high-visibility initiatives to improve medication use. Medication reconcilation improvement is a high-priority goal for the Joint Commission and the Institute for Healthcare Improvement, for example.[13, 18]

Appendix A:

Medication Optimization Opportunities in Context

This paper has discussed three medication optimization opportunities (Medication Adherence, Medication Reconciliation, and Medication Monitoring) in the context of the mission and goals of the Center for Technology and Aging. The following table places these opportunities into a broader context, and highlights in yellow those areas that are most relevant to the Center's Medication Optimization initiatives.

Mapping the three medication optimization opportunities to the medication-use process provides the opportunity to identify solutions that optimize outcomes. First the three opportunities map to five process phases, which categorize the main actions of medication management: assess, prescribe, dispense, administer, and monitor. (Note that phases vary by care setting, health care professional role, and patient involvement). Phases can be further divided into process steps, starting from patient identification and medication history, and progressing to routine dosing, tracking, and reporting of patient medication use. A number of technology innovations can optimize process step efficiency, mitigate medication-use problems, and improve the health and independence of older adults. Technology solutions range from standalone to integrated technologies and are utilized by patients and caregivers, clinicians, or both.

Medication Optimization Opportunities in Context
Adapted from A Guide for Health Care Payers to Improve the Medication Management Process (pgs 9-11)[5]

Opportunity	Phase	Key Steps	Optimal Step Outcome	Technologies
Medication Reconciliation	Assess (physician's office, hospital)	Patient Identification	Identified patient information including name, address, birth date, gender	RFID (Radio-frequency identification) Barcoding
		Medication History	Obtained complete list of previous and current medications used by patient	Medication list software Personal Health Records (PHR)
		Diagnosis	Clinician accurately diagnoses patient problem	
	Prescribe (physician's office, hospital)	Medication Selection	Optimal medication for patient selected by clinician. Pulled from lists specific to diagnosis, commonly prescribed, etc	Clinical decision support tools EHR
		Safety Check	Patient medication selection passes safety check and does not interfere with patient allergies, other drugs or medical conditions, taking into account patient body size and pharmacokinetics for proper dose	Clinical decision support tools EHR
		Formulary and Benefits Check	Patient medication selected from pharmacy benefit list, has prior authorization, with the lowest possible co-pay	Clinical decision support tools EHR
		Medication Ordered	Electronic or hand written medication orders from clinician transmitted seamlessly to dispenser	e-prescribing CPOE
		Ordered Medication Documented	Medication order documented where patients can access the information	Medication list software PHR
Medication Adherence	Dispense (medication packing facility)	Evaluate/Approve Order	Medication order reviewed and approved to dispense	CPOE
		Medication Preparation	Medication order identified, prepared and packaged for delivery to dispensing location	RFID service robots
		Medication Distribution	Medication delivered to dispensing location	
	Dispense (pharmacy, hospital)	Patient and Medication Identification	Health care professional identifies and verifies patient and medication order	Barcoding, RFID
		Safety Check	Patient medication passes safety check and does not interfere with patient allergies, other drugs or medical conditions, taking into account patient body size and pharmacokinetics for proper dose	Clinical decision support tools
		Patient Education and Cognitive Assessment	Patient educated on medication use, dosing, side effects, and contraindications. Cognitive assessment determines patients' ability to adhere to medical regime.	TeleConsultations Online patient education Cognitive Assessment tools
		Medication Dispensed to Clinician	Medication order dispensed and picked up by clinician	Robotic dispensers and carousels
		Medication Dispensed to Patient	Medication order dispensed and picked up by patient	Pharmacy kiosk
	Administer (hospital, LTC facility, patient home)	Medication Information Identification (by clinician)	Clinician identifies and verifies correct patient and medication	Barcoding RFID
		Medication Information Identification (by patient or caregiver)	Patient identifies correct medication by reviewing drug name, dose, time of day, drug interactions	Talking pill bottles
		Dispense Individual Dose (by clinician)	Accurate individual medication dose (pill, IV bag, shot or liquid) properly dispensed to clinicians	IV Smart pumps Service robots
		Dispense Individual Dose (by patient)	Accurate individual medication dose (pill) properly dispensed to caregivers or directly to patient	Automated dispenser devices
		Take Dose	Patients takes proper dose at the right time	Reminder alert devices
Medication Monitoring	Monitor (LTC facility, patient home, hospital)	Routine Dosing and Tracking	Patient/caregiver routinely takes proper medication dose and records time medication is taken or not taken	Automatic dispenser devices
		Reporting and Trending	Caregiver/patient/clinician receives overview and trending of medication log and outcomes	Wireless communication devices Automatic dispenser devices PHR
		Refill prescriptions, contact clinician	Patient/caregiver refills medication or contacts clinician to adjust	Prescription reminder systems

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About the Center for Technology and Aging

Supported by a generous grant from The SCAN Foundation, the Center for Technology and Aging is devoted to helping California and the nation more rapidly implement technologies that improve home- and community-based care for older adults, and help older adults lead healthier lives and maintain independence.

The Center identifies promising strategies to promote the adoption and diffusion of technologies and provides grant funding to test selected strategies. In collaboration with grantees and key stakeholders, the Center will disseminate best practices and lessons learned from grant making initiatives. The Center serves as a state and national resource for those engaged in the promotion and implementation of successful technology diffusion strategies.

Center for
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MEDICATION REGIMENS: CAUSES OF NONCOMPLIANCE

OFFICE OF INSPECTOR GENERAL

OFFICE OF EVALUATION AND INSPECTIONS

JUNE 1990

OFFICE OF INSPECTOR GENERAL

The mission of the Office of Inspector General (OIG) is to promote the efficiency, effectiveness, and integrity of programs in the United States Department of Health and Human Services (HHS). It does this by developing methods to detect and prevent fraud, waste, and abuse. Created by statute in 1976, the Office of Inspector General keeps both the Secretary and the Congress fully and currently informed about programs or management problems and recommends corrective action. The OIG performs its mission by conducting audits, investigations, and inspections with approximately 1,400 staff strategically located around the country.

OFFICE OF EVALUATION AND INSPECTIONS

This report is produced by the Office of Evaluation and Inspections (OEI), one of the three major offices within the OIG. The other two are the Office of Audit Services and the Office of Investigations. Inspections are conducted in accordance with professional standards developed by OEI. These inspections are typically short-term studies designed to determine program effectiveness, efficiency, and vulnerabilities to fraud or abuse.

Entitled "Medication Regimens: Causes of Noncompliance" this report identifies why elderly people have difficulty following instructions for prescription medication use.

The study was carried out under the direction of Linda Herzog, Regional Inspector General, Office of Evaluation and Inspections, Atlanta Region. Participating in the project were the following people:

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MEDICATION REGIMENS: CAUSES OF NONCOMPLIANCE

Richard P. Kusserow
INSPECTOR GENERAL

OEI-04-89-89121 JUNE 1990

EXECUTIVE SUMMARY

PURPOSE

The purpose of this inspection is to determine why elderly people fail to follow prescription medication regimens.

BACKGROUND

Failure to adhere to medication instructions, either willful or inadvertent, has been termed noncompliance with medication regimens. Instances of noncompliance can include failing to initially fill a prescription, taking either more or fewer doses than instructed, and taking medications that have been prescribed for someone else.

Current research indicates that 55 percent of the elderly do not follow the medication regimens prescribed by their physicians.

METHODS

This inspection examines and summarizes extensive prior research in the area of noncompliance with medication regimens.It also draws on congressional testimony, reports issued by consumer groups involved with medication issues, and reports of government agencies concerned about the elderly, medications, and medical compliance.

FINDINGS

The consequences of noncompliance are serious and costly.

Noncompliance with medication regimens can result in the increased use of medical resources such as nursing homes, hospitals, physician visits, and unnecessary treatment. Noncompliance with medication regimens may also result in therapeutic failure. For example, missed doses of cardiac anti-arrhythmics can lead to arrhythmia and cardiac arrest.

There are many inter-related reasons for noncompliance.

Reasons why elderly people fail to comply with medication regimens fall into four main categories:

Physiological factors: Loss of vision or hearing can impede an elderly person's ability to read important information about his prescription or to hear instructions about his regimen. Mobility limits, type of disease, the presence of symptoms, memory loss, depression, and cognitive impairment are other physiological variables that can negatively affect compliance.

Behavioral factors: These include social isolation, social and health beliefs, and economic condition. Many elderly people live alone. Studies have shown that people who live alone more often fail to comply with medication regimens. For those elderly on fixed, minimal incomes, the ability to purchase expensive medications may also be a factor in noncompliance.

Treatment factors: These include the duration and complexity of the medication regimen. Compliance rates decrease when the treatment is long-term and when the regimen includes many different medications that must be taken concurrently. Other treatment factors include the type of medication prescribed, and the patient's perception of the medication.

Health Care Provider/Patient Interaction factors: These include how well the physician, the pharmacist, and the patient communicate with each other. The quality and content of a physician's instructions, the content of a pharmacist's label, and the ability of a patient to ask questions can all affect compliance.

Education is the key to improving compliance.

Strategies to improve compliance include physicians and pharmacists better educating patients about their medication regimens. Effective counseling by the physician and pharmacist may be the single best intervention for patients with compliance problems. Public education groups are also currently involved in informing and educating elderly citizens about medication issues. Compliance aids such as medication reminder charts may be useful tools for patients with memory impairments, or patients on complex medication regimens.

Attempts to improve compliance through educational and other behavioral strategies do work, as long as they are matched to the individual patient's needs. There is evidence to suggest that with the proper education and support the elderly can overcome compliance difficulties.

TABLE OF CONTENTS

INTRODUCTION

PURPOSE

Research has shown that a significant proportion of elderly people do not correctly follow their physicians' instructions for taking prescribed medications. The purpose of this study is to determine why elderly people may fail to follow prescription medication regimens.

BACKGROUND

In April 1989, the Office of Inspector General issued a report entitled "Medicare Drug Utilization Review" (OAI-01-88-00980). The report describes patterns of mismedication among elderly adults, identifies components of the drug delivery system that contribute to the problem, and describes drug utilization review (DUR) interventions that appear most promising to Medicare.

This inspection is related to that April report. Its focus is noncompliance among the elderly with medication regimens. Willful and inadvertent noncompliance contribute significantly to the problem of mismedication.

Appendix A lists additional studies related to medication and the elderly which have been completed, are underway or are planned by the Office of Inspector General.

DEFINITIONS

Mismedication occurs when a patient fails to take medication as prescribed by his physician. This failure, either willful or inadvertent, is termed noncompliance. Noncompliance can include:

- failing to initially fill a prescription;
- failing to refill a prescription as directed;
- omitting a dose(s);
- over dosing;
- prematurely discontinuing medication;
- taking a dose at the wrong time;
- taking a medication prescribed for someone else;
- taking a dose with prohibited foods, liquids, and other medications;

- taking outdated medications;
- taking damaged medications;
- storing medications improperly; and
- improperly using medication administration devices (e.g. inhalers.)

METHODS

This report is based on the findings of numerous researchers in the field of medical compliance. The number of original studies on compliance is itself extensive. The number of *reviews* of the literature now exceeds the number of original studies.[1] This inspection draws on both the original research and the reviews for many of its findings. The literature ranges from small, narrowly focused studies on aspects of noncompliance, to books which extensively discuss the elderly and their medication problems, including noncompliance. In addition, various authors of the literature were contacted for information and clarification of issues. This report also draws on congressional testimony, reports issued by consumer groups involved with medication issues, and reports issued by government agencies which are concerned about the elderly, medications, and compliance. See Appendix C for a list of compliance-related literature reviewed for this inspection.

FINDINGS

MANY ELDERLY DO NOT COMPLY WITH MEDICATION REGIMENS; THE CONSEQUENCES OF THEIR NONCOMPLIANCE ARE SERIOUS.

Extent of Prescription Medication Use By the Elderly

Adults aged 65 and over comprise approximately 12 percent of the United States population, but they consume 30 percent of all prescription medications dispensed.[2] By the year 2030, the proportion of elderly to the total population is expected to reach 23 percent.[3] It is likely that their consumption of prescription medications will also rise, as more and more elderly come to rely on medications for management of chronic disease. Eighty-six percent of the elderly have at least one chronic disease requiring medication.[4] The following table shows that those over 65 have a greater incidence of chronic disease which commonly requires medication therapy.

Extent of Chronic Disease Commonly Treated with Medication by Age Group

	Under 45	45-54	65 and Over
Arthritis	3%	27%	48%
Hypertension	4%	25%	35%
Heart Disease	3%	12%	30%
Diabetes	.8%	5%	10%

Adapted from: National Center for Health Statistics, C.A. Shoenborn and M. Marano, 1988 "Current Estimates from the National Health Interview Survey: United States 1987. *Vital and Health Statistics* Series 10, No. (PHS) 88-1594, Public Health Service. Washington: U. S. Government Printing Office.

There is heightened concern in the health care field about patients with chronic conditions. Their use of prescription medication shifts the mode of their treatment from direct medical care to continuous patient self-management.[5] Ninety-five percent of the elderly live outside of institutions and are responsible for their own medications.[6]

One researcher found that 25 percent of elderly patients discharged from a hospital received six or more prescriptions.[7]

A community-based sample showed that 25 percent of the elderly use four or more prescriptions regularly.[8]

The types of prescription medications most used by the elderly are:

- cardiovascular;
- diuretic;
- anti-infective; and
- psychotropic.[9]

The American Association of Retired Persons (AARP) has estimated that the total amount spent by elderly persons for medications (including over-the-counter preparations) in a single year is over $9 billion.[10]

Frequency of Noncompliance Among the Elderly

Prior research indicates that 55 percent of the elderly fail to comply in some way with their medication regimens.[11] Podell and Gary have suggested that one-third of the elderly always comply, one-third sometimes comply, and one-third never comply with their medication regimens.[12]

An American Association of Retired Persons (AARP) survey of ambulatory elderly found that 33 percent said they had prematurely discontinued a prescribed medication, and 14 percent failed to initially fill a prescription at least once.[13]

Noncompliance with medication regimens is a problem not only among the elderly. Forty-three percent of the general population made errors in self-administration of their medications according to one study. However, the same study showed that 58 percent of the elderly made errors when taking their medications.[14] In one of the early studies done on the subject of noncompliance, 26 percent of the elderly studied made errors which had potentially serious consequences as judged by the patients' primary physicians.[15]

Rates of medication compliance are difficult to generalize. An individual patient's compliance behavior may not be consistent. A patient may comply with one medication but not another.[16] Compliance behavior may change over time due to the patient's perceptions of efficacy of treatment and other factors.[17]

Methodological difficulties associated with conducting compliance studies may lead to an underestimation of the extent of the compliance problem.[18] The development of electronic compliance monitoring devices may help researchers, clinical trial investigators, and practicing physicians better track noncompliance in their patients.

Consequences of Noncompliance

Of all age groups the elderly benefit the most from taking medications and risk the most from failing to take them properly. The consequences are more serious, less easily detected, and less easily resolved than in younger age groups.[19]

Noncompliance with medication orders can increase the use of medical resources.

- Across the general population it has been estimated that noncompliance with treatment for cardiovascular disease results in an excess of 125,000 deaths and several thousand hospitalizations per year. (Six of the ten most frequently used drugs for patients 75 years and older are cardiovascular.)[20]
- Up to 23 percent of nursing home admissions may be due to elderly patients' inability to self-administer medications.[21]
- About 10 percent of hospital admissions may be due to poor patient compliance with medication orders.[22]
- Over a two-month period, researchers at a large teaching hospital found that drug-noncompliance-related hospital admissions for 23 patients accounted for 590 hospital days and approximately $60,000 in avoidable costs.[23]
- Emergency care may be required if patients fail to take their medications properly.
- Increased physician visits may be required if, because of medication noncompliance, the patient's condition does not improve. If the physician is not aware of the noncompliance, higher doses or additional medications might be prescribed which are unnecessary and possibly dangerous.[24]
- Additional diagnostic tests may be ordered if, because of medication noncompliance, the patient's condition does not improve or worsens.
- Additional or unnecessary alternative treatments may be prescribed as a result of noncompliance.

There is documentation that medication noncompliance is directly related to therapeutic failure. For instance:

- Missed doses of anti-glaucoma medications lead to optic nerve damage and blindness.
- Missed doses of cardiac anti-arrhythmics lead to arrhythmia and cardiac arrest.
- Missed doses of anti-hypertensives lead to rebound hypertension (sometimes worse than if no medication had been taken in the first place).
- Missed doses of antibiotics lead to recurrent infection and also to the emergence of resistant micro-organisms.[25]

The foregoing section described the adverse consequences of patients' failure to take medication as prescribed. However, there is another side to the story. Noncompliance can reveal when a medication has been unnecessarily prescribed. The patient who has been prescribed an unnecessary medication may be better off if he/she does not comply, provided that the physician is aware of the noncompliance. Otherwise the physician may keep prescribing the unnecessary medication.[26]

THERE ARE MANY INTER-RELATED REASONS FOR NONCOMPLIANCE.

One group of researchers identified over 200 variables that have been examined in relation to compliance with medical regimens.[27] This report by the Office of Inspector General identifies those variables that have the most bearing on reasons why the elderly may fail to comply with their medication regimens. These variables fall into four main categories:

- physiological factors
- behavioral factors
- treatment factors
- health care provider/patient interaction.

Despite the fact that the variables are discussed as separate classes, in practice they overlap substantially. They should not be viewed as independent.

It is also important to keep in mind that age by itself is not a determining factor in noncompliance. Rather, the many factors discussed below may combine to render the elderly less able to comply with their medication regimens.[28]

Finally, there is evidence to suggest that with the proper motivation, education, and support, the elderly can overcome compliance difficulties.[29]

Physiological Factors

Sensory Impairment: Well over a million older adults have impaired vision - a critical factor in compliance with prescription medication regimens.[30] Loss of vision can impair reading and understanding of prescription labels and other printed instructions handed out by the physician or pharmacist.

- Fifty-four percent of partially sighted persons are estimated to be at least 65 years old. (Most partially sighted persons are unable to read newspaper column type at normal reading distances even with the help of eyeglasses, and have difficulty recognizing faces even when they are close.)[31]
- Forty-six percent of the functionally blind group are 65 years or older.[32]

Critical communication with the physician or pharmacist can be missed by the patient with a hearing deficit.[33]

- At least 30 percent of individuals 65 and older have significant impairment of hearing in the frequencies associated with normal speech.[34]

Mobility Limits: Decreased mobility and dexterity can limit a person's ability to have prescriptions filled, and to open and close childproof containers.[35]

- Almost half of all noninstitutionalized elderly are limited in mobility because of chronic conditions.[36]

Type of Disease: Studies of patients with chronic conditions show that compliance is worse when:

- the medicine is taken preventively;
- the disease is without symptoms; and
- there are no immediate negative consequences of noncompliance.[37]

Presence of Symptoms: An illness with easily recognized and unpleasant symptoms that are relieved by the use of medication is more likely to promote compliance with medication regimens.[38] However, Haynes claims that it is the degree of disability brought about by symptoms that promotes good compliance. He speculates that compliance improves because the disability results in closer supervision of the patient.[39]

Some symptoms may fail to stimulate the commitment to follow medication orders. The elderly in particular may adapt to a steady state of symptomatic discomfort, or resign to "feeling pretty good for my age."[40] Some of these elderly may prefer to live with minor symptoms than deal with the inconvenience of a medication regimen.

Some patients use symptoms as barometers to determine when they should discontinue taking medication. Such decisions to discontinue medication are based on the mistaken assumption that the abatement of symptoms indicates recovery.[41] In a study of a group of hypertensives, some patients reported that they only took their medication(s) when they knew their blood pressure was high. Their assessments of blood pressure levels were based on symptoms such as headaches and stress, although research shows that hypertension is a disease without symptoms.[42]

Memory Loss: Memory loss is a critical problem for many elderly trying to recall a physician's or pharmacist's instruction for medication use.

- Memory loss can be caused by prescribed medications.
- Memory loss may indicate senile dementia, a condition difficult to recognize in its earliest stages.[43] The prevalence of dementia in the noninstitutionalized elderly population is about five percent.[44]

Depression: Depression is one of the most important psychological disorders of late age. A community-based sample estimated the prevalence of depressive symptoms among the elderly to be approximately 15 percent.[45] The older adult with depression can present serious problems to the health care provider who depends on the patient's cooperation to achieve compliance with a medication regimen. Some depressive symptoms include:

- sadness;
- loss of gratification;
- constant fatigue;
- apathy;
- psychomotor retardation;
- diminished social interaction; and
- insomnia.[46]

Cognitive Impairment: According to Lamy, approximately 15 percent of the noninstitutionalized elderly have significant cognitive impairments likely to affect their ability to give an accurate medical history as well as to follow physicians' instructions.[47]

Some older persons do not seem to process new information as thoroughly as younger persons and may need more time to learn new information. Distractions and information presented at a fast pace can seriously disrupt learning.[48]

Trying to learn a great deal of information in a short period of time (such as learning a complex medication regimen), can create a state of information overload. People deal with information overload by:

- omission - failing to process information;
- error - processing information incorrectly;
- delay - processing information at a later time;
- filtering - fitting input into existing belief;

- approximation - processing only a part of the information; and
- avoidance - ignoring information.[49]

Behavioral Factors

Social Isolation: People who live alone more frequently fail to comply with medication regimens. This suggests that for those not living alone, the spouse, companion, or associate assumes a role in ensuring that medications are taken as prescribed.[50]

- Approximately 35 percent of individuals over 65 live alone (the large majority of whom are women).[51]

The effects of social isolation include:

- rusty social skills, including difficulty asking and answering questions; and
- cognitive impairment, including difficulty understanding directions.[52]
- Even regular contact with children may not compensate for the loss of a spouse or a dwindling social network.[53]

Social and Health Beliefs: Patients hold many beliefs about their health and about the potential efficacy of any proposed treatment action. Patients' beliefs can be based on:

- misconceptions;
- faulty information; and/or
- cultural conditioning.

For example, some elderly people may believe:

- *"You need to give your body some rest from medicine once in awhile or else your body becomes dependent on it or immune to it,"* or
- *"You only take medicine when you are ill and not when you feel better,"* or
- *"If one dose is good, two must be better."*

These beliefs and feelings may be shared and supported by significant others in the patient's life.[54]

Economic Condition: Elderly people on minimal fixed incomes may be unable to afford necessary medications. Overall, the elderly pay 14 percent more per prescription than the nonelderly because of the mix of medications and the number of doses, which is often greater due to long-term therapy. Furthermore, the elderly pay a larger percentage of their prescription medication costs out of pocket.[55]

Since 1980 prescription medication prices have increased two to three times faster than all consumer prices, while real income has remained relatively static.[56] Social Security payments have increased at about the same rate as general inflation, but medication price inflation has far exceeded general inflation.[57]

About 14 percent of the noninstitutionalized elderly live below the poverty level. An additional 25 percent live just above the poverty line.[58] Some of these patients may need to make choices between medications and food.[59] A survey conducted for the American Association of Retired Persons (AARP) in 1986 found cost the second most frequently cited reason for not getting a prescription filled.[60]

Treatment Factors

Side Effects of Medications: Although some researchers think that side effects of medications contribute to noncompliance, the research evidence is inconclusive.

- Two controlled studies found no difference in the frequency of side effects between persons who comply with medication regimens and those who do not.[61]
- In thirteen studies in which patients were asked their reasons for not taking medication as directed, side effects were mentioned by only five to ten percent.[62]
- In an anti-hypertensive drug trial, seven percent of the actually treated group complained of symptoms that may or may not have been medicine related; the placebo group had the same frequency and distribution of complaints.[63]

The AARP has drawn a different conclusion about the relationship between side effects and noncompliance. In a survey of people 45 and older, 40 percent of the respondents stated they had experienced some form of side effect during medication use. Of this 40 percent, 59 percent responded that they stopped taking the medication as a result of the side effect. Of the 65 and older respondents, only 47 percent informed their physicians of the discontinuation.[64]

Furthermore, the elderly may be more prone to side effects, because their metabolic response to doses of medications tested on younger people may be different.[65]

Finally, for diseases (such as hypertension) which have no unpleasant symptoms, a medication that causes unpleasant effects may well increase the likelihood of noncompliance.[66]

Medication Class: There is evidence to suggest that compliance will vary with the type of medication. Researchers have observed:

- an 89 percent compliance rate with cardiac medicines;
- a 78 percent compliance rate with insulin and anti-diabetic medicines;
- a 72 percent compliance rate with diuretic medicines;

- a 61 percent compliance rate with anti-hypertensive medicines;
- a 41 percent compliance rate with sedatives;

Research in this area is not complete. Researchers do not offer conclusive reasons for their findings.[67]

Perception of Medication: Researchers have found that the size, form, and color of medication affect compliance.

- Capsules are viewed as significantly stronger than pills.
- Larger preparations are equated with greater strength.
- Capsule or pill colors can elicit expectations of medication action. Green is associated with tranquilizing effects, and yellow is associated with energizing effects.[68]

A patient may decide to discontinue or alter medication use because the pill or capsule simply looks like it will have an effect that the patient does not want to experience.

Some elderly patients with vision or cognitive deficits may be confused by similarly shaped and colored medications.[69]

The nature of the dosage form, such as the size of the pill or a liquid preparation, can negatively affect compliance if it is inconvenient to take or unpalatable.[70]

Duration of Treatment: A consistent finding in the research on medication compliance is that compliance rates decrease over time. This is significant for the elderly because of the higher frequency of chronic conditions which require long-term or permanent medication therapy.[71]

Complexity of Treatment: The number of medications taken can negatively affect compliance. The more medications taken, the worse the compliance.[72]

It has not conclusively been shown that the frequency of dosing (how often medications are taken during the day) affects compliance, but differing concurrent dosage schedules can be inconvenient, confusing, and easy to forget.[73] Furthermore, the number of medications prescribed can affect the frequency of dosing.[74]

Health Care Provider/Patient Interaction

Role of the Physician: Although most research focuses on the issue of compliance as a patient problem, compliance is the physician's responsibility as well as the patient's.[75]

Physicians generally underestimate the levels of noncompliance among their own patients.[76] They have also been shown to be unreliable predictors of whether or not individual patients will comply.[77]

Physicians' beliefs about and attitudes toward elderly patients can affect their interaction and communication with them.

Studies have shown that many physicians have an overall negative attitude toward treating elderly patients.[78] Gerontological studies suggest that while people form impressions of younger persons on a wide variety of characteristics (sex, occupation, ethnicity), these distinctive categories are ignored when forming impressions of older adults, and the stereotypes (mental weakness, contrariness, physical frailty) associated with age tend to dominate.[79] One study of physician attitude noted that 67 percent of physicians interviewed attributed noncompliance primarily to the patient's uncooperative personality.[80]

The physician-patient encounter is a situation in which patients must learn a very specific role and set of expectations about:

- the purpose of the medication;
- which medication should be taken;
- how long each medication should be taken; and
- the dosage schedule that should be followed.[81]

In Svarstaad's study on physician-patient interaction it was evident that physicians frequently did not discuss their expectations in an explicit manner. Of the 347 medications prescribed during the course of that study:

- Seventeen percent were never discussed at all.
- In only ten percent of the cases were patients told how long to take the medication.
- Dosage schedules were discussed ambiguously--*"Take two capsules every four hours"*--without specifying how many should be taken in a twenty-four hour period.
- Patients were not always given printed or written instructions for proper use of medications.

During the patient interviews of this same study, many misconceptions were discovered. Fifty-two percent of the patients made at least one error when describing the physician's expectations. For example, patients who had been prescribed anti-hypertension medication sometimes thought the medication was for the relief of other ailments such as low back pain or asthma.[82]

The traditional physician-patient encounter is ill-suited for learning to take place.

- The encounter is perhaps the most anxiety-laden of all lay-expert consultations.
- Too much information is often transmitted in too short a time.
- A potentially upsetting diagnosis and advice may disrupt learning.
- Traditional learning tools, such as note-taking, are not used.
- The patient's ability to learn can also be hampered by the physician's use of technical language.[83]

Older patients are often reticent to ask questions of their physicians perhaps because of:

- respect for professional authority;
- fear of looking unintelligent or unsophisticated; or
- anxiety about the medical condition.

Furthermore, physicians rarely invite questions from patients regarding proposed medication therapy.[84]

A Food and Drug Administration survey of physicians discovered that 79 percent feel they spend the right amount of time discussing medication therapy with their patients, and 32 percent feel their patients are very well informed about prescribed medications. An additional 56 percent feel their patients are adequately informed.

Seventy-two percent of the physicians feel that patients frequently discontinue taking medication. However, only seven percent of physicians surveyed who prescribe antibiotics tell their patients to finish the medication.

Twenty percent of the physicians surveyed said that sharing of medications is a problem, but only three percent of the physicians who prescribe tranquilizers tell their patients not to share the medication.

No physicians who prescribe thiazides (anti-hypertension medication) report that they tell their patients the therapy is long-term or permanent.[85]

The small percentage of physicians in the survey who feel that they don't spend enough time discussing medications with their patients cite practice demands and limited time. Physicians see an average of three patients per hour. Physicians who are high prescribers are more likely to use supplemental education materials such as brochures or pamphlets to explain medications.[86]

Role of the Pharmacist: One study discovered discrepancies between what the physician wanted on the label and the information the pharmacist actually printed on the label in 20 percent of 179 prescriptions studied. Types of discrepancies most commonly found were:

- The condition or symptom(s) to be treated were either omitted or incorrect.
- The label omitted the physician's individualized instructions for frequency or amount of dose.
- The label did not include a language translation for foreign speaking patients.[87]

In regard to patient interaction, pharmacists who were surveyed indicated that:

- Seventy-nine percent would like to have more time for patient consultation.
- Limited time and practice demands are responsible for the lack of patient consultation. Pharmacists dispense seven to nine prescriptions per hour.
- Forty-five percent of pharmacists say patient questions interrupt their work not at all, and an additional 26 percent say patient questions interrupt their work just a little. So, while pharmacists do not often offer information voluntarily, they do not seem to feel that patients' questions are an imposition on their time.
- Ninety-six percent report that they provide auxiliary labels on prescriptions and 69 percent provide pamphlets for certain medications.[88]

Patient Expectations and Attitude: The AARP survey of Americans over 45 years of age discovered that 69 percent of respondents go first to their physicians when they have questions about prescription medications.[89] However, the FDA survey of physicians found that 38 percent of physicians screen out most or all calls about medications.[90]

Twenty-five percent of respondents to the AARP survey turn to their pharmacists for information, and a small percent use books or other reference materials to get their information about medications.[91]

Forty-nine percent of the over-65 age group report that they never ask their doctors or pharmacists questions about medications. Respondents in general, and especially the over-65 age group, report dissatisfaction about the information they receive from both their physicians and pharmacists about:

- the name and purpose of the medication;
- how and when to take the medication;
- whether adverse effects are a possibility;
- whether side effects are a possibility;
- what the storage requirements are;
- how many refills are required; and
- whether there are alternative therapies for the condition.[92]

Finally, over 45 percent of the above-65 respondents report that their physicians and pharmacists do not ask them what prescription and nonprescription medications they are taking before writing or filling a prescription.[93]

EDUCATION IS THE BEST WAY TO IMPROVE COMPLIANCE.

The complex nature of the medication compliance issue suggests that there are not likely to be any quick or simple remedies for this problem.[94] A number of suggestions have been offered by various researchers. Haynes has pointed out that any efforts to improve compliance should target only treatments for which there is reasonable evidence of therapeutic efficacy.[95]

Educating Patients and Health Care Providers

Physician/Pharmacist Level: Patient education has been suggested as a primary means of improving patient compliance, and has been shown to be successful in many cases. However, as Falvo has pointed out, patient education is not simply repeating directions or handing out printed materials. It is a process involving skill in data gathering; individualization of instructions; prompting and support; and evaluation and follow-up of the patient's success in implementing the treatment regimen.[96] Furthermore, the patient must be involved in designing any intervention to improve his compliance. Only when the patient has been allowed to express his or her point of view can the health care provider best decide what strategies will be most appropriate to improve compliance.

Meichenbaum has suggested that when health professionals view patient education as a process rather than a single intervention, they may fear that the process will become too time consuming. However, the process of patient education, if incorporated into the daily interactions of each patient encounter, can actually save time by increasing patient

compliance. Fewer calls or visits to the physician or pharmacist, as well as other benefits of compliance such as avoiding hospitalization, may result if proper educational techniques are employed early in the therapy.[97] Studies have shown that compliance-improving programs have cost/benefit ratios as high as 1:14.[98]

Public Education Programs: There are currently many programs for informing and educating elderly patients about medication issues. Some of the better known programs are:

- The Elder-Ed and Elder Health Programs conducted by the University of Maryland's School of Pharmacy: In the Elder-Ed program retired pharmacists are teamed with pharmacy students to provide counseling to senior citizens in group settings. Within the Elder-Health Program, pharmacy students are required to form a relationship with an elderly patient. The student visits the elderly patient periodically to help educate the patient about medications. In this way the student learns first-hand some of the problems elderly people face with medication regimens.

- The San Francisco SRx (Senior Medication Program): Sponsored in part by the San Francisco Department of Health, SRx involves pharmacies in community outreach programs to inform and educate elderly people about their medication regimens.

- The National Institute of Drug Abuse (NIDA): The Institute developed a film and a booklet about the elderly and medication issues. These are distributed to State agencies involved in prevention of medication abuse.

- The American Association of Retired Persons (AARP): Among other activities, AARP developed, with the help of the FDA, patient package inserts known as MILS (medication information leaflets for seniors) which contain information about medications and their proper use. The MILS are distributed with over 90 percent of medications dispensed through the AARP's mail-order pharmacy service.

- The National Council on Patient Information and Education (NCPIE): The Council employs public service announcements, education campaigns, and special events such as the "Talk About Prescription Month" to raise public awareness about problems associated with prescription medications.[99]

Using Compliance Aids

It has been suggested that various electronic and mechanical devices called "compliance aids" might help to improve compliance.[100] There are a wide range of compliance aids available, from simple charts to record and remind patients of medication use, to sophisticated micro-electronic bottle caps that have alarms and flashing indicators to alert a patient when a

dose is due. Compliance aids can range in price from a few cents for a chart to fifteen dollars for a micro-electronic cap. Such aids may be useful for patients with memory impairments or patients on a complex medication regimen.

Other strategies and mechanisms proposed to improve patient compliance include:

- providing reminder cards for refills;.
- providing written or printed information that is easy to read (large type);
- keeping medication histories;
- using large type and specifying instructions on prescription labels; never writing "*take as directed;*"
- simplifying the regimen as much as possible;
- involving family members in support and/or supervisory roles; and
- demonstrating the proper technique for using a medication application apparatus.

Compliance Can Be Improved

Green et al. conducted a quantitative review of 10 experimental studies specifically addressing the elderly with education and behavioral interventions designed to improve medication compliance. They discovered that all methods, with the exception of written materials used alone, were effective in significantly and substantially improving knowledge of medication use, and decreasing the incidence of error.[101]

However, strategies employed to improve patient compliance have been shown to be effective only insofar as they are matched to individual patient needs.[102]

APPENDIX A

Office of Inspector General Studies of Elderly Medication Issues

Studies Completed	Request Report Number
Medicare Drug Utilization Review	01-88-00980
Physician Drug Dispensing	01-88-00590
Implications of the Medicare Prescription Drug Benefit's Electric Claims Processing System	01-89-89170
State Discipline of Pharmacists	01-89-89020
The Clinical Role of the Community Pharmacist	01-89-89160
The Clinical Role of the Community Pharmacist: Case Studies	01-89-89161

Studies Underway

Adverse Drug Reaction Reporting System	12-90-01000

Studies Planned

Prescription Drug Advertising	01-90-00480

APPENDIX B

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APPENDIX C

COMPLIANCE ISSUES
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