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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 specifically 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 supplements, 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] Healthcare 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 counterintuitive 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 co-morbid 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

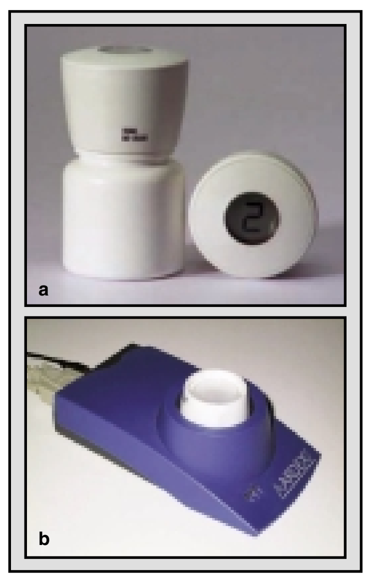

Fig. 1. Medication-Events-Monitoring System (MEMS®) device: (a) MEMS®V Smart Cap, with display showing that two doses have been taken; (b) MEMS® V Communication Device (photographs courtesy of AARDEX® Ltd./Aprex).

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,

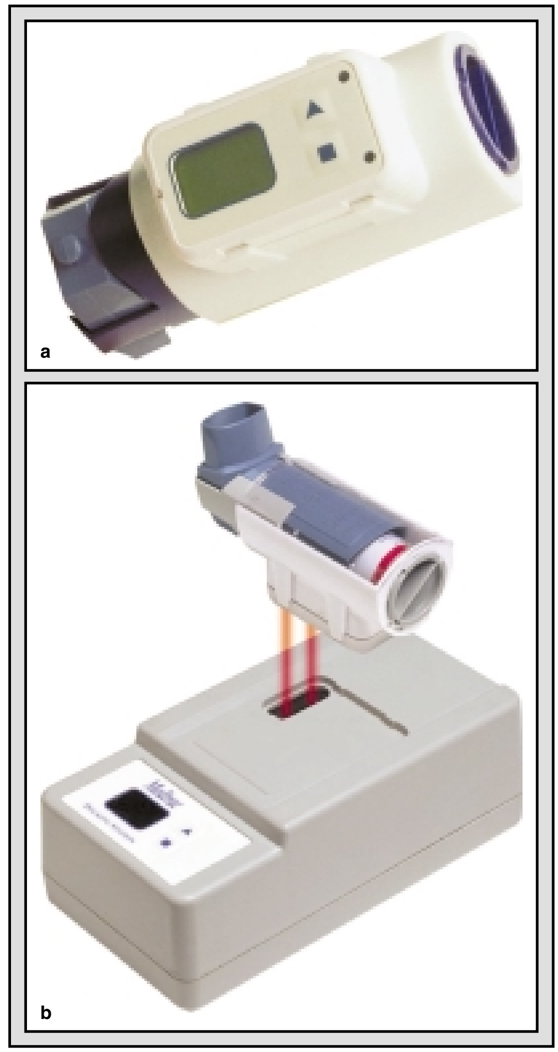

Fig. 2. MDILog™ metered dose inhaler (MDI) adherence measuring device: (a) MDILog™ attached to MDI; (b) MDILog™ and Docking Station (photographs courtesy of Westmed™ Inc.).

$p = 0.003$), 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 $91.8 \pm 8.0\%$ and $90.1 \pm 6.9\%$ for the MDILog™, 100% and $94.3 \pm 2.9\%$ 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

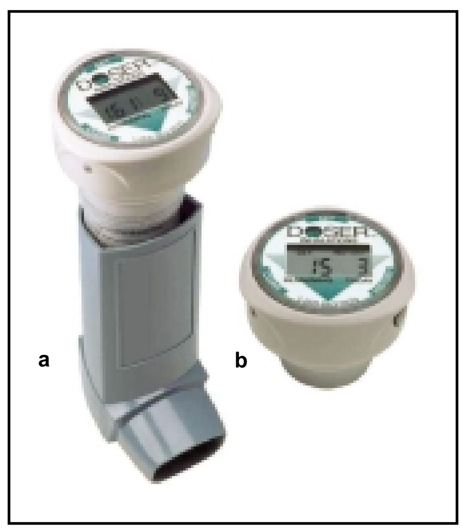

Fig. 3. Doser™ (**a**) attached to a metered dose inhaler and (**b**) not attached to a metered dose inhaler (photograph courtesy of Medi-Track™ Products).

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-

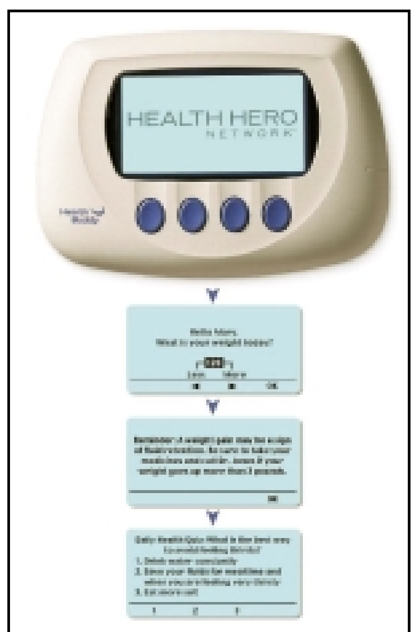

Fig. 5. Health Buddy® electronic medication reminder system, with example of interactive question for the patient (photograph courtesy of Health Hero®).

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.

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