Aiming at Strategies for a Complex Problem of Medical Nonadherence

Jose M. Castellano^{*,†}, Robert Copeland-Halperin^{*,†}, Valentin Fuster^{*,†,‡} New York, NY, USA; and Madrid, Spain

ABSTRACT

The deteriorating health of the population and the increasing prevalence of chronic diseases are global problems whose causes are multifactorial and complex. The Western lifestyle does not promote healthy living, and the consequences are most devastating when social inequalities, together with the economic and population explosion of recent decades, are considered. The expansion of poor nutritional habits, obesity, sedentarism, and hypertension are increasingly contributing to the development of a cardiovascular disease epidemic. Recent data on the rates of compliance with lifestyle modification and adherence to prescribed medication are alarming. Over 50% of patients, on average, decide to abandon the treatment prescribed, and the objectives to improve their habits (quit smoking, lose weight, or engage in physical activity) are met by an equal or lower percentage. Beyond the impact it has on individual health, it carries a huge economic cost, as it is associated with a failure in achieving therapeutic goals, higher rate of hospitalization, and death. Improving communication between doctors and patients, the active involvement of other health professionals, and the development of combination drug formulations (polypill) are potential strategies for improving adherence and reducing costs.

Cardiovascular therapy has seen a decade of exciting new advances in efficacious drugs as well as sophisticated devices that improve clinical outcomes. The costs of developing these advances in the therapeutic milieu have been immense, and the effects of such proven interventions (whether they are drugs, devices, or lifestyle modifications) are often hindered by the fact that patients do not adhere to the recommendations of their caregivers. In fact, despite evidence of improved outcomes from adherence, the average medication compliance rates in developed countries are estimated to be just 50% [1].

The global problem of nonadherence was recognized more than 3 decades ago, and results in poor clinical outcomes, unnecessary disease progression, increased cost of care, as well as premature death (an estimated 125,000 deaths per year in the United States are attributed to medication nonadherence) [2]. Nonadherence carries a huge economic cost that is derived from both direct and indirect costs. Failure to identify and improve low adherence often results in increased pharmacotherapy with increased doses of medication (with the inherent increase in the overall cost of treatment, risk of adverse side effects, misdiagnoses, and, in certain situations, unnecessary treatment) and increasing disease burden. Undesirable outcomes resulting from nonadherence may lead to a loss of work productivity on the part of patients and caregivers.

A recent World Health Organization (WHO) report stated that because the magnitude of nonadherence and the scope of its consequences are so alarming, more health benefits worldwide would result from improving adherence to existing treatments than by developing new ones [3]. All strata involved in the health system (healthcare providers, policymaking officials, scientists, the academic community, consumers, and industry) have called for action in order to address medical adherence and reduce the consequences of this growing public health issue.

WHAT IS ADHERENCE?

Medical adherence refers to the extent to which patients follow medical instructions and implies an active patient participation about the timing, dosage, and frequency of taking drugs. Although most research has focused on adherence to medication, adherence also encompasses numerous health-related behaviors that extend beyond taking prescribed pharmaceuticals. Medical compliance encompasses these processes, which imply a passive participation by the patient. These typically include lifestyle modifications or behavioral interventions and can fluctuate over time. For example, smoking cessation might be achieved for some time, but patients frequently relapse and continue to smoke. Similarly, following a diet, losing weight, or undertaking physical activity fluctuate depending on the behavior of a patient at any given time. Medical persistence refers to the duration of taking a medication and is defined as the duration from the time of initiation to discontinuation of therapy.

In 2003, WHO [4], recognizing the increasing clinical and economic costs of nonadherence, issued the "Adherence to Long-Term Therapies: Evidence for Action" statement [3]. WHO defined nonadherence as the extent to which a person's behavior—taking medication, following a From the *Zena and Michael A Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY. USA; †Marie-Josée and Henry R Kravis Cardiovascular Health Center, Icahn School of Medicine at Mount Sinai, New York, NY. USA; ‡Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain. Correspondence: J. M. Castellano (imcastellano.cardio@ gmail.com).

GLOBAL HEART © 2013 World Heart Federation (Geneva). Published by Elsevier Ltd. All rights reserved. VOL. 8, NO. 3, 2013 ISSN 2211-8160/\$36.00. http://dx.doi.org/10.1016/ j.gheart.2013.06.001 diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider. WHO also recognizes 2 distinct categories of nonadherence—preventable and nonpreventable (Table 1) and recommends targeting tailored treatment interventions for the former.

THE SCALE OF NONADHERENCE: A WORLDWIDE REALITY

The Institute of Medicine has recently published a document that presents some of the key features directed to promoting cardiovascular health in the world, with special emphasis in low- and middle-income countries, where cardiovascular disease (CVD) accounts for nearly 30% of all deaths [5]. The increased prevalence of risk factors of CVD and related chronic diseases in developing countries, including tobacco use, unhealthy dietary patterns, reduced physical activity, increasing blood lipids, and hypertension, reflects significant global changes in behavior and lifestyle. These changes now threaten once low-risk regions, a shift that is accelerated by industrialization, urbanization, and globalization. The Institute of Medicine document has raised awareness on the fact the prevalence of CVD is increasing not only in low- and middle-income countries, but also worldwide, in relation to an increase in global population associated to an increase in cardiovascular risk factors such as pernicious nutritional habits and obesity, which without question is having a detrimental impact on global health [6]. We are facing a worldwide epidemic that is very complex in nature, underlined by multifactorial causality, and implicates various strata of society.

The Manhattan Project was carried out in 2004 in an effort to quantify the various degrees of compliance and adherence among a large U.S. population affected by different chronic diseases. According to the results of this study, 50% of patients were unable to comply with lifestyle modification regarding smoking cessation and weight loss. Medical adherence was alarmingly low, showing rates lower than 60% in the case of antihypertensive, antidiabetic, and cholesterol-lowering drugs. More startling perhaps are the results of the current guidelines recommendations on the actual use of aspirin, antihypertensive medications, and statins, especially for secondary

 TABLE 1. Preventable and nonpreventable reasons for discontinuation or nonadherence

Preventable	Nonpreventable
Low health literacy	Serious mental illness
No-fill of first prescription identified	Serious adverse effects
Nonresponder or no clinical evidence of effectiveness of the medication	Polypharmacy
Cost prohibitive for the patient	

prevention in patients with CVD. Although results vary depending on the pharmacologic regimen, medical adherence averages around 60% [7]. For example, the degree of adherence to treatment with salicylic acid was found to be lower than 45% despite its use being recommended to the totality of this population (Table 2).

The PURE (Prospective Urban Rural Epidemiological) study [8] set out to quantify the degree of medical adherence worldwide in the context of coronary artery disease and cerebrovascular disease. This study included 153,996 patients, ages 35 to 70 years, from rural and urban areas of countries around the world in an effort to study the impact of middle-class income of each country in the real use of drugs with proven efficacy in secondary prevention (namely, antiplatelet drugs, beta adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins). The results indicate that adherence to medical treatment is directly related to income and, although far from being acceptable in higherincome populations, it is particularly low in low-income and rural areas. The conclusions of this and other studies call for action on the urgent need to improve access to treatment through the use and the development of more efficient and cheaper treatments that guarantee adherence to medical treatment in secondary prevention.

Different epidemiological studies have found that only 20% to 30% of patients achieve optimal cardiovascular risk factor control. In a study to measure the degree of compliance with the Sixth Joint National Committee guidelines [9] for treatment of high blood pressure, only 37% of patients reported consistent adherence to their antihypertensive regimens. Dailey et al. [10] studied 37,431 Medicaid-funded patients in the United States and used pharmacy records to show that patients with type 2 diabetes averaged about 130 days per year of continuous drug therapy, and that at the end of 1 year, only 15% of the patients who had been prescribed a single oral medication were still taking it regularly. Similar results have been found in related clinical trials such as BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) [11] and COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) [12], in which a tremendous effort was made to address lowadherence rates.

The available data suggest the healthcare system is facing a critical challenge, with various implications and consequences. The solution to this complex problem requires exploration of the responsibilities not only of the patient who fails to comply with medical recommendations, but also of physicians, the healthcare system, and the regulatory organizations. In this context, WHO published a document in which it recognized low pharmacological adherence as a complex, international problem that affects especially those long-lasting therapeutic regimens for chronic diseases, such as diabetes mellitus, hypertension, asthma, cancer, human immunodeficiency virus, and tuberculosis among others [3]. The main conclusion of this

	Age \geq 55 yrs (n = 2,554)			History of CVD (n = 592)		
	Recommended Use	Actual Use	%	Recommended Use	Actual Use	%
Aspirin	84.2	31.6	37.5	100	44.5	44.5
Antihypertensives	60.1	47.8	79.5	69.3	61.0	87.8
Statins	63.7	37.3	58.6	88.3	57.0	64.0
Values are percentages. Based on data, used with permission, from Munther et al. [7], CVD, cardiovascular disease						

TABLE 2. Current guideline recommendation and actual use of aspirin, antihypertensive medications, and statins among U.S. adults \geq 55 years of age and those with a history of CVD

document was that patients must receive more support from the healthcare system and a multidisciplinary approach are required to offer tailored solutions to individual cases.

PAYING THE PRICE FOR POOR ADHERENCE

Adherence is the single most important modifiable factor that compromises therapeutic outcome. The consequences of medication nonadherence are not only poor clinical outcomes but also unnecessary healthcare costs. The total cost estimates for nonadherence range from \$100 billion to \$300 billion each year and include both direct and indirect costs [13]. The costs of drug-related hospitalizations has been estimated to be around \$47 billion a year [14]. Furthermore, nonadherence to medication has been associated with and additional \$2,000 a year per patient in medical costs from visits to physicians' offices [15]. In the specific case of heart failure, it has been shown that nonadherence plays a major role in preventable rehospitalizations [16]. Indirect costs include loss of productivity derived from nonadherence to prescribed medical treatment, as well as higher costs for private managed care insurance benefits. Furthermore, WHO predicts the problem of nonadherence will grow as the burden of chronic diseases increases worldwide [3]. Available evidence suggests that better adherence leads to improved clinical outcomes and lower healthcare costs [17]. It is critical, therefore, that the agenda of policymakers include the issue of improving patient adherence as a pivotal way to address the escalating costs of health care not only in the United States, but also worldwide.

TIMING: A CRITICAL WINDOW OF OPPORTUNITY

Recent evidence shows that adherence to treatment of certain chronic diseases decreases significantly during the first 6 months after the prescription [18]. Furthermore, patients who abandon treatment within this time frame are less likely to go back into treatment [19]. Therefore, the first 6 months of treatment are a critical window of opportunity to act upon the problem of nonadherence. On the other hand, good adherence to cardioprotective drugs has demonstrated better outcomes and reduced mortality in patients with coronary artery disease and diabetes mellitus [19]. In this context, a recent review found that

improvements in guideline adherence, as measured by performance indicators, have led to significant reductions in mortality [20]. Their findings suggest that improving quality achieves reductions in death in excess of those observed for any new therapy. It is estimated that the use of clinical guidelines for acute myocardial infarction could prevent 80,000 deaths annually in the United States alone [21]. Therefore, the potential global implications are significant if effective ways to improve adherence to guidelines can be developed.

BARRIERS TO ADHERENCE

Several factors appear to be associated with poor adherence. Nonadherence to medications can be intentional or unintentional. Intentional nonadherence is an active process whereby the patient chooses to deviate from the treatment regimen [22]. WHO has categorized potential reasons for medication nonadherence into 5 broad groupings that include patient-, condition-, therapy-, socioeconomic-, and health system—related factors [3,23]. Although it is true that patients are ultimately in control of the fashion in which they take their prescribed medications, there are various reasons why that can facilitate nonadherent behavior.

Patient-related factors

Patient characteristics have been the focus of numerous investigations of adherence. Age, sex, education, occupation, income, race, religion, ethnic background, and urban versus rural living have not, however, been definitely associated with adherence [24]. Similarly, attempts to define stable personality traits of a typical nonadherent patient have been futile, as no single pattern of patient characteristics predicts nonadherence [25]. With the exception of extreme disturbances of functioning and motivation, personality variables have not emerged as significant predictors. Thus, contrary to previous belief, there is no such thing as a "nonadherent personality," and the causes of failure to follow treatment are not associated with certain personality traits of the patients [26].

Among the most common reasons patients do not take their medicines is simply forgetfulness [1]. Practitioners (and other health enablers) often assume that the patient is, or should be, motivated by illness to follow a treatment protocol.

The presence of psychological problems, particularly depression [27], correlates with poor adherence to medication across a range of chronic diseases [25]. This is of particular significance when one takes into consideration that depression is widely associated with heart disease (1 in 3 patients with congestive heart failure, recent myocardial infarction, or acute coronary syndromes will meet criteria for either major or minor depression) [28] and even mild depression is sufficient to significantly alter compliance with essential therapy [4].

A patient's motivation to adhere to prescribed treatment is influenced by the value that he or she places on following the regimen (cost-benefit ratio) and the degree of confidence in his or her ability to follow it. Conversely, when medications such as antidepressants and corticosteroids are slow to produce intended effects that are apparent to the patient, there may be a tendency to believe the medication is not working and to discontinue use.

Condition-related factors

Silent chronic conditions represent a significant challenge because of patients' perception about the nature and the severity of their illnesses. Adherence rates are typically higher among patients with acute conditions, as compared with those with chronic conditions; persistence among patients with chronic conditions is disappointingly low, dropping most dramatically after the first 6 months of therapy. Factors such as perceived susceptibility to illness, perceived severity of illness, self-efficacy, and control over health behaviors are more robust correlates [6]. For adherence to occur, symptoms must be sufficiently severe to arouse the need for adherence, be perceived as being resolvable and acute, and remedial action must effect a rapid and noticeable reduction in symptoms. An internal locus of control appears crucial for effective adherence.

Therapy-related factors

Medication-related factors can also act as a barrier to adherence. The complexity of the regimen, concern about medication side effects, and patient's lack of confidence in the benefit of treatment all play a role in the lack of adherence.

The number of medications has a negative impact on adherence, and elderly patients tend to take more prescription medicines than any other group [29]. Studies evaluating dose frequency have shown rapid decreases in adherence rates with increasing dose frequency (Table 3). Simple dosing (1 pill, once daily) helps maximize adherence, particularly when combined with frequent reinforcing visits [30]. In fact, it has been shown that minimizing the total number of daily doses is more important in promoting adherence to antihypertensive regimens than minimizing the total number of medications [31]. **TABLE 3.** Relations between dosing regimen and compliance

 averaged from 76 studies using electronic monitoring

Dosing	Took Most Doses (%)	Took on Time (%)			
Once daily	79	74			
Twice daily	69	58			
3 times daily	65	46			
4 times daily	51	40			

Based on data, with permission, from Garner [32].

Medication costs represent a key source of nonadherence in all fields of medicine, particularly in patients with low or fixed incomes, those with chronic medical conditions, and those on disability [32]. One-third of Americans report they did not fill a prescription or reduced the dose in the past year because of out-of-pocket costs [33]. The cost of medication and its relationship to adherence has been the source of extensive studies. Recently, Choudhry et al. [34] reported the results from a controlled trial that assessed whether the elimination of copayments for statins, beta-blockers, angiotensinconverting enzyme inhibitors, and angiotensin-receptor blockers for recent survivors of an acute myocardial infarction could improve adherence, reduce future cardiovascular events, and save costs. The elimination of copayments significantly increased adherence in the control group. However, an alarming finding of this study, consistent with previous findings [35], was that less than one-half of patients in the full-coverage group were fully adherent to prescribed medication. One can draw the conclusion that in order to adequately address the solution to low adherence, interventions must focus on other contributors to nonadherence other than drug costs.

Socioeconomic-related factors

Available evidence has shown that the strongest sets of socioeconomic factors related to adherence are social support and other related constructs such as living alone and marital status. Presence of adequate social support, living with others, and being married have been shown to be associated with better adherence [16].

Health system-related factors

There is a total lack of communication between healthcare providers and patients. Whereas 74% of healthcare providers believe their patients comply with their recommendations, 83% of patients fail to tell their healthcare providers about medical adherence [36,37]. The amount of time a physician spends going over new medications with patients is scarce and certainly a cause for nonadherence. The results of a survey conducted over more than 500 physicians revealed that among the central problems of medical nonadherence is the time physicians spend going over new medication with their patients. In this survey, that time averaged 49 s [38,39]. Furthermore, patients

demonstrate better adherence when they receive care from the same provider over time [29].

Correlative studies revealed positive relationships between adherence of patients to prescribed treatment and provider communication styles characterized by providing information, "positive talk," and asking patients specific questions about adherence [40]. The clarity of diagnostic and treatment advice has been correlated with adherence to short-term but not to long-term regimens and chronic illnesses. Warmth and empathy of the clinician are central factors. Patient satisfaction with the medical regimen affects adherence favorably, so that when the patient's level of trust in the physician is low, patients are more likely to forego the use of medications [41].

Another important barrier is inability to understand or act on instructions for taking medication. In fact, 1 study [2] found that 60% or more of patients could not correctly report what their physicians told them about medication use between 10 and 80 min after receiving the information. Table 4 summarizes the various barriers to adherence.

TENETS OF LOW ADHERENCE TO MEDICATION: AIMING AT NEW APPROACHES TO IMPROVE ADHERENCE

The impact of adherence on clinical results has been the focus of numerous studies over the past years. Although the scope of the problem and the magnitude of the consequences of nonadherence are well identified, solutions have not always come across in a clear, concise manner, and too often have been short-sided in placing most of the responsibility on the patients. Moreover, evolving data have provided us with more questions than solutions because of the complex nature of the problem. The data provided so far has identified various barriers to adherence (patient-related, conditionrelated, therapy-related, socioeconomic-related, and health system-related factors) that account for the low levels of adherence that are found today throughout the world. However, it is the intricate relationship among patient, provider, and health system that might explain the reasons for, and should ultimately provide the solutions to, this complex problem (Fig. 1). There are, in our view, 7 basic tenets of low adherence that can serve as the basis to propose mechanisms of correction:

- 1. The causes that lead to failure in adherence to treatment are not related, as shown, to personality traits of the patients, that is, there is not a characteristic nonadherent personality.
- 2. There is a total lack of communication between physicians and patients, and therefore, a very low concordance between the level of communication that doctors perceive to have with their patients and the real information that patients transmit to their physicians.
- 3. Medication adherence shows little or no relationship with medication compliance [42]. For example, smoking cessation or physical exercise are not associated with a higher medical adherence, because the latter implies a more rational and active decision on the patient's part.
- 4. Patients' sociodemographic characteristics have little relationship with nonadherence and are more related with other variables, such as disease type [43].
- 5. Patients want to know why they take prescription drugs, the expected duration of the regimen, possible adverse effects of drugs, the expected impact on their lifestyle, and the consequences of nonadhering to the recommended treatment [42,44,45].
- b. Healthcare professionals communicate deficiently with their patients and provide little information about medical prescriptions, which could give rise to misinterpretation by patients. Patients' perceived lack of information contributes decisively to nonadherence.
- 7. Adherence to pharmacological treatment is a decisionmaking process in which the patient rationally and actively decides to engage in the convenience of following treatment after taking into account different motivations. Professional support and the correct communication with the physician can have a profound impact, particularly in patient populations such as the elderly, who often find themselves in a situation of social isolation, emotional vulnerability, and economic struggle [46].

Adherence cards

Among the interventions found to be most effective in randomized clinical trials, successful interventions address known barriers, regardless of whether the barrier is owned by the patient, provider, community healthcare system, or

TABLE 4. Barriers to adherence

Patient-Related	Illness-Related	Provider-Related	System-Related
Psychiatric illness (depression)	Asymptomatic disease	Adequate follow-up/ discharge planning	Availability/accessibility of services
Cognitive impairment	Medication side effect	Warmth and empathy	Cost of treatment
Confidence in benefit of treatment	Complexity of treatment	Poor communication	Support for patient education
Insight into illness	Acute vs. chronic	Continuity of care	Data/information management
Trust in provider			Community support
Satisfaction w/medical regimen			Training provided



FIGURE 1. Tenets of low adherence and strategies aimed at improving adherence. HRP, high risk plaque initiative.

governmental agency [29]. There is no doubt that communication between patients and healthcare professionals is one of the main variables that impact adherence, and that by simply improving the quantity and quality of communication there can be a significant improvement on medical adherence. However, in the current healthcare system, physicians lack the ability to increase the time, and the already overloaded office visits do not allow physicians to put in place a system of continuous monitoring and regular follow-ups. Therefore, alternative methods must be pursued that allow for an increased level of communication that does not dramatically increase the time physicians spend on this matter. One such method could be in the form of a questionnaire that measures in an objective manner the expected level of adherence for each patient. Such a questionnaire should include simple and concise variables with which to obtain information about the patient's concerns regarding treatment, the degree of willingness to follow treatment, and that patient's economic solvency to adhere. Once the patient has gone over the questionnaire, the physician could answer the concerns raised by the treatment. One such questionnaire, the Adherence Estimator, has been tested using 3 drivers of self-reported adherence: perceived concerns about medications; perceived need for medications; and perceived affordability of medications [42]. By simple summation of the weights assigned to the category responses of the 3 items, a total score was obtained and patients were placed into 1 of 3 segments based on the total score-low, medium, and high risk for nonadherence. Sensitivity was 88%: of the nonadherers, 88% would be accurately classified as medium or high risk by the Adherence Estimator. The 3 risk groups differed on theoretically relevant variables external to the Adherence Estimator in ways consistent with the hypothesized proximal-distal continuum of adherence drivers. The Adherence Estimator is readily scored and is easily interpretable. Due to its brevity and transparency, it should prove to be practical for use in everyday clinical practice and in disease management for adherence quality improvement. This system, however, should also involve nurses, physician assistants, and nurse practitioners.

Simplified drug regimens

Modifying a patient's drug regimen to reduce the number of pills a patient is required to take at each dose is one way to address adherence. One study found that among hypertension patients, those who took once-daily therapy had 11% better adherence (as defined by the percentage of correct doses) than those who took twice-daily therapy. Similar improvements were seen among patients with high cholesterol. Patients prescribed to take their medication twice daily had 10% better adherence than did patients who had a 4-times-daily dosing schedule [47].

Polypill: toward achieving secondary prevention

Given the inverse relationship between complex regimens and adherence, a different approach involves the concept of the polypill (fixed-dose combination drugs). Available evidence regarding the use of such treatments shows significant increases in adherence rates, significantly reduced production and distribution costs, and improvement of treatment availability, especially in low- and middleincome countries [48]. The results of a meta-analysis [49] of such drugs showed a 20% relative reduction in the rate of nonadherence compared with that of component drugs taken separately.

Regarding the potential clinical benefits of the polypill, Yusuf [50] published a review illustrating how aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins together could theoretically decrease worldwide cardiovascular events by 75% in at-risk patients. In the case of secondary prevention for patients with previous history of coronary artery disease or cerebrovascular disease, the use of a polypill could potentially decrease the incidence of future events. In the United States alone, it has been calculated that the use of a polypill (with efficacy-proven compounds that are used alone), could prevent 3.2 million cardiovascular and 1.7 million cerebrovascular events [7]. Data arising from the recently published PURE study [51] further strengthens the case for a polypill in secondary prevention, especially in low-income countries. The study aimed to study the prevalence of unhealthy lifestyles in 7,519 individuals with coronary heart disease or stroke in various regions of the world with different incomes. The results are worrisome, as the prevalence of healthy lifestyle was low (18.5% continued to smoke, only 35.1% undertook physical activity, and 39.0% had healthy diets), with the lowest prevalence of healthy lifestyles taking place in low-income countries [51]. The rationale for the use of the polypill in secondary prevention is that it can reduce the cost of medication and also improve patient adherence to treatment. Cost of medication is determined mainly by the price of raw materials (generics) and the cost of manufacturing, packing, and distribution [48]. In addition, the process of packing and distribution of a polypill containing several active drugs is less expensive than the management of those drugs separately. In fact, the price of the 1 commercially available polypill (Trinomia), recently introduced in Central America, is less than 50% of the price of its components purchased separately. The effect of the polypill on patient adherence to treatment is unknown. However, there is some evidence in the literature that the use of fixed-dose combination drugs in the treatment of hypertension improves adherence by almost 25% [52]. Therefore, it can be anticipated that the polypill will demonstrate a similar positive effect on patient adherence in secondary prevention.

The polypill is, therefore, an interesting therapeutic option to improve clinical outcomes, because it significantly facilitates therapeutic regimens and considerably reduces costs, both of which have been proven to be major barriers to adherence. However, just as with conventional treatments, its prescription must be accompanied by adequate information and should not hinder the communication between patient and physician.

The Grenada and Cardona studies: community and communication

Recently, a novel approach to improve adherence has been addressed, based on a program of communication and community aid that involves adults helping other individuals, much in the way already existing organizations (e.g., Alcoholics Anonymous). This method of reinforcing healthy habits has successfully been implemented as a case/ control study on the island of Grenada and does not require active involvement of healthcare professionals. In this case, 100,000 individuals were divided into groups of 11 people who helped each other achieve certain lifestylerelated goals, such as change in diets, weight loss, achieve blood pressure goals, and engage in physical exercise [6]. This model has allowed putting into practice an efficient system of local control, which has shown an important lesson about the changes needed to be undertaken to control chronic disease. Similarly, the Cardona Project (in the Spanish town of Cardona, with a population of 5,000 inhabitants and currently undergoing a major economic recession) is currently underway to study the impact of communication among adults over 50 years of age in controlling cardiovascular risk factors and healthy habits. Together, the Cardona and Grenada experiences may serve as a template for other communities around the world with similar characteristics, which have proven that collaboration and reinforcement among individuals of the same community striving to reach the same goal is a valuable tool to reach better adherence and compliance.

Discharge counseling

Patients who receive counseling immediately preceding and/or following a discharge from the hospital are more apt to adhere. Interventions often include in-hospital discharge counseling by a pharmacist or nurse, as well as postdischarge home visits to provide pharmaceutical counseling. One study found that among elderly patients with more than 3 medications, adherence improved by 43% among patients who received counseling from a pharmacist before and after hospital discharge, compared with patients who did not receive the intervention [53]. Another successful intervention to improve adherence is counseling by community pharmacists. The details of the counseling may vary, but would likely include a review of the medication list, assessment of patient knowledge about their condition and medications, education on adherence strategies, and suggestions for lifestyle changes to decrease symptoms. One study of patients with heart failure found that among patients who received monthly pharmacist counseling, nonadherence (defined as a percentage of missed daily doses) was less than one-half of that observed among the usual care patients [54]. Similarly, another study of patients with heart failure found that pharmaceutical counseling combined with dose simplification increased adherence by 46% ("adherence" was defined as medication possession ratios between 80% and 120%) [55].

SUMMARY

There are both enormous challenges and opportunities associated with addressing the public-health crisis of medication adherence. The multifactorial basis of nonadherence calls for a multifaceted solution. Ultimately, the economic force behind the continuing rise in the cost of health care will leave policymakers no choice but to deeply revise, and come up with, efficient solutions to improve medical adherence. In a healthcare system that is continually becoming more complex, where efficacious drugs and sophisticated devices continue to improve clinical outcomes, part of the focus should be placed back on the mechanisms that allow patients to follow and adhere to medical recommendations, which in turn will improve health outcomes and reduce costs.

REFERENCES

- Bosworth HB, Granger BB, Mendys P, et al. Medication adherence: a call for action. Am Heart J 2011;162:412–24.
- Gottlieb B. Medical nonadherence: finding solutions to a costly medical problem. Drug Benefit Trends 2000;12:57–62.
- De Geest S, Sabaté E. Adherence to long-term therapies: evidence for action. Eur J Cardiovasc Nurs 2003;2:323.
- Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. Arch Intern Med 2005;165:2508–13.
- Fuster V. Promoting Cardiovascular Health in the Developing World: A Critical Challenge To Achieve Global Health. Washington, DC: Institue of Medicine; 2010.
- Fuster V, Kelly BB, Vedanthan R. Promoting global cardiovascular health: moving forward. Circulation 2011;123:1671–8.
- Muntner P, Mann D, Wildman RP, Shimbo D, Fuster V, Woodward M. Projected impact of polypill use among US adults: medication use, cardiovascular risk reduction, and side effects. Am Heart J 2011;161: 719–25.
- Yusuf S, Islam S, Chow CK, et al, for the PURE Study Investigators. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet 2011;378:1231–43.
- Cheng JW, Kalis MM, Feifer S. Patient-reported adherence to guidelines of the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Pharmacotherapy 2001;21:828–41.
- Dailey G, Kim MS, Lian JF. Patient compliance and persistence with antihyperglycemic drug regimens: evaluation of a Medicaid patient population with type 2 diabetes mellitus. Clin Ther 2001;23:1311–20.
- Holper EM, Brooks MM, Kim LJ, et al, for the BARI Investigators. Effects of heart failure and diabetes mellitus on long-term mortality after coronary revascularization (from the BARI Trial). Am J Cardiol 2007;100:196–202.
- 12. Shaw LJ, Berman DS, Maron DJ, et al, for the COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. Circulation 2008;117:1283–91.
- Senst BL, Achusim LE, Genest RP, et al. Practical approach to determining costs and frequency of adverse drug events in a health care network. Am J Health Syst Pharm 2001;58:1126–32.
- Johnson JA, Bootman JL. Drug-related morbidity and mortality: a cost-of-illness model. Arch Intern Med 1995;155:1949–56.
- Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. J Am Pharm Assoc (Wash) 2001;41:192–9.

- Wu JR, Moser DK, Lennie TA, Burkhart PV. Medication adherence in patients who have heart failure: a review of the literature. Nurs Clin North Am 2008;43:133–53. vii—viii.
- Dunbar-Jacob J, Erlen JA, Schlenk EA, Ryan CM, Sereika SM, Doswell WM. Adherence in chronic disease. Annu Rev Nurs Res 2000; 18:48–90.
- Gadkari AS, McHorney CA. Medication nonfulfillment rates and reasons: narrative systematic review. Curr Med Res Opin 2010;26: 683–705.
- Ho PM, Magid DJ, Masoudi FA, McClure DL, Rumsfeld JS. Adherence to cardioprotective medications and mortality among patients with diabetes and ischemic heart disease. BMC Cardiovasc Disord 2006;6: 48.
- Mehta RH, Peterson ED, Califf RM. Performance measures have a major effect on cardiovascular outcomes: a review. Am J Med 2007; 120:398–402.
- Wagner GS, Bahit MC, Criger D, et al. Moving toward a new definition of acute myocardial infarction for the 21st century: status of the ESC/ ACC consensus conference. European Society of Cardiology and American College of Cardiology. J Electrocardiol 2000;33(Suppl):57–9.
- Lowry KP, Dudley TK, Oddone EZ, Bosworth HB. Intentional and unintentional nonadherence to antihypertensive medication. Ann Pharmacother 2005;39:1198–203.
- Bardel A, Wallander MA, Svärdsudd K. Factors associated with adherence to drug therapy: a population-based study. Eur J Clin Pharmacol 2007;63:307–14.
- Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med 2008;31:213–24.
- Grenard JL, Munjas BA, Adams JL, et al. Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. J Gen Intern Med 2011;26:1175–82.
- Hevey D, McGee HM, Horgan J. Relationship of initial level of distress to changes in health-related quality of life during cardiac rehabilitation or usual care. Psychosom Med 2007;69:793–7.
- 27. van Servellen G, Chang B, Garcia L, Lombardi E. Individual and system level factors associated with treatment nonadherence in human immunodeficiency virus-infected men and women. AIDS Patient Care STDS 2002;16:269–81.
- 28. Jiang W, Glassman A, Krishnan R, O'Connor CM, Califf RM. Depression and ischemic heart disease: what have we learned so far and what must we do in the future? Am Heart J 2005;150:54–78.
- Osterberg L, Blaschke T. Adherence to medication. New Engl J Med 2005;353:487–97.
- Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001;23:1296–310.
- Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 1990;150:1881–4.
- **32.** Garner JB. Problems of nonadherence in cardiology and proposals to improve outcomes. Am J Cardiol 2010;105:1495–501.
- Rector TS, Venus PJ. Do drug benefits help Medicare beneficiaries afford prescribed drugs? Health Aff (Millwood) 2004;23:213–22.
- Choudhry NK, Avorn J, Glynn RJ, et al, for the MI FREEE Trial Investigators. Full coverage for preventive medications after myocardial infarction. New Engl J Med 2011;365:2088–97.
- Choudhry NK, Setoguchi S, Levin R, Winkelmayer WC, Shrank WH. Trends in adherence to secondary prevention medications in elderly post-myocardial infarction patients. Pharmacoepidemiol Drug Saf 2008;17:1189–96.
- Lapane KL, Dube CE, Schneider KL, Quilliam BJ. Misperceptions of patients vs providers regarding medication-related communication issues. Am J Manag Care 2007;13:613–8.
- Goldberg AI, Cohen G, Rubin AH. Physician assessments of patient compliance with medical treatment. Soc Sci Med 1998;47:1873–6.
- Tarn DM, Paterniti DA, Kravitz RL, et al. How much time does it take to prescribe a new medication? Patient Educ Coun 2008;72:311–9.

- 39. Tarn DM, Heritage J, Paterniti DA, Hays RD, Kravitz RL, Wegner NS. Physician communication when prescribing new medications. ArchIntern Med 2006;166:1855–62.
- Hall JA, Roter DL, Katz NR. Meta-analysis of correlates of provider behavior in medical encounters. Med Care 1988;26:657–75.
- Piette JD, Heisler M, Krein S, Kerr EA. The role of patient-physician trust in moderating medication nonadherence due to cost pressures. Arch Intern Med 2005;165:1749–55.
- McHorney CA. The Adherence Estimator: a brief, proximal screener for patient propensity to adhere to prescription medications for chronic disease. Curr Med Res Opin 2009;25:215–38.
- DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care 2004;42:200–9.
- **44.** Ziegler DK, Mosier MC, Buenaver M, Okuyemi K. How much information about adverse effects of medication do patients want from physicians? Arch Intern Med 2001;161:706–13.
- 45. Bailey BJ, Carney SL, Gillies AH, McColm LM, Smith AJ, Taylor M. Hypertension treatment compliance: what do patients want to know about their medications? Prog Cardiovasc Nurs 1997;12:23–8.
- 46. Williams SL, Haskard KB, DiMatteo MR. The therapeutic effects of the physician-older patient relationship: effective communication with vulnerable older patients. Clin Interv Aging 2007;2:453–67.
- Brown BG, Bardsley J, Poulin D, et al. Moderate dose, three-drug therapy with niacin, lovastatin, and colestipol to reduce low-

density lipoprotein cholesterol <100 mg/dl in patients with hyperlipidemia and coronary artery disease. Am J Cardiol 1997;80:111–5. Sanz G, Fuster V. Polypill and global cardiovascular health strategies.

- Sanz G, Fuster V. Polypill and global cardiovascular health strategies. Semin Thorac Cardiovasc Surg 2011;23:24–9.
- Glass G. Cardiovascular combinations. Nat Rev Drug Discov 2004;3: 731–2.
- 50. Yusuf S. Two decades of progress in preventing vascular disease. Lancet 2002;360:2–3.
- Teo K, Lear S, Islam S, et al, for the PURE Investigators. Prevalence of a healthy lifestyle among individuals with cardiovascular disease in high-, middle- and low-income countries: the Prospective Urban Rural Epidemiology (PURE) study. JAMA 2013;309:1613–21.
- Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med 2007;120:713–9.
- Lipton HL, Bird JA. The impact of clinical pharmacists' consultations on geriatric patients' compliance and medical care use: a randomized controlled trial. Gerontologist 1994;34:307–15.
- Bouvy ML, Heerdink ER, Urquhart J, Grobbee DE, Hoes AW, Leufkens HG. Effect of a pharmacist-led intervention on diuretic compliance in heart failure patients: a randomized controlled study. J Card Fail 2003;9:404–11.
- Varma S, McElnay JC, Hughes CM, Passmore AP, Varma M. Pharmaceutical care of patients with congestive heart failure: interventions and outcomes. Pharmacotherapy 1999;19:860–9.