Improving medication adherence in cardiometabolic disease

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Why medication adherence is still an important health issue today

by R. Messina and C. Taranto, Italy

Thanks to an improvement in quality of life and to new technologies, the number of older people is increasing year by year in Europe and, in general, all over the world. In Western countries in particular, older people consume the most resources in terms of care and medicines. Until recently, there has been little-to-no concern about the real burden of poor adherence to treatment regimens in European countries, even though it has long been recognized to be an issue affecting health outcomes and increasing health care costs. The literature shows that, each year, nonadherence causes almost 194,500 deaths and costs €125 billion in the European Union, and costs $300 billion in the USA.

It is estimated that in developed countries only 50% of those who suffer from a chronic condition are compliant with therapies. This lack of compliance, according to the World Health Organization (WHO), is one of the most important reasons for the failure to attain good blood pressure control in patients with hypertension, hyperlipidemia, or diabetes. Moreover, it has been demonstrated that patients who are able to maintain high levels of medication adherence are less likely to suffer exacerbations of their medical conditions than those with low levels of adherence. This means that the greater the adherence and medication expenditure, the lower the need to resort to costly health care interventions.

There are several factors that play a role in poor compliance. The WHO has classified them into five distinct dimensions: patient-related, therapy-related, condition-related, health system–related, and a social and economic dimension. We will focus on the first two dimensions in this article because they are the ones that most concern our federation, Senior Italia FederAnziani.

Patient-related dimensions may include forgetfulness (30%), a deliberate decision to omit doses (11%), a lack of information (9%), emotional factors (7%), and having other priorities (16%). Therapy- and condition-related dimensions can be easily found in aged and frail individuals, due to the co-occurrence of multiple diseases in the same subject, which makes optimal care a challenging task. With regard to this dimension, there are other relevant issues, like the severity of symptoms, prevalence of disability, length of treatment, previous adverse drug reactions and/or therapeutic failures, and the complexity of the therapeutic regimen.

In relation to this last issue, it is useful to highlight that polypharmacy (prescription of ≥5 drugs) is now very common in older subjects. An Italian study carried out in most (94.2%) of the Italian elderly population ≥65 years old indicated that almost
half (49%) were receiving 5 to 9 drugs and that 11.3% were receiving 10 drugs or more simultaneously. The age group that was most exposed to polypharmacy (69.1%) was that of the 75 to 84 year-olds, with 55% receiving 5 to 9 drugs and 14.1% receiving 10 drugs or more. The very elderly (≥85 years) fared little better: two-thirds (66.4%) were on polypharmacy. Polypharmacy was less common (52.2%) in the young elderly (65-74 years). Unsurprisingly, in subjects aged 75-84 years, low levels of adherence to treatment were found.

To combat issues like these, the most important Italian federation for the elderly (with more than 3.8 million members), Senior Italia FederAnziani, has held several events within the last few years dealing with adherence to therapy in order to empower both medical and patient groups. Senior Italia FederAnziani, with its center for health economics studies, made the first estimation of the economic burden of lack of adherence in Italy. The methodology used was based on the application of an American benchmark to health expenditure in Italy. Potential savings for the main chronic illnesses amounted to €6.1 billion: cardiovascular diseases, €2 billion; respiratory diseases, €1.4 billion; urologic diseases, €1.1 billion; metabolic diseases, €1.1 billion; psychiatric diseases: €0.5 billion. When all illnesses were considered, the projected savings amounted to €11.4 billion.

Savings were related mainly to a reduction in hospitalizations (67%), but also to reductions in outpatient visits (22%), emergency admissions (8%), and inappropriate pharmaceutical spending (5%). Improvements in adherence to therapy could, however, increase pharmaceutical expenditure (as more medication might be taken) and, for this reason, it would be wise to keep an eye on the benefits and costs of better treatment adherence. This caveat aside, it is easy to understand—from both a health and financial perspective—the importance of good medication compliance by chronically ill patients: better health and quality-of-life outcomes and better use of limited health resources.

In order to make constructive plans to improve the levels of adherence, especially in older people, Senior Italia FederAnziani gathered different experts from different European countries to form a scientific advisory board with the duty to create a strategy to help institutions and politicians to enhance the availability of health resources for elderly people and their quality of life.

Seven relevant interventions were identified and classified according to their target: patient, therapy, or public health organization. The interventions were the following: (i) comprehensive geriatric assessment; (ii) optimization of treatment (reviewing medication and dosage schemes); (iii) use of adherence aids; (iv) patient (and caregiver, if needed) education to improve patient empowerment; (v) education of physicians and other health care professionals; (vi) adherence assessment; and (vii) facilitating access to medicine by better connection of health services.

Tackling nonadherence effectively requires the common determination of all the stakeholders involved in addition to a well-organized health system, providing different but complementary and connected health services that assist the patient in moving toward the same health objective. Patient-level approaches should be improved, taking into account that patient behavior can be influenced by knowledge (information, education, and communication), skills (training, coaching, and tools), and personal motivation (empowerment, encouragement, and concerns). In addition to this, the scientific literature shows that improvement of adherence requires a good relationship between patient and physician, so the latter plays a key strategic role.

Simplifying drug regimens represents another important facet of better treatment adherence, as critical nonadherence issues include complicated drug administration and a heavy pill burden. Alliation of these detrimental issues aids adherence. In this context of assisting patients with adherence, information and communication technologies—such as telemedicine, internet-linked clinical support models, standardized wireless sensor networks, and so on—may help both patients and caregivers with the self-management of chronic diseases. Last but not least, integrated care at a national level, eg, closer, bidirectional collaboration between general practitioners and pharmacists, could improve the quality of care and enhance the efficiency of health providers and the satisfaction of patients.
Adherence to medication is paramount for optimizing health and economic outcomes, especially in the management of chronic conditions. Unfortunately, there is abundant evidence to show that adherence is often suboptimal and this causes a significant cost in terms of forgone clinical and economic benefit. Nonadherence is associated with increased morbidity, mortality, and health care expenditures. By contrast, better adherence is beneficial for health outcomes and results in lower resource utilization and total health care costs. These findings come from a significant number of studies undertaken across different chronic disease modalities and health care systems, and this reinforces the need to improve performance, for the sake of patients, providers, funding bodies, and tax payers. The latter can be achieved through a comprehensive approach aiming to improve the physician-patient relationship and the patient’s self-management and treatment experience. Recent technological advances in the field of drug discovery and new models of drug delivery, in conjunction with the emerging internet-based revolution in health care may play a pivotal role. The advent and fast growth use of e-devices and e-health systems and all the related innovations in this field generate optimism for improving adherence, even though many developments are still in their infancy and the promise needs to be realized in due course. Apart from the humanistic justification, there is a compelling economic case for improving adherence to pharmaceutical therapy, to reduce wastage of scarce resources, and to eliminate forgone economic benefits in other sectors of health care. Improving adherence to medication must become a top priority for health care systems and health policy, otherwise we will continue to pay a huge price for our inefficiency and tolerance of a significant deficiency of health care systems.

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Paying the price of nonadherence: health and financial costs

by N. Maniadakis and G. Gourzoulidis, Greece

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Medicines are often the first and sole choice for intervention in the management of many chronic and acute diseases. Even in cases where they are used in combination with other interventions, medicines remain a significant contributor to the effectiveness and safety of care. Ensuring that patients adhere in full to provider recommendations in respect to the timing, dosing, and frequency of their medication administration, all along the prescribed length of therapy (persistence), is essential in order to optimize health and economic outcomes. Adherence is of particular importance in the management of chronic diseases such as diabetes, arthritis, hypertension, hypercholesterolemia, and arthritis, where thera-
Moreover, nonadherence has been associated with increased morbidity and mortality among patients with chronic diseases.6,7,8,9,10,11,12,13,14 Moreover, nonadherence has been associated with a high incidence of unwanted side effects, poor quality of life, high rates of hospitalization, poorer health outcomes, and more comorbidities.11,12,13,14 Apart from the health consequences, the economic burden of nonadherence may be significant, since it may exacerbate chronic conditions, generate adverse health events, and increase health care utilization, and, in turn, total health care costs.11,14 Thus, adherence of patients with chronic disease is of paramount importance for both clinical and economic reasons.

Nonetheless, health care systems are not performing well in this aspect of care. World Health Organization estimates indicate that adherence among people taking long-term therapies for chronic diseases is as low as 50% in developed countries,1,11,14 and may be far lower in less developed countries.2,6,11,15 Hence, nonadherence represents a serious challenge in chronic disease management.11,12,14 However, tackling this challenge is not straightforward. Adherence is driven by factors associated to the patient (age, sex, marital status, motivation, ethnicity, culture, lifestyle, communication abilities, income, education, health status, quality of life, and comorbidities), the system of care provision (physician access, education and ability for good communication, frequency, quality and time spent on consultations, reimbursement systems and prescription policies, and monitoring mechanisms) and to the medication itself (route, place and frequency of administration, number of concomitant drugs used, safety, efficacy, tolerability, and duration of therapy). All the aforementioned points indicate that adherence represents a complex and multifactorial issue.11,12,13,14

There are multiple ways to improve adherence. These may focus on improving physician and patient education, the frequency and quality of consultations, the implementation of guidelines, or providing support for drug use at home. Moreover, e-health and m-health devices and new novel technologies and systems offer new and better opportunities for direct and indirect support and monitoring of drug use. Big system data availability and developments in analytics and behavioral research may help us to understand the complex mechanisms of human behavior and the drivers of drug use. Also, improvements in dosage frequency, modes of delivery, fixed-dose combinations, and package infographics are also important. Moreover, as with any problem, it is important for all to understand the magnitude of the costs it imposes and the implications of inactivity and inefficiency. Thus, this article presents evidence from the published literature on the “price” of nonadherence and its economic and medical implications in chronic disease management.

Measuring adherence

The present article presents the findings of many published research studies on adherence. In daily medical practice and in empirical research, it is somewhat difficult to measure medication adherence. The validity of adherence assessment is based on the method of measurement, which needs to satisfy criteria of validity, reliability, sensitivity to change, and feasibility. Unfortunately, there is currently no single approach satisfying adequately all these properties. However, adherence is measured in a variety of direct and indirect methods (Table I).11,14 Direct methods encompass mechanisms such as direct observation of therapy use, measurement of concentrations of a drug or its metabolite in the blood or urine, and detection or measurement in the blood of a biologic marker added to the drug formulation. Although direct methods may be more robust than indirect methods, they have limitations as well. First, they are expensive, burdensome to the health care provider, and susceptible to distortion by the patient.11,14 Furthermore, the use of biological markers only reflects short-term adherence, and can overestimate patients’ long-term adherence and can be applied mostly for drugs with long elimination half-lives. Also, interindividual differences in drug absorption and metabolism can also lead to inaccurate conclusions regarding medication adherence.

<table>
<thead>
<tr>
<th>Methods</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indirect</td>
<td></td>
</tr>
<tr>
<td>MPR</td>
<td>= (total days supplied)/(number of days between the first and last refill)</td>
</tr>
<tr>
<td>PDC</td>
<td>= (total days supplied)/(number of days in refill interval)</td>
</tr>
<tr>
<td>Self-report</td>
<td>Patient recalls medications taken in response to care team query</td>
</tr>
<tr>
<td>Questionnaire</td>
<td>Use of validated tool for adherence markers</td>
</tr>
<tr>
<td>Pill counting</td>
<td>Staff member reviews patient supply for doses remaining</td>
</tr>
<tr>
<td>Dose-counting device</td>
<td>Device includes electronic or manual counter that tracks doses released</td>
</tr>
<tr>
<td>Electronic prescribing</td>
<td>Reports transmitted from a pharmacy benefit manager to provider usually via EMR link</td>
</tr>
<tr>
<td>Direct</td>
<td></td>
</tr>
<tr>
<td>Direct observation</td>
<td>Patient receives and takes medication at health care facility</td>
</tr>
<tr>
<td>Drug levels and markers</td>
<td>Patient blood or urine sample tested</td>
</tr>
</tbody>
</table>

Table I. Methods for measuring adherence.

Abbreviations: EMR, electronic medical records; MPR, medication possession ratio; PDC, proportion of days covered.

Indirect methods represent the most common approach to measuring medication adherence. Commonly used indirect measures are based on pharmacy refills, electronic monitoring of prescriptions, and tablet counts. Commonly used methods to quantify adherence include the medication possession ratio (MPR) and the proportion of days covered (PDC). MPR is calculated as the total number of days supplied, divided by the number of days between the first and last refills, while PDC is calculated as the total number of days supplied during an interval, divided by the total number of days during that interval. An MPR of 80% is often used as the cutoff between adherence and nonadherence, based on its ability to predict hospitalizations across a selection of highly prevalent chronic diseases. Moreover, other indirect methods of adherence assessment are based on questionnaires and diaries completed by patients or electronic medication monitors and other medication use markers from electronic databases and patient records. These are easier to use but suffer from many shortcomings as indicated below.

Pharmacy refills provide a convenient, noninvasive, objective and inexpensive method for estimating medication adherence, but such data reflect mainly dispensing rather than actual consumption. Often, electronic monitoring devices may be used to provide more accurate and detailed information on medication-taking behavior, but they come at a cost and may also increase patient awareness and hence they may modify and bias their behavior. Tablet counts are frequently used in clinical trials and adherence research, but are notoriously unreliable and usually provide overestimates. A few self-reported medication adherence questionnaires have been used in the literature, but none of them is without limitations and there is no widely accepted standard. Despite these caveats lots of research using different methods has been undertaken and some useful finding are presented in the following sections.

Adherence and outcomes in the care of chronic disease

Cardiovascular disease
Approximately 50% of patients with cardiovascular disease have poor adherence to their prescribed medications. Nonadherent heart disease patients have been estimated to have significantly higher mortality rates than adherent patients. This could be attributed to the fact that nonadherent patients fail to achieve their therapeutic targets. More specifically, in a retrospective study of 557 patients with heart failure (HF), it was reported that nonadherence was associated with a statistically significant increase in mortality risk. Moreover, a systematic review showed that the risk of hospitalization, re-hospitalization, and premature death among nonadherent patients was 5.4 times higher in hypertension, 2.8 times higher in dyslipidemia, and 1.5 times higher in heart disease compared with adherent patients. Additionally, a retrospective cohort study that evaluated the impact of adherence to statins on nonfatal coronary artery disease (CAD) showed that adherence which exceeds 90% resulted in significant reduction in nonfatal CAD events.

Furthermore, two studies conducted in HF patients showed that poor medication adherence leads to more frequent hospitalizations, which, in turn, results in higher hospitalization costs. Notably, a study reported that in Medicare and Medicaid beneficiaries with HF, those with adherence rates of more than 95% had about 15% lower health care costs than those with adherence rates between 80% and 95% ($17,665 vs $20,747). Moreover, a retrospective study of 1,495 patients with HF (799 patients) or myocardial infarction (696 patients) after acute hospitalization, revealed that adherence and persistence with angiotensin receptor blockers and angiotensin-converting enzyme (ACE) inhibitors resulted in lower risk of re-hospitalization and lower health care costs. Similarly, in a retrospective cohort study of 381,422 patients using an integrated pharmacy and medical claims database, higher MPR was associated with reductions in subsequent total health care costs and cardiovascular disease-related hospitalizations. Another retrospective cohort study of 137,277 benefit plan patients reported that high levels of adherence were significantly associated with lower overall health care costs for hypertension patients, but not for patients with congestive HF. Lastly, a study of 2,204 beneficiaries with congestive HF reported that a 10% increase in daily pill counts of ACE inhibitors, β-blockers, diuretics, and cardiac glycosides resulted in savings of $390, $510, $13, and $923, respectively, on total health care costs.

Diabetes
Multiple studies have evaluated the relationship between medication adherence and outcomes in diabetes and in general they support a correlation between increased adherence and better health outcomes, which, in turn, result in reduced total cost. More specifically, one study reported that the number of disability days was significantly lower in adherent patients than in nonadherent patients. Moreover, two studies reported that a 10% increase in medication adherence leads to a 0.1% and 0.12% decrease in HbA1c levels, while another study indicated that a 25% decrease in medication adherence leads to a 0.35% increase in HbA1c levels. In ad-
dition, one study found that a 50% increase in medication adherence reduced by 23.3% and 46.2% the hospitalization rates and the emergency department visits, respectively. Similar findings were detected in another study, which reported that a 10% increase in medication adherence resulted in a 1.2% decrease in hospitalization rates and emergency department visits. Furthermore, increased adherence with pharmaceutical therapy has been associated in one study with decreased use of medical care services, due to improved disease control and well-being, though this was not reflected in total therapy costs. By contrast, another study found that a 10% increase in adherence of adult patients with type 2 diabetes mellitus was associated with an 8.6% to 23.9% decrease in total annual health care costs. Similarly, another study reported that a 10% increase in adherence was associated with a 2% reduction in total medical costs and a 4% reduction in diabetes-related medical costs. Finally, a study reported that better medication adherence was associated with decreased hospitalizations and emergency department visits for diabetes or related conditions and that higher total health care costs were observed initially, but were lower 5 years after the time of diabetes onset.

**Chronic obstructive pulmonary disease**

Several studies were carried out to explore the impact of non-adherence on health and economic outcomes in chronic obstructive pulmonary disease (COPD). More specifically, a study conducted in this patient group showed that good adherence was associated with a decreased risk of severe exacerbations and a decreased risk of death, even though there are other studies that show no significant difference in mortality between adherent and nonadherent patients. Moreover, a 7-year retrospective administrative claims study of 55,076 COPD patients showed that a 5% increase in adherence leads to a 2.6% reduction in hospital visits and a 1.8% reduction in emergency department visits. A similar study of 33,816 Medicare beneficiaries diagnosed with COPD found that the annual Medicare spending per patient was $2,185 lower in patients with PDC >80% than in patients with PDC <80%. Furthermore, a retrospective study compared adherence and outcomes between COPD patients initiating tiotropium (n=1,561) or salmeterol/fluticasone (n=2,976) therapy using claims data from a large national US health plan. This study showed that pharmacy costs were higher in adherent patients compared with nonadherent patients. In contrast, inpatient stay costs were lower in adherent patients than in nonadherent patients. Finally, another study compared users and nonusers of maintenance medication for COPD and found that the use of maintenance therapy was associated with significantly lower risks of hospitalization and re-hospitalization and reduced health care expenditures.

**Asthma**

Studies in asthma patients have shown that better adherence in asthma cohorts was associated with better outcomes across populations and cost savings in those at higher risk. In particular, a retrospective study of 18,456 Medicaid children aged between 2 and 18 years and diagnosed with asthma reported that greater adherence was associated with lower rates of emergency department visits; however, higher medication expenditures outweighed the cost savings related to fewer visits. Moreover, a retrospective study using two years of claims data for 21,234 commercially insured asthmatics indicated that better adherence reduced total therapy costs in high-risk patients who had a past history of emergency department visits or hospital admissions. Both studies suggest that improving medication adherence improves outcomes and is cost-saving in patients with severe disease, while it increases overall cost in patients with mild disease.

Another study sought to measure changes in inhaled corticosteroid adherence over time and to estimate the effect of this changing pattern on asthma exacerbations. Adherence to inhaled corticosteroids was estimated from electronic prescription and fill information for 298 participants in the SAPPHIRE study (Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity). The study results showed that adherence was associated with a reduction in exacerbations, but this association reached statistical significance when patients whose adherence was greater than 75% of the prescribed dose (hazard ratio, 0.61; 95% CI, 0.41-0.90) were compared with patients whose adherence was 25% or less. This pattern was largely confined to patients whose asthma was not well controlled initially. An estimated 24% of asthma exacerbations were attributable to nonadherence to inhaled corticosteroid medications.

**Human immunodeficiency virus**

Not many studies have been carried out to explore the impact of adherence on health and economic outcomes in human immunodeficiency virus (HIV) therapy. A retrospective cohort study of 325 previously antiretroviral medication-naive HIV-infected individuals initiating first antiretroviral therapy during the period 1997-2003 was carried out in the USA. The study showed that better adherence to antiretroviral medication resulted in decreased health care utilization and associated costs, but the total medical cost was higher due to a higher cost of antiretroviral therapy. However, the dramatic clinical benefits of antiretroviral therapy suggest that while interventions that promote adherence may not be cost-saving, they can be cost-effective. Similar findings were detected in an observational study using administrative data in which highly adherent patients with antiretroviral treatment were found to have higher medication costs but lower acute hospital costs. In contrast, patients with lower adherence to antiretroviral treatment were associated with higher total cost. Moreover, an observational study of 99 HIV-infected patients in a Veterans Affairs medical center revealed that patients with adherence of 95% or greater had fewer days in the hos-
pital (2.6 days per 1000 days of follow-up) than those with less than 95% adherence (12.9 days per 1000 days of follow-up; \( P < 0.001 \)).\(^{47}\)

**Depression**

A retrospective study\(^{49}\) of patients initiating selective serotonin reuptake inhibitor (SSRI) therapy for depression and/or anxiety between July 2001 and June 2002 showed that only approximately 43% of patients were adherent to antidepressant therapy, and those adherent patients were associated with the lowest yearly medical cost. Another study of 65 753 managed care patients found that medical charges due to inpatient treatment, excluding pharmacy charges, were lower for patients remaining on antidepressant drug therapy for at least 90 days, and only when drug costs were added there was no cost difference between adherent and nonadherent patients.\(^{50}\)

Moreover, a study of 60 386 adult patients with depression showed that adherent patients had 6-month median unadjusted total health care expenses that were higher compared with nonadherent patients ($5169 vs $2734), and this was also the case for mental health expenditures ($1922 vs $677). After adjustment, adherent patients compared with nonadherent patients incurred an additional cost of $644 in mental health expenditures and $806 in overall health care expenditures in the 6 months following initiation of antidepressant therapy.\(^{50}\)

**Parkinson disease**

Poor compliance has been recognized as an important issue in Parkinson disease (PD).\(^{51}\) In PD, low adherence to therapy may be associated with unsatisfactory control of motor symptoms, more time spent in worse health states, and worse quality of life.\(^{52}\) A study of PD patients from a national database in the USA found that nonadherent patients had significantly higher rates of hospitalizations (2.3 vs 1.8), office visits, and ancillary care visits and higher total medical costs ($15 826 vs $9228) per annum, despite lower prescription drug costs ($2684 vs $3854; \( P < 0.05 \)).\(^{53}\) After adjusting for confounders and comorbidities, nonadherence was associated with a $3451 yearly increase in medical costs.

On the other hand, a study of 7583 beneficiaries examining the association of adherence to anti-parkinson drugs (APDs) with health care utilization and economic outcomes reported that increased adherence is associated with decreased health care utilization and expenditures.\(^{53}\) For example, compared with patients with low adherence, those with high adherence (MPR, 0.90-1.00) had significantly lower rates of hospitalization (RR, 0.86), emergency room visits (RR, 0.91), skilled nursing facility episodes (RR, 0.67), home health agency episodes (RR, 0.83), physician visits (RR, 0.93), as well as lower total health care expenditures ($2242) over a period of 19 months.

Additionally, a multicenter European study conducted to assess the medicine-taking behavior in PD patients found that suboptimal adherence was significantly associated with higher Parkinson motor scores (median, 29; IQR, 20–40) and with greater disability, compared with satisfactory adherence (median, 19; IQR 13–26).\(^{54}\)

**Osteoporosis**

A retrospective study\(^{55}\) of 17 770 women examined the association between adherence with oral bisphosphonate therapy and fracture risk as well as health care resource utilization. The study results showed that during the second-year post–treatment initiation, the risk of osteoporotic fracture was 2.1% in adherent patients and 2.5% in nonadherent patients (\( P < 0.1 \)). Moreover, when analysis was limited to patients aged 75 years or older, nonadherence with bisphosphonates was associated with a probability of osteoporotic fractures that was almost 50% higher than that of adherent patients (OR, 1.49; 95% CI, 1.08-2.04). Nonadherent patients had 13.4% higher medical costs than their adherent counterparts among patients aged 75 years and older (\( P = 0.002 \)).\(^{55}\)

Furthermore, in another study,\(^{56}\) which was performed to investigate the impact of adherence to bisphosphonate therapy on the risk of hip fracture, it was reported that for a 1% decrease of the MPR, the risk of hip fracture increased by 0.4% (OR, 0.996; 95% CI, 0.994-0.998; \( P < 0.001 \)). The relative risk reduction for hip fracture was 60% (HR, 0.404; 95% CI, 0.357-0.457; \( P < 0.0001 \)) for persistent patients compared with nonpersistent patients.\(^{56}\) Additionally, a retrospective study\(^{57}\) of 685 505 women with osteoporosis showed that noncompliance was associated with a 20% higher risk of any fracture, a 26% higher risk of inpatient utilization (incidence rate ratio [IRR], 1.26) and a 3% lower rate of outpatient utilization (IRR, 0.97). Noncompliant patients had 13% higher medical costs (cost ratio, 1.13) than compliant patients.\(^{57}\)

**Arthritis**

There is also evidence regarding the effects of adherence on outcomes in arthritis management. A multicenter prospective observational cohort study recently investigated self-reported nonadherence to anti-TNF therapy and response to therapy in individuals with rheumatoid arthritis. The study included 392 patients who reported being nonadherent to their treatment at least once within the first 6-month period. Multivariate linear regression analysis showed that nonadherence was significantly associated with a poorer response to therapy.\(^{58}\)

Another study assessed adherence to therapy and consumption of care resources (drugs, outpatient services, hospitalizations) using an observational retrospective cohort analysis of administrative databases containing data from 1219 patients with rheumatoid arthritis, psoriasis, and Crohn disease. The mean annual nonpharmacological expenditure for each
patient in analysis was €988 for adherent patients and €1255 for nonadherent patients. Higher adherence was thus associated with lower costs.30

A multicenter cohort study of 206 patients with rheumatoid arthritis and 1 year of follow-up found that nonadherence was associated with higher health care costs in the first year of treatment for arthritis. The study results indicated that improving adherence was not only associated with better outcomes, but also with health care cost savings.30

Moreover, a study evaluated adherence to subcutaneous anti-TNFs among rheumatoid arthritis patients who were either new to therapy (naïve) or existing users over 1 year, and it found that adherent patients had fewer ambulatory, emergency department, and inpatient visits compared with nonadherent patients.30

Conclusions
Adherence is a primary determinant of the effectiveness of treatment because poor adherence attenuates optimum clinical benefit. Unfortunately, many studies show that high levels of nonadherence are common across many different chronic disease modalities and health system settings. This should not be acceptable in light of abundant evidence which indicates that, in chronic disease management, better adherence decreases mortality, morbidity, hospitalizations, and emergency department or physician visits and, in most cases, lowers overall total health care costs. Nonadherence is common and contributes significantly to higher morbidity, mortality, and increased health care costs.

Thus, it is paramount to tackle this issue and improving adherence must be a priority for health policy. As it is a phenomenon with multifactorial causes it needs a comprehensive approach. Adherence can be improved through better education, more frequent and qualitative consultations, economic incentives, abolition of barriers in access to medicines and other similar interventions.32-34 Nonetheless, the big promise emerges from the technological developments in the medical field and the e-health revolution. Specifically, new innovative drugs and drug delivery approaches improve effectiveness, safety, tolerability, and convenience for patients.

Also, the emerging internet based ecosystem with e-health, m-health, big data, and IT systems and devices, provides an opportunity to aid, monitor, analyze, and improve drug use in an effective way. This endeavor requires the contribution of all stakeholders: patients, clinicians, pharmacists, payers, and pharmaceutical firms.

Nonadherence has a significant human cost and is responsible for economic opportunity loss. The worldwide pharmaceutical expenditure is higher than 1 trillion US dollars and to a large extent it concerns chronic drug use. In many chronic diseases nonadherence reaches levels as high as 50%. Put together, these figures make a straightforward and compelling economic case for improving adherence in order to reduce wastage in pharmaceutical expenditure and also forgo economic benefits in other sectors of care. In conclusion, improving adherence to medication must become a top priority for health care systems and health policy. We cannot afford to tolerate this inefficiency. The price is too high.
Improving medication adherence in cardiometabolic disease


Keywords: adherence; compliance; drug; medicine; persistence; pharmaceutical
Living with a chronic medical condition places significant behavioral and treatment demands on the individual. Nonadherence to medication and lifestyle self-management plans is a major challenge in chronic condition management, as it is both common and associated with poor clinical outcomes. Human behavior is extraordinarily complex, and different reasons for nonadherence will apply to each individual and their different circumstances. In this article, I will review the barriers—personal, medication-related, and health-care professional–related—that explain why adherence is imperfect in the real world. Although lack of self-management education is an important reason for nonadherence, insufficient knowledge does not entirely explain the situation. Behavior is also critically dependent on motivation, which, in turn, is affected by health beliefs, self-efficacy, disease perception, and mental well-being. In situations where the person with the chronic condition is empowered to take responsibility for their self-management, adherence improves. Coping strategies and problem-solving skills influence the individual’s response to their condition and subsequent self-management. People with chronic conditions do not live in isolation and the support they receive from their friends and family, as well as the health care team, affects adherence. With regards to pharmacotherapy, side effects of treatment and therapeutic complexity reduce medication adherence. Understanding the multiple reasons for nonadherence should provide the basis for the design of interventions to improve support for individuals with chronic medical conditions.

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"Drugs don't work in people who don't take them."
Dr C. Everett Koop, the 13th US Surgeon General, who served under President Ronald Reagan from 1982 to 1989

Medication nonadherence is a major challenge in chronic condition management and increasing the effectiveness of adherence interventions may have a greater impact on population health than any improvement in specific medical treatments. Fewer than 50% of people receiving oral antidiabetes treatments, antihypertensive agents, and statins persist with their medication 2 years after treatment initiation and up to 20% never start treatment. Nonadherence to diabetes medication is associated with poorer glycemic control and significantly higher rates of hospitalization and mortality. Self-management extends beyond medication to a range of other behaviors, including diet, physical activity, smoking cessation, and self-monitoring of, for example, glucose. In the second Diabetes Attitudes Wishes and Needs (DAWN2) study, people with diabetes self-reported taking med-
Improving medication adherence in cardiometabolic disease

Barriers to self-management of chronic medical conditions

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<tr>
<th>Personal</th>
<th>Medication-related</th>
<th>Health-care professional–related</th>
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<tbody>
<tr>
<td>• Lack of education</td>
<td>• Side effects</td>
<td>• Poor communication</td>
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<tr>
<td>• Competing demands of life</td>
<td>• Treatment complexity</td>
<td>• Poor service organization</td>
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<td>• Health beliefs</td>
<td>• Disease perception</td>
<td>• Lack of patient–centered approach</td>
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<td>• Disease perception</td>
<td>• Poor self-efficacy</td>
<td>• Inconsistency</td>
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<td>• Poor self-efficacy</td>
<td>• Lack of empowerment</td>
<td>• Clinical inertia</td>
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<td>• Lack of empowerment</td>
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<td>• Poor coping strategies</td>
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<td>• Mental illness and psychological stress</td>
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<td>• Poverty</td>
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Table I. Personal, medication-related, and health-care professional–related barriers to optimal self-management of chronic medical conditions.

Human behavior is extraordinarily complex, and it is far too simple to suggest that the same reasons for poor self-management of chronic medical conditions apply to every person and circumstance (Table I). In order to illustrate this, consider driving a car over the speed limit. Most people accept the need for speed limits to promote road safety, yet most drivers have broken the speed limit at some time. The reasons inevitably vary between drivers and at different times, but may include:

• not knowing the speed limit
• thinking that accidents will not happen to them
• enjoying the thrill of speeding
• feeling that everyone else is doing it
• not caring
• being distracted by other things, such as work, the phone, or children in the back seat
• being in a rush

Recognizing ourselves in these behaviors can help us empathize with our patients; if we consider these reasons further, it becomes apparent that many have parallels in health care adherence. For example, “not knowing the speed limit” might reflect a lack of education, which also applies in a health care setting, eg, newly diagnosed patients. “Thinking that accidents will not happen to them,” which equates to an individual’s assessment of personal risk, might translate into a false perception of the risk of long-term complications.

When I was a student, one professor described three types of diseases: “those that you know you have, those that others know you have, and those that your doctor tells you that you have,” each of which evokes a markedly different behavioral response. Consider how pain in the right iliac fossa, nausea, and malaise will drive a person with appendicitis—an example of the first type of disease—to seek help. The lack of memory and self-care that characterizes Alzheimer’s disease might lead family members to seek medical help for their relative—an example of the second type of disease. The last group of diseases is the most challenging and includes many cardiometabolic conditions, such as hypertension, hyperlipidemia, and diabetes. With these conditions, the patient often has no symptoms and yet may be “given” a diagnosis and management plan, for which there is no immediate benefit or incentive to change behavior. Most people living with a chronic condition spend no more than 6-8 hours a year with a health care professional, leaving them to manage the condition for the remaining 8762 hours themselves. There are no holidays from this constant demand and so perhaps we ought to be more surprised that people with diabetes are taking their medication on average 6 days a week and eating healthily for 5 days a week.

This review will explore further the challenges facing people with long-term cardiometabolic conditions, with a focus on diabetes. This analysis is informed by my clinical practice, a long-standing academic interest in the psychosocial aspects of diabetes, and a review of the literature that focused on recent articles on adherence in chronic conditions.

Knowledge, understanding, and education

Understanding a chronic condition and its management is a necessary prerequisite to self-management. In the case of diabetes, both literacy and numeracy skills are needed to translate health care–related information, such as food labels, into decision-making and self-management, for example, appropriate insulin administration. Self-management education has been defined as “an ongoing process of facilitating the
knowledge, skill, and ability necessary for self-management behaviors," with educational activity being based on the needs, goals, and life experiences of the person with the chronic condition. Many people and their family members find educational courses valuable and enjoy learning more about their condition. Despite their importance, however, few people have had the opportunity for education; in the DAWN2 study, only 49% of people with diabetes and 23% of their family members reported ever participating in a diabetes education program.

Self-management education of older people and their family members is often deficient, leading to serious gaps in diabetes knowledge. This is particularly challenging for a group of individuals who have an increased risk of cognitive decline and dementia and consequent memory problems. Recently, the UK National Health Service introduced a financial incentive for general practitioners to refer to structured diabetes education programs. This led to an increase in referrals, but uptake remained unchanged, leading to questions about whether these programs address patient needs and are provided at suitable times and locations. The poor uptake may also reflect how health care professionals communicate the role of education; for example, if health care professionals view this as an optional extra, patients will be less likely to attend than if it is seen as an integral part of treatment. The best measure of successful education is not simply that the person knows more, but instead that they use the new knowledge to enhance their self-management.

While necessary, education alone is insufficient to change behavior substantially and we need to explore how motivation interacts with knowledge and skills.

Motivation

Motivation can be seen as a reason for acting or behaving in a particular way and reflects an individual’s identity, self-esteem, and values. It can be divided into external and internal; extrinsic motivation leads to activities that achieve a reward or avoid a threat or punishment, while intrinsic motivation is driven by an interest in or enjoyment of the task itself. In general, intrinsic motivation is more powerful than extrinsic motivation, and short-term rewards are bigger drivers than long-term gains. This perhaps explains why threatening individuals with the long-term complications of the condition is a poor way of changing health behavior. Motivation is often construed in an abstract manner, but a better way of considering this is to understand that people are motivated to do what they value.

Health care professionals often deride individuals with chronic conditions as having little motivation, but this is untrue. Very few people are unmotivated to live a long and healthy life, but often conflict arises between different motivators (Table II). Consider a taxi driver with diabetes; he values earning a living from driving and recognizes that recurrent hypoglycemia may jeopardize his licence to drive. He may be more motivated to avoid hypoglycemia than to achieve good glycemic control to avoid the long-term complications of diabetes. A further example may be a young woman who does not want to inject insulin in front of her friends because she values avoiding the embarrassment that this would cause. If an individual has been told of the health importance of a behavior change and understands this, but still does not do it, it is because they value something else more highly. Exploring this ambivalence is one of the tenets of motivational interviewing.

Patient empowerment has been defined as “the discovery and development of one’s inherent capacity to be responsible for one’s own life.” This concept recognizes that knowing about an illness is not the same as knowing the context within which each individual lives with the condition. The theory identifies the person with the condition as best placed to understand how to self-manage and places them in the position of primary decision-maker. In practice, management moves from a rigid prescribed regimen to one where the individual makes informed choices to suit their individual circumstances. Encouraging people with diabetes to take this responsibility improves motivation, leading to improved medication adherence as well as better diet, exercise, glucose testing, and foot self-care.

There are several theories that attempt to explain motivation and health behavior and I will explore some of these in the next section.

Health beliefs

The health belief model hypothesizes that health-related behavior depends upon three different things happening together:

- The existence of sufficient motivation or health concern to make health issues relevant
- The belief that an individual is vulnerable to a serious health problem or its complications
- The belief that following a particular health recommendation would be beneficial in reducing the perceived threat at a subjectively acceptable cost.

<table>
<thead>
<tr>
<th>Personal value</th>
<th>Obstacle to diabetes self-management</th>
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<tr>
<td>Experiencing no pain</td>
<td>“The injections hurt.”</td>
</tr>
<tr>
<td>Fitting in with your friends</td>
<td>“I get teased.” and/or “I look stupid.”</td>
</tr>
<tr>
<td>Being left alone</td>
<td>“They always nag me, whatever I do.”</td>
</tr>
<tr>
<td>Doing what you want to do</td>
<td>“It takes too much time.”</td>
</tr>
<tr>
<td>Looking good</td>
<td>“Insulin makes you gain weight.”</td>
</tr>
<tr>
<td>Not being different</td>
<td>“‘Hypos’ are so embarrassing.”</td>
</tr>
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</table>

Table II. Examples of ways in which different personal values can impair diabetes self-management.
In one study of people with new-onset type 2 diabetes, only 64% believed that this was a lifelong condition, while only 22% believed that the diabetes would affect their health, and 9% thought that diabetes would shorten their lives. Given these beliefs, it is understandable why some of these individuals would not dedicate the necessary time and effort to managing their diabetes.

Health beliefs that confuse the effect of the disease and its treatment often adversely influence care. For example, many people are reluctant to initiate insulin therapy because of their experience of a family member who has died or developed a diabetes complication shortly after starting insulin; in their mind, the insulin precipitated the event rather than the poorly controlled diabetes.

Self-efficacy refers to an individual's belief in their capabilities to organize and execute the courses of action required to produce given attainments. Such beliefs relate both to the confidence that the individual has to perform the behavior and the belief that a behavioral change will have a positive outcome. Higher self-efficacy is associated with better self-management and, in the case of diabetes, better glycemic control.

**Illness perceptions**

An individual's perception of their illness can affect their health behavior, particularly when perceptions are specific and focus on issues that are central to the individual's experience of illness and its management. According to Leventhal, health and risk behaviors have a bidirectional interplay, which changes according to symptoms, beliefs, and circumstances. People interpret their condition through personal knowledge and experience, with dynamic illness representations being central to determining self-management behavior.

For example, in one study, people with diabetes rated medication as more important than diet and exercise, and reported higher adherence to drugs than lifestyle interventions. However, those who perceived that exercise could help diabetes control were more likely to be physically active. Perceived personal control was also associated with better self-management.

**Coping and problem-solving skills**

The diagnosis of a chronic condition is a stressful event and how people cope with the problem has a major influence on subsequent self-management. Coping strategies differ according to the nature of the stressor, the individual, and the social environment, some of which are more effective in terms of self-management than others. The person may appraise the problem and change the way they think about it, for example, denial or looking for humor in a situation. This approach can self-evidently be maladaptive; while denial of a chronic condition may reduce the stress, it will not promote necessary lifestyle changes or regular medication use.

Another approach is to manage the emotions that stem from the perception of stress and include escape-avoidance, acceptance of responsibility or blame, exercising self-control, and positive reappraisal. The aim of these strategies is to find a more positive meaning to the situation to reduce the emotional component of the stressor. Emotion-focused coping is well suited for uncontrollable situations, such as the diagnosis of a terminal illness or a bereavement.

The most constructive strategy involves dealing with the cause of the problem, by seeking information about the problem and learning new skills to manage it. The success of a problem-focused approach is dependent on the individual's ability to solve the problems associated with self-management. Good problem-solving ability in people with diabetes is associated with healthier eating patterns, more frequent glucose self-monitoring, and better diabetes self-management.

**Depression and diabetes distress**

It is important for clinicians to recognize that psychotic illness, anxiety, and alcohol and drug misuse are all associated with poor self-management and worse outcomes; however, a detailed description of the interactions between these mental health conditions and adherence is beyond the scope of this review. Instead, I will concentrate on depression and diabetes-related distress as exemplars.

The prevalence of depression and depressive symptoms increases in people with chronic illness. Among people with diabetes, ~10% have a formal diagnosis of depression while up to a quarter exhibit significant depressive symptoms. Similarly, 20%-50% of those with cardiovascular disease have depression. The comorbidity worsens clinical outcomes, which may be partly explained by the effect of depression on adherence; results from a meta-analysis of 47 independent studies shows that depression, including low levels of depressive symptoms, was associated with reduced adherence, with the greatest effect on missed medical appointments and composite measures of self-care.

Diabetes-related distress captures the emotional distress associated with living with diabetes and is more common than diagnosed depression. Although diabetes-related distress correlates modestly with depressive symptoms, it remains distinct from depression and is a better predictor of self-management behavior and glycemic control.

**Social support - “no man is an island”**

Living with a chronic condition is influenced by the context in which people live and the social support obtained from family, friends, and health care professionals. Social support improves self-efficacy and adherence to diabetes self-management behaviors, by encouraging optimism and self-esteem while buffering the stressful effects of the chronic condition. Conversely, lack of support is an important barrier to active...
Weight gain and hypoglycemia—two common unwanted side effects of antidiabetes drugs—can lead both physicians and patients to abandon treatments.

Poverty is associated with worse adherence, particularly in societies where individuals have to pay for treatment out-of-pocket. For example, in one study from the USA, food insecurity—defined as being without reliable access to a sufficient quantity of affordable, nutritious food—was associated with low medication adherence and poorer glycemice control. A further example from the USA explored how insurance coverage influences adherence; adherence improved by 13.4%-17.9% for those with hyperlipidemia, hypertension, or diabetes when prescription costs were subsidized through Medicare Schedule D.

Poverty is also associated with living in a poor neighborhood. Both physical factors (eg, traffic, noise, and lack of pavements) and social factors (eg, poor social cohesion, violence, and residential instability) reduce the opportunity for a healthy lifestyle and consequently may increase the risk of chronic cardiometabolic disorders.

Medication

Most people taking cardiometabolic drugs do not feel better yet experience unwanted side effects. Studies have reported different adherence between classes of oral antidiabetes agents that may reflect, in part, differences in adverse events. For example, in one study from Germany, after 2 years only 51% were still taking sulfonylureas compared with 61% for DPP-4 (dipeptidyl peptidase-4) inhibitors. Weight gain and hyperglycemia are common unwanted side effects of certain classes of antidiabetes drugs and can lead both physicians and patients to abandon treatments.

Adherence drops as treatment regimens become more complex, both for the condition and for other comorbidities. For example, in one community study, the overall rate of adherence over 6 months to oral antidiabetes drugs therapy was 67%, but this ranged from 79% in those receiving once-daily regimens to only 38% in those on thrice-daily regimens. Studies have suggested that single-pill combination formulations can improve adherence and treatment satisfaction compared with loose-pill combination therapies. Increasing complexity of treatment is also important for insulin management, as the perceived treatment burden increases with the number of injections and requirement for glucose monitoring.

Treatment satisfaction

Treatment satisfaction, the belief that the benefits of treatment outweigh the burden, improves treatment adherence and glycemic control. Peyrot and Rubin deconstructed the factors associated with treatment satisfaction in a clinical trial of pramlintide and demonstrated that individual-level clinical outcomes—such as hypoglycemia, change in postprandial and long-term glucose levels, and weight—accounted for almost half of the judgments of treatment satisfaction and preference. Interestingly, change in glycated hemoglobin (HbA1c) was not associated with treatment satisfaction, suggesting that things that matter to patients are not always the same as those that matter to health care professionals.

Role of the health care professional

People with chronic cardiometabolic conditions are not passive recipients of health care, and optimal management occurs when the multidisciplinary care team and person with the condition work actively together as equal partners. Regular lifelong contact between the patient and health care team is essential in order to support the person through the changing demands of their condition. Facilitating choices based on the best evidence available, and providing the person with the chronic condition with autonomy in consultations leads to better self-care and improved metabolic control. In the DAWN2 study, poor coordination between organizations and health care professionals was reported as an impediment to optimal diabetes management.

Given the limited time in contact with health care professionals, it is crucial that the opportunities in the consultation are maximized in a collaborative, patient-centered, and goal-focused manner. Poor communication prevents patients from discussing their concerns, leading to disagreement about the core problem. Health care professionals often give conflicting advice, both within the team and from one consultation to the next, and goals are often not pursued, leaving the patient feeling frustrated. Such disagreement and inconsistency are associated with confusion, poorer adherence, and worse outcomes. Clear messages, support, and treatment are particularly needed at diagnosis, when the newly diagnosed individual needs to assimilate a huge amount of information and skills at the very time when they may be least able to do so, perhaps because of denial or anger with the diagnosis.

The knowledge, beliefs, and attitudes of health care professionals may also influence self-care management. Several studies have demonstrated that significant delays in treatment intensification in people with type 2 diabetes with suboptimal glycemic control occurred despite opportunities to make changes; as a result, many remained with poor glycemic control for several years before treatment was intensified. Clinical inertia, which may potentially account for 80% of cardiovascular events, occurs for numerous reasons, many of which are related to the health care professional, including overestimation of care provided, use of soft reasons to avoid intensification of therapy, and a lack of training, education, or practice organization.

Professional beliefs about treatment efficacy, the need for treatment intensification, and concerns about side effects may all be barriers to treatment intensification. Other clinician-lever-
el barriers stem from concerns over patient adherence, with physicians perceiving their patients as unable or unwilling to adapt to increasingly complex regimens.

Conclusion

Living with a chronic medical condition places significant behavioral demands on the individual. In this article, I have considered the personal, medication-related, and health-care professional-related barriers that explain why adherence is not perfect.

Understanding these should provide the basis for designing interventions to improve support for individuals with chronic medical conditions.

References

This article is devoted to the psychological aspects associated with non-compliance in chronic diseases. To study compliance, it is essential to focus on refusal of treatment—an open and conscious expression of the patient’s disagreement with the recommended treatment. Noncompliance has both emotional-cognitive and behavioral components. The degree of adherence/resistance of patients to their treatment can be represented as a continuum of behavioral patterns—from treatment refusal to treatment addiction. Given the high incidence and the wide variety of refusals it is necessary to consider patients as individuals with their own personal beliefs about their illness. These beliefs often differ from the biologically oriented views held by medical professionals. The discrepancy between the patients’ conceptualizations and the doctors’ specialized medical knowledge is actualized in the doctor/patient relationship and leads to refusal of treatment. Evaluating the patient from both a medical and psychological perspective prompts doctors to have a dual role: on the one hand, doctors have medical knowledge, but on the other hand, they need to consider the patients’ ideas, expectations, fears, and misconception while trying to persuade them of the necessity of following a long-term treatment and making lifestyle changes. This psychological element of the doctor/patient relationship should be taken into account in the fight against noncompliance.

Compliance has become a stumbling block in modern medicine, because adherence to the doctor’s directions regarding medications and important lifestyle aspects is often a decisive factor in the success or failure of any treatment, regardless of the effectiveness of the drugs prescribed. The problem of compliance is multifactorial and reflects the biopsychosocial complexity of the majority of somatic and mental diseases.

Incidence of noncompliance

The urgency of this problem should not be underestimated as extremely high levels of noncompliance have been found in various areas of clinical medicine. For example, one study found that 55.3% of patients stopped antihypertensive and antilipidemic therapy after 3 months of treatment, and that 64.2% of patients stopped their treatment after 12 months. In another study it was found that 37% of patients with diabetes completely stopped taking their drugs 12 months after the initial prescription of therapy. Moreover, only 7% of patients with insulin-dependent diabetes...
were found to follow all the recommendations necessary to control their disease. In patients with acute myocardial infarction, a study found that preventive therapy was discontinued by 7% of patients after 1 month, 32% after 1 year, and 50% after 2 years. In patients with asthma, the ADERE study showed that the level of noncompliance to anti-asthmatic therapy reached 49.1% after 90 days. In patients with venous leg ulcers preventive therapy was stopped after 1 year in 50%-60% of cases. Finally, the level of noncompliance in patients with chronic mental diseases, in particular schizophrenia, was found to be 59.1% after 4 months of treatment, and in patients with depression, it was of 60% on average.

These data on the incidence of noncompliance are striking, especially given the fact that, first and foremost, patients want their illness not to recur. This high level of noncompliance cannot be interpreted by economic aspects, since drug therapy expenses are reimbursed by health insurance in the vast majority of developed countries. At the same time, since the incidence of noncompliance is similar for many medical conditions (ie, ranging between 50% and 60% after 1-2 years), neither the nature of the disease nor its severity can fully explain such high levels of noncompliance. Furthermore, noncompliance levels for different classes of drugs have also been found to be alike: the level of noncompliance in 36,984 patients taking psychotropic drugs was found to be similar for all types of drugs (34.6% for antipsychotics, 34.7% for sedatives/hypnotics, 38.1% for anxiolytics, 44.9% for mood stabilizers, and 45.9% for antidepressants). This only conclusion that can be drawn from these studies is that the level of noncompliance tends to grow dramatically as the duration of the treatment increases, regardless of the illness, its severity, and the treatment prescribed.

However, great difficulties arise with regard to the definition of the term “noncompliance.” According to the DSM-IV (1994), the category of “noncompliance with treatment” can only be used when “the focus of clinical attention is noncompliance with an important aspect of the treatment for a mental disorder or a general medical condition.” Consequently, it is only the important aspects of therapy that are taken into account. Moreover, the notion of “importance” is determined by doctors, not patients, which leads to frequent discrepancies in the points of view of doctors and patients and may actually result in noncompliance. The term “adherence” used to refer to this problem is fundamentally different and indicates the degree to which the patient’s behavior is consistent with medical requirements, that is, with any deviation from the prescribed medical recommendations. This term implies that the patient has the right to choose between compliance and noncompliance with recommendations, and emphasizes the patient’s right to choose. Finally, the more neutral term of “concordance” is more commonly used in the UK, and indicates that there is a partnership in the process of making a therapeutic decision.

The various conceptual models of compliance, which reflect the variety of research approaches used to study this problem, are equally contradictory. They include (i) a biomedical model; (ii) a behavioral model; (iii) an educational model; (iv) a self-regulation model. The differences between these various models, which make it difficult to compare the studies that investigate compliance, and the lack of a unified theory regarding its development have led to criticism of the models themselves and of the results obtained with their use. Aside from the differences in the definition of “compliance” and the different models that have been proposed, there is also a lack of full-fledged standardized methods for its evaluation. As a result, the evaluation methods used in various studies are often incomparable (qualitative and quantitative; subjective and objective; direct and indirect; with variations in the duration of the observation period and disparity in the criteria used to define noncompliance [any deviation from the recommended drug regimen or only unacceptable ones]), and this partly explains the wide discrepancies in the compliance levels of patients with chronic diseases reported in some studies. For example, the compliance level of diabetic patients in 11 retrospective studies ranged from 36% to 93%.

**Factors contributing to noncompliance**

The majority of studies have focused on the causes of patients’ disagreement with their treatment and the many factors that increase or decrease it. For example, there are about 250 factors that affect patient compliance to psychopharmacological treatment. These factors pertain to patients, doctors, the doctor-patient relationship, treatment-specific aspects, and disease-specific features. It should be emphasized that these kaleidoscopic determinants of noncompliance are extremely variable and fluctuate according to the situation: for example, loss of confidence in a doctor or iatrogeny can turn compliance into noncompliance in just one day, which demonstrates the subjectivity of certain factors. The factors that contribute to noncompliance are closely associated with treatment duration, which, as it increases, reduces the role of factors pertaining to the patient’s condition and therapy, increases the role of factors pertaining to the patient and the doctor/patient relationship, and as a result amplifies the importance of the social, legal, ethical, and even philosophical and cultural aspects of therapy.

Only a few of the factors contributing to noncompliance are solely negative while most factors contribute to both compliance and noncompliance (eg, patient awareness about possible side effects, prescribed medications, once-daily administration). In our view, full compliance is just the midpoint in a broad continuum of adherence/resistance to ongoing therapy—from total or partial withdrawal from therapy to an addiction to it—and is the goal to achieve (Figure 1). At the same time, noncompliance—ie, anything less than full compliance—has many different forms and needs careful analysis and study.
The terms “compliance” and “noncompliance,” despite their importance in clinical practice, are concepts that are too broad and difficult to investigate. So, in many ways, agreement/disagreement with a treatment often appears as a subjective category that cannot be objectively analyzed with ease. At the same time, it should be noted that compliance is often achieved in patients with certain disorders (e.g., hypochondria) or in certain settings (e.g., rental), which raises the question of its desirability.

**Refusal of treatment**

To facilitate immediate evaluation, and therefore, to facilitate scientific research, it is first necessary to characterize the most important and measurable components of noncompliance. In this sense, refusal of treatment can be regarded as the most obvious or extreme form of noncompliance, since it is an open and conscious expression of the patient’s disagreement with the recommended treatment, accompanied by a corresponding behavioral response. Proceeding from this definition, the structure of any refusal of treatment includes two components: (i) an emotionally-cognitive component: the patient’s decision to refuse to take the treatment is an inference accompanied by an emotional reaction; and (ii) a behavioral component: a violation of the treatment regimen, most often congruent to the decision (behavior pattern). If the emotional-cognitive component does not correspond to the behavioral component, the patient may display an “ambivalent” behavior—i.e., formal adherence to the doctor’s instructions despite internal rejection—or a “selective” behavior—i.e., carrying out of the medical recommendations depending on their correspondence with the patient’s own ideas. In some cases, when the cognitive component of the refusal of the recommended or ongoing treatment is underdeveloped in the patient’s mind, we talk about “latent failures,” which are often masked by simple “forgetfulness.” At the same time, the component of “experiencing” or comprehending one’s disagreement with the proposed therapy is reduced, and the behavioral component is realized outside the framework of conscious assessment and control of behavior, as if automatically.

Thus, refusal of treatment is a kind of “turning point” in the construction of the “psychiatrist-patient” relationship, and acts as the central model for the study of noncompliance. It is the result of all the factors causing its emergence, thanks to which it can be not only primarily diagnosed, but also comprehensively evaluated and measured. So, the evaluation of noncompliance is, in fact, an assessment of treatment refusal. Among the different types of refusals, we can distinguish: full or partial refusals (Axis I); primary/early or secondary/late refusals (Axis II); single or recurrent refusals (Axis III); competent (conscious) or incompetent (hidden) refusals (Axis IV) (Figure 2).

**Figure 1. Continuum of patient adherence/resistance to pharmacotherapy.**

**Figure 2. Refusal of treatment in patients with depression.**

Axis I: full or partial refusals. Axis II: primary/early or secondary/late refusals. Axis III: single or recurrent refusals.
The incidence of the different types of treatment refusal depends on the stage of care at which they occur. Outpatients with chronic diseases most often show fewer primary and total refusals—i.e., when patients refuse the whole “package” of care even before the beginning of treatment—than secondary (usually partial) refusals. Consequently, partial (70.4%), secondary, (72.3%), and recurrent (71.1%) refusals predominate in patients with chronic depressive disorders (Figure 2). It should be noted that the number of complete (as well as primary) refusals of pharmacotherapy is likely to be much higher than registered since some people with medical problems do not seek medical help at all (which amounts to refusal of treatment). Primary refusals are potentially unfavorable for two reasons: they significantly increase the risk of deterioration caused by the refusal of preventive treatment, and at the same time they are indicators of the deterioration itself.

There are specific motivations for the different types of treatment refusal in patients with chronic diseases. Their study in patients with chronic depressive disorders receiving antidepressant therapy showed that adverse events are one of the most significant causes of secondary (complete/incomplete) treatment failure. However, what is important is not only the quantity and spectrum of adverse events, but also how they are tolerated; some adverse events are so subjectively painful and difficult to bear that patients refuse to take their medications, despite understanding the need for their administration. The results of a survey of outpatients with depressive disorders (according to the points of the UCU scale) regarding the degree of tolerability of adverse events (tolerable, moderately tolerable, intolerable) after administration of a drug (presumed or a priori tolerability) showed that there was a high degree of subjectivity for the vast majority of them. At the same time, patients generally show the least tolerance for various vegetative/neurological adverse events, and the most for psychiatric adverse events. The main sex differences in the a priori tolerability of therapy are primarily associated with a much higher risk of refusals due to intolerance to adverse events (sometimes several times) among men than women, for all major groups of adverse events.

Motivations that are not related to the tolerability and efficacy of the treatment are prevalent for total and primary refusals and account for about 30% of secondary and complete/partial refusals. For the latter, motivations include distrust of medicine, preference for traditional methods of treatment or psychotherapy, distrust of the doctor, fear of a reduction in their quality of life, well-being, recovery—and therefore belief that drug therapy is not needed; fear of the reoccurrence of side effects in case of a previous experience with the treatment, financial constraints, etc.

The high incidence and wide array of refusals that are not related to treatment efficacy and tolerability dictate the need to consider patients as having an active role in their treatment. Acceptance of the patient’s subjectivity allows us to assess him/her not only from a medical point of view, but also from a psychological point of view by integrating his/her knowledge and awareness of the disease, attitude toward it, understanding of the role and influence of the disease on personal-environmental interactions, knowledge of the complex reactions associated with the disease and of the features of protective-adaptive and coping mechanisms. Adherence to medical recommendations is an important aspect of the psychological side of the treatment process, which is determined not only by objective reasons, but also by subjective beliefs. Based on their own subjective beliefs, patients predict the possible outcomes of their illness and make decisions about whether to refuse the treatment.

According to Groeben and Scheele, subjective theories are to be understood as a “cognitive aggregate of the view of the self and of the world, which allows (at the very least) a partial explication, or rather, a reconstruction parallel to structures of scientific theories.” These theories are the result of the sufferer’s search for an explanation for their illness. They are formed when patients ask themselves whether they believe themselves to be really sick (or whether, for example, their condition is the result of poor lifestyle) and when they consider their current disease state (severity), their understanding of the causes and subsequent course of their disease (eg, “I got this from my mother” and “I’ll never get well” or “it’s all due to stress” - “If I rest, it will go away”), which methods they think are adequate and useful for improving their condition (eg, “no drugs” or “no lifestyle changes at all”), and what they expect from the treatment (eg, “full recovery”). At the same time, patients rely on the cultural beliefs surrounding their disease, the social environment (medical personnel, relatives), and personal experience, etc. It is not a question of whether the patients’ subjective beliefs about their disease are “correct” or “wrong.” The point is that they often differ from the biologically oriented perspective of doctors, and it is the discrepancy between the patients’ subjective conceptualizations and the doctors’ specialized medical knowledge (regarding the etiology of the disease, its course, and prognosis) that often predetermines refusal of treatment in patients with chronic diseases. This discrepancy is usually realized in the relationship between doctor and patient. Arthur Frank, an expert in medical ethics, describes the process of a patient seeking medical help as one of agreeing to tell his/her story in medical terms.

The results of focused interviews between two groups of respondents—patients with chronic psychiatric disorders (consumers of medical care) and their doctors—on the question of long-term therapy and the reasons for refusing it clearly showed that these two categories of respondents have a different outlook on the course and prognosis of the chronic disease, that is, different health/disease models.

The results of a survey of outpatients with depressive disorders (according to the points of the UCU scale) regarding the degree of tolerability of adverse events (tolerable, moderately tolerable, intolerable) after administration of a drug (presumed or a priori tolerability) showed that there was a high degree of subjectivity for the vast majority of them. At the same time, patients generally show the least tolerance for various vegetative/neurological adverse events, and the most for psychiatric adverse events. The main sex differences in the a priori tolerability of therapy are primarily associated with a much higher risk of refusals due to intolerance to adverse events (sometimes several times) among men than women, for all major groups of adverse events.

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Conceptual models of health and illness

The first model, the biomedical model, is focused on the identification of genetic factors and biological processes, and is based on a dimensional approach, according to which categories such as “health” and “disease” can be located on opposite sides of a one-dimensional continuum. In this model, remission of a chronic disease should not be considered as a stabilization of the condition, but rather as a temporary decrease in the pathological process activity due to various factors (including therapeutic intervention). This position corresponds to the basic postulates of the biological sciences, which actively involve the use of arguments obtained as a result of genetic, instrumental, pharmacological, and morphological studies, and sees the clinical manifestations of a chronic disease as the final result of lifelong biological anomalies. According to this model, patients do not recover; the same approaches should thus be applied for a chronic disease patient in remission as for patients with disease decompensation. When doctors consider that refusal of treatment is one of the symptoms of the disease (anosognosia), they are in full agreement with the biological approach.

The second model is the psychodynamic model, and corresponds to the patients’ subjective conception of their disease. It is based on a categorical approach (list of symptoms) and requires a separation of the concepts of “norm” and “pathology.” “Sick” and “cured.” This position, which is that of the majority of consumers of health care, actually directly reflects the natural reluctance of most people to consider themselves sick (ie, taking drugs, changing their habitual lifestyle) after achieving a stable improvement in their condition. An interesting aspect of this point of view is that the concept of recovery includes not only the disappearance of pathological symptoms, but also psychological recovery from the consequences of the disease. Thus, treatment refusal (which in this case is defined as secondary), is subjectively regarded as one of the stages of psychological recovery, in addition to the expected improvement in daily activities due to the absence of adverse events.

The expectation of doctors that their patients will choose the biomedical model of the disease and “speak the same language” as them is the central mistake of the medical profession, and leads to a one-sided view of the problems of the doctor/patient relationship. Stemming from that mistake, numerous programs aiming to increase the compliance of patients with certain chronic diseases focus only on the “medical” model of the disease (in particular, programs to improve the level of medical knowledge of patients).

However, modern theories of medical communication consider that patients have complex personalities, with very personalized and unique ideas about their health and illness. Motivating patients with chronic diseases to follow medical recommendations is an extremely difficult task for doctors. They need to have a dual role when talking to their patients: on the one hand, they provide biologically oriented medical knowledge about the etiology and pathogenesis of the disease and its treatment, and on the other hand, when arguing the need for long-term treatment and lifestyle changes, they should take into account the “consumers” and their language, their ideas, expectations, fears, misconceptions, and adjust to each patient patiently and persistently. It is known that imposed medical requirements, if they do not fit in with the patient’s ideas of the disease, will not take root. In this case, medical requirements may lose their subjective effectiveness, sometimes giving way to absurd recommendations, retaining their appeal, despite the objective harm, only by their correspondence to the patient’s ideas.

A more modern and effective strategy to establish an effective doctor/patient relationship is to take into account the fact that patients are the best source of information about the problems that affect their decision to agree to long-term therapy. The paradox is that treatment adherence is observed and evaluated by clinicians, while the related problems are largely psychological and require appropriate knowledge, thus making it necessary to first provide training for doctors.

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**Keywords:** behavior; chronic disease; compliance; doctor-patient relationship; noncompliance; psychological factor; refusal of treatment
The association between nonadherence to medication and morbidity and mortality: the current state of evidence

by S. B. Harrap, Australia

Given the accumulated data of consistent benefits of cardiovascular therapies for hypertension, diabetes, hypercholesterolemia, and related risk factors, it might seem self-evident that nonadherence to prescribed treatment would be bad. Knowing how bad should be part of the discussion between doctors and their patients with the goal of achieving committed and sustained adherence to therapeutic regimes for chronic conditions that are often asymptomatic. Distilling the effect of nonadherence to a specific drug is made difficult by misclassification of adherer status, multimorbidity, the frequent use of complex drug regimens, and the so-called “healthy adherer” effect, where the likelihood of adhering to prescribed medication correlates with general interest in healthy behavior. Nevertheless, there is good evidence that nonadherence comes at a significant cost in terms of increased morbidity, hospitalizations, and death. This is true across all cardiovascular risk factors in primary prevention studies and for secondary prevention of existing coronary artery disease. This brief overview summarizes the methodological approaches and data that have defined the dangers of nonadherence. It is our job as clinicians to share responsibility with our patients to adhere to prescribed treatments and maximize the benefits they deliver.

Chronic disease demands a commitment to consistent care from both physician and patient for the rest of life. Cardiovascular disease and its risk factors, such as hypertension, diabetes and hypercholesterolemia, are not only typical examples of such chronic disease, but also the most common and important causes of death and disability in society today. Effective, safe, and generally readily available modern pharmacological therapies are key elements for reducing cardiovascular risk.

They offer people longer and healthier lives. But only if commitment is maintained and therapy is taken religiously. The sad truth is that only about 50%-75% of patients with cardiovascular risk maintain their adherence to prescribed treatments. The important issue for doctors and patients is the risk that accompanies nonadherence, and this paper examines the available evidence in relation to this question.

Before considering the available data, there are a number of factors that need to be considered related to research designed to determine the impact of nonadherence.
The impact of nonadherence

Defining nonadherence

Consideration of the effects on major cardiovascular outcomes that accompany nonadherence to medications has to take into account the degree of nonadherence. Thus, it is relevant to question: is there a threshold minimum level of adherence needed to obtain benefit? Studies that measure adherence in terms of the proportion of days when patients are assumed to take their medications often define partial adherence for values between 60% and 79% and full adherence for values of ≥80%. Early studies demonstrated that reliable blood pressure reductions are achieved only when adherence with antihypertensive drugs was ≥80%. This threshold has been validated in studies of statins, β-blockers, and renin-angiotensin system blockers. For these reasons, nonadherence is usually defined as taking <80% of the course of prescribed medications.

Measuring nonadherence

The three general approaches to estimating nonadherence offer varying reliability. Least reliable are subjective measurements that depend on information from patients, family, or friends. The factors that might distort such estimates, such as giving the benefit of any doubt, are obvious. More objective methods include pill counting, dispensing records, and medication-related insurance claims. However, these methods cannot prove that tablets were actually taken. More direct assessment of drug intake includes biochemical measurements of drug or drug metabolite levels in individual patients. However, even biochemistry is a single snapshot that may fail prone to what is sometimes called “whitecoat adherence,” a phenomenon whereby nonadherent patients, knowing that a test is imminent, will take their medications around that time. In reality, a variety of methods are used, sometimes systemized into research instruments, such as the Morisky Medication Adherence Scale-8 (MMAS-8) and the Adherence Scale by Culig et al.

Measurement implications

Nevertheless, whichever measure is used, none would be likely to exaggerate nonadherence. This means that the estimates obtained are likely to underestimate the true magnitude of the problem. In comparisons of outcomes between adherent and nonadherent patients, misclassification of nonadherent patients as adherent would dilute any real differences between the groups and serve to undervalue the effect of nonadherence on health or financial outcomes.

Partitioning drug-related effects

The second challenge is to separate the specific effect of not taking prescribed drugs from the effects of other related environment or behaviors that might contribute to risks for cardiovascular problems. Studies of the characteristics of those more likely to be nonadherent to prescribed medications report associations with socioeconomic disadvantage.

In these circumstances, the cost of medication and reduced health literacy are direct barriers to adherence. More importantly, disadvantage itself brings with it a broad increase in cardiovascular risks.

Depression is another comorbidity that is associated with nonadherence, particularly with diabetes. The effects of depression extend beyond nonadherence to prescribed medication to factors with a broad health impact, such as missed medical appointments and poor self-care. Even marital status has been linked with medication adherence and event-free survival in heart failure.

Some, but not all, studies have accounted for such confounding in their comparisons of cardiovascular outcomes by adjusting for observed differences in socioeconomic circumstances, comorbidities, etc., between adherent and nonadherent patients.

Confounding by the “healthy adherer” effect

Less easy to detect and account for is a phenomenon known as the “healthy adherer” effect. Here, drug adherence reflects an individual’s concern for good health and dedication to a healthy lifestyle in general. It also reflects trust in medical advice. Nonadherent patients are likely to include those for whom a healthy diet and lifestyle are not high priorities. The “healthy adherer” phenomenon has been inferred from the observation in randomized placebo-controlled trials that the outcomes (including mortality) in the placebo group are worse for those who were nonadherent compared with those patients who took their placebos. In a meta-analysis of the association between adherence to placebo and mortality in just under 20,000 subjects who took part in 8 cardiovascular or diabetic trials, the average observed effect was a reduction in the risk of mortality by almost half (odds ratio, 0.56; 95% confidence interval [CI], 0.43 to 0.74) with 415 deaths in those who adhered with placebo treatment compared with 581 deaths in those who did not. The very existence of a “healthy adherer” effect means it can be difficult to determine the real contribution of taking medication as prescribed. Conversely, the effects of nonadherence are not easy to define, but methods have been devised that look at adherence over time in the same patient and the correlation between periods of lower adherence and the emergence of clinically relevant outcomes. One such method is the “self-controlled case series” approach that allows better control for interpersonal confounders. This has been used to follow patients prescribed β-blockers for 1 year after myocardial infarction.
dial infarction to examine patterns of recurrent infarction. Each individual’s observation time was divided into periods exposed or unexposed to β-blockers (as judged by pharmacy dispensing records) and the relative myocardial infarction incidence rate ratio (IRR) of β-blocker–exposed versus β-blocker–unexposed periods was 0.79 (95% CI, 0.69 to 0.90; P=0.001). In other words, over time adherence to recommended β-blocker therapy was associated with a 20% reduction in recurrent myocardial infarction. This result was generally consistent with previous research that compared adherent and nonadherent patients, suggesting that at least in studies of the secondary prevention of myocardial infarction, the “healthy adherer” effect might not be a major factor.

Other studies have cast doubt on the “healthy adherer” effect after myocardial infarction. If there were implications for healthy behaviors generally then this might be obvious as reductions in the incidence of other noncardiovascular disease. However, analysis in 31 455 patients over 4 years for lung, prostate, or breast cancer could not define any difference in rates of hospitalization for these cancers between those who were shown to be adherent or nonadherent to cardiovascular medications following myocardial infarction.

The point is that the drugs themselves make a difference, but they can’t achieve benefit unless the patients take their medication as prescribed. This is true for a number of outcomes for a variety of drugs for cardiovascular disease and diabetes.

**Treatment and adherence**

**Blood pressure treatment**

A simple example is the difference in blood pressure in those adherent and nonadherent to antihypertensive medications. A recent meta-analysis reported that as many as 45% of 12 603 patients failed to adhere to prescribed antihypertensive treatments as assessed using the MMAS-8 instrument. However, among patients with uncontrolled blood pressure, the prevalence of medication nonadherence was especially high at 84%. Other studies have shown high rates of nonadherence (63%) among those classed as having resistant hypertension. This emphasizes that the consequences of nonadherence are not only increased risk for cardiovascular complications of high blood pressure per se, but also the potential exposure to alternative nontrivial treatments of uncertain benefit that might be offered to people with “resistant” hypertension, such as renal denervation.

Nonadherence to blood pressure medication in hypertensive subjects has significant associations with the risk of major cardiovascular end points such as stroke, myocardial infarction, or cardiovascular death. The ANBP2 (Australian National Blood Pressure–2) study compared the effects of angiotensin-converting enzyme inhibitors with diuretic medications in hypertensive subjects. Those who did not adhere to their medications were significantly more likely to experience a cardiovascular event or death from any cause compared with those who adhered to the treatment regime (hazard ratio [HR], 1.28; 95% CI, 1.04 to 1.57). Large studies based on population screening of newly treated hypertensive subjects reveal similar findings. An Italian study of 31 306 patients in Florence taking antihypertensive medications for primary cardiovascular prevention revealed that the risk of all-cause death, stroke, or myocardial infarction was approximately halved in those with excellent adherence compared with those with poor adherence (HR, 0.53; 95% CI, 0.46 to 0.61).

A recent Australian survey also suggested that over 48 months the risk of death was significantly lower in those who persisted better with their prescribed cardiovascular therapies. In this case better adherence was reported in those prescribed a combined tablet of perindopril and amlopidine compared with those taking 2 single tablets of an angiotensin inhibition therapy and a calcium channel blocker. The advantages of fixed-dose combination formulations for adherence are discussed elsewhere in this issue.

So, adherence to blood pressure medications has significant benefits in terms of both control of blood pressure and major cardiovascular complications.

**Cholesterol treatment**

In a parallel analysis of people and records in Florence, Degli Esposti et al examined the differences in cardiovascular outcomes in relation to adherence to treatment with statin cholesterol-lowering drugs. Similar rates of adherence were observed for statins as seen for antihypertensive drugs in this Florentine population. Furthermore, high adherence was significantly associated with decreased risk of all-cause death, acute myocardial infarction, or stroke compared with low adherence (HR, 0.61; 95% CI, 0.54 to 0.71). A systematic review of the impact of adherence to statin treatment found consistent evidence across 28 studies that significantly increased risk of cardiovascular events and death was associated with poor adherence to statin drugs for both primary and secondary prevention studies.

**Diabetes treatment**

Diabetes is a condition that demands more active self-management than most other cardiovascular risk factors, yet a systematic review of antidiabetic therapies found a wide range of adherence rates, from 36% to 93%. Type 2 diabetes is also commonly associated with other cardiovascular risk factors, including hypertension and hypercholesterolemia; only 29% and 52% of diabetic patients achieve guideline targets for blood pressure and low-density lipoprotein cholesterol. Whether as a result of poor glycemic control per se or coincident nonadherence to blood pressure and cholesterol medications, the cardiovascular risk profile of diabetic patients who are nonadherent to diabetic medication is especially concerning. In a prospective cohort of 11 532 patients with diabetes...
mellitus, Ho et al found that the 21% of patients who were nonadherent to diabetic treatments had significantly higher glycosylated hemoglobin, diastolic blood pressure, and low-density lipoprotein cholesterol. They were 58% more likely to be hospitalized and 81% more likely to die than adherent patients after adjustment for relevant covariates.

- **Antiplatelet therapy**

Studies of nonadherence to aspirin in primary prevention trials for cardiovascular disease are sparse. Where post hoc analyses have been attempted, no significant impact of aspirin nonadherence on total cardiovascular events or mortality could be demonstrated.

However, the contrast couldn’t be greater for secondary prevention with antiplatelet agents. For example, following insertion of drug-eluting stents for coronary artery stenosis, those patients who were nonadherent during their prescribed 3 to 6 months of ticlopidine therapy (ticlopidine or clopidogrel) were nine times more likely to die (7.5% vs 0.7%) in the year following stent placement than patients adhering to their treatment.

- **Heart failure therapy**

Given the prognostic implications of untreated heart failure, it might be surprising that as few as 10% of patients are fully compliant with their pharmacotherapy over a full year and only 80% of heart failure patients fill their discharge prescription for angiotensin-converting enzyme inhibitors by 30 days post-discharge. Indeed, in one retrospective cohort, nonadherence (defined as <80% adherence) was associated with a doubling of the risk of the primary outcome of all-cause mortality plus cardiovascular hospitalizations.

- **Specific drug effects**

Are there priorities for pursuing adherence to particular drugs over others? One might imagine that the prognosis of the underlying condition and the estimated magnitude of benefit for a particular drug or drug class might be relevant here. However, it is becoming increasingly difficult to accurately define the beneficial contributions of a specific drug in clinical trials. For example, multiple drugs from different classes are used together commonly for the treatment of hypertension, diabetes, or heart failure. The situation is further complicated by the frequent associations of these conditions. The corollary is that where nonadherence exists, it is unlikely to target a specific drug, so it is difficult to separate the effects of lack of adherence to one drug from another.

The situation is exacerbated in the case of secondary prevention for cardiovascular disease, where the exposure to drugs is greater again with frequent combinations of antiplatelet, β-blocker, statins, and antihypertensive medications. Where this has been studied, it also appears that the effects of nonadherence to individual drugs do not seem to be additive when patients are nonadherent to two or more drugs. For example, in one study of secondary prevention following myocardial infarction, adherence to a single agent (statin, β-blocker, or renin-angiotensin system blocker) resulted in an average 23% reduction in risk of a major vascular event or revascularization compared with nonadherent patients, while the comparison of those who were adherent or nonadherent to two of the three classes of drugs showed an average risk reduction of 29%, with only a 35% reduction in risk comparing those adherent and nonadherent for all 3 drug classes. This makes it hard to design targeted approaches to encourage drug adherence towards particular treatments for which nonadherence might have the greatest individual detrimental effects.

**Conclusions**

Better health, fewer deaths, and reduced costs to the community are all proven benefits of adherence with prescribed cardiovascular medications. The means by which we can attain better adherence are examined elsewhere in this issue. However, our patients need to understand that they cannot afford to miss their cardiovascular medications more than one day per week and should aim for a perfect score. Positive feedback and meaningful involvement of patients in their own care will reinforce and sustain commitment. Above all, we should encourage them to become “healthy adherers” and take advantage of the specific cardiovascular and more general health benefits that follow.

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Improving medication adherence in cardiometabolic disease

Keywords: adherence; cardiovascular disease; cholesterol; compliance; coronary disease; diabetes; hypertension; thrombosis

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Therapy-related strategies to improve adherence to cardiovascular medications

by S. Rasheeqa Ismail, Malaysia; S. Tsoli and R. Chowdhury, United Kingdom

Objective: To determine the efficacy of various therapy-related strategies in improving adherence to cardiovascular disease (CVD) medications. Design: Systematic review and meta-analysis of prospective interventional studies. Data sources: Medline, Embase, and Cochrane electronic databases, supplemented by a search of the reference lists of relevant studies. Study selection: Randomized controlled trials in adults (age >18 years) on existing CVD medications (antihypertensives, antiplatelets, or statins) that evaluated the effects of three key therapy-related strategies (ie, those related to education and support, technology, and the use of combination pills) on subsequent changes in medication adherence compared with usual care or equivalent. Data extraction and analysis: Two investigators extracted data and a consensus was reached with involvement of a third. Study-specific effect estimates were combined using random-effects meta-analysis. For the studies that could not be quantitatively synthesized, a systematic narrative review was performed. Results: Of the 2383 unique citations retrieved following the initial screening, a total of 27 articles met our inclusion criteria. In these studies, a wide range of interventions was evaluated for each key therapy-related strategy. The included studies vary widely in efficacy and overall quality. Nonetheless, in aggregate, education and support programs increased adherence to nonspecific CVD medications for both short-term (6 months) and longer-term (12 months) interventions. Overall, these strategies were equally effective for improving adherence to specific CVD medications such as statin or clopidogrel, when taken alone. Similarly, technology-based programs as well as the use of fixed-combination pills also improved adherence to CVD medications significantly. Nonetheless, the overall number of trials available for each of these strategies and their quality were generally inadequate. Conclusion: The findings of this review indicate that several therapy-related strategies may significantly improve medication adherence. However, there are significant differences across all types of interventions such as education and support, technology-based interventions, and fixed-combination pills. Since the overall quality and extent of evidence was generally low, further trials are required to reliably quantify the effects of these diverse interventions.
Introduction

Rising cardiovascular burden and lack of adherence to medications

The death and disability burden of cardiovascular diseases (CVD) has increased rapidly worldwide in the past few decades, emphasizing the need to develop effective primary and secondary prevention strategies to halt such rising trends. Meta-analyses of global intervention data have consistently demonstrated that pharmaceutical interventions with antihypertensives, aspirin, and statins are able to reduce major CVD outcomes and associated premature mortality.\(^1\)\(^\text{5}\) However, as the level of adherence to these CVD medications is generally low,\(^3\)\(^\text{5}\) optimal measures to improve adherence are essential for maximizing the potential benefit of these therapeutic agents.

Lack of adherence and associated impact on clinical consequences

Adherence is defined as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider."\(^6\) Adherence should not be confused with compliance, as the latter lacks the agreement from the patient to the recommendations given.\(^6\) Adherence is a complex behavioral process that results from the interplay of various factors, and therefore remains a challenge for health care providers.\(^6\) Worldwide, a substantial proportion of people do not adhere adequately to cardiovascular medications. Evidence suggests that good adherence is achieved in only 60% of patients on CVD medications.\(^7\) The prevalence of suboptimal adherence has been reported to be significantly high, irrespective of the type of CVD medication, and is on the rise.\(^8\)\(^\text{9}\) Suboptimal drug therapy, often resulting from a lack of adherence to essential CVD medications, leads to inadequate control of symptoms, and subsequently increases the risk of morbidity and mortality.\(^1\)\(^\text{0}\) The level of optimal adherence to CVD medications has been shown to have an inverse relationship with subsequent adverse CVD outcomes,\(^7\)\(^\text{1}\) with more adherent patients having a lower risk of developing future CVD than poorly adherent patients, for both statins and antihypertensives.

Objective of the present review

Several therapy-related measures can be used to improve adherence to CVD medications; however, they have rarely been systematically reviewed in a single, comprehensive investigation. To help evaluate these strategies, we have attempted to synthesize all available evidence to quantify the efficacy of different types of therapy-related strategies in improving adherence to various CVD medications.

Methods

Data sources, search strategy, and eligibility criteria

We systematically searched Medline, Embase, and Cochrane Central electronic databases to identify relevant published articles (date of last search: March 12, 2017). The computer-based searches combined terms related to the medications (eg, antihypertensives, aspirin) and outcomes (eg, adherence, compliance), without any language restriction. Details of the search strategy are provided in Supplementary Table I (online only). We searched for studies that evaluated the effects of adherence-enhancing strategies compared with usual care or equivalent in adults (>18 years old) participants taking any CVD medications. CVD medications were defined as any class of antihypertensive medications, antithrombotics, and statins frequently used for secondary prevention of CVD.

Study selection

We included randomized controlled trials that (i) followed participants prospectively, (ii) evaluated various interventions that provided education and support programs, used technology or combination pills to promote medication adherence, and (iii) had assessed medication adherence using a validated measurement tool. Direct measurement tools were defined as directly observed therapy and measurement of the level of medicines, metabolites, or biologic markers in the blood. Indirect measurement tools were defined as patient questionnaires, self-reports, pill counts, rates of prescription refills, and electronic medication monitors.\(^1\)\(^2\) Two independent reviewers screened the titles and abstracts of all identified articles against the inclusion criteria. Full texts were retrieved for articles that satisfied all the selection criteria. The reference lists of the selected articles and relevant reviews identified on the topic were searched for additional publications.

Data extraction

A predesigned data extraction form was used to extract relevant information. Two reviewers piloted the data extraction form for a sample of the included papers until an agreement was reached among reviewers. Extracted data included information on study size, study design, baseline population, country of study, duration of follow-up, type(s) of CVD medications used, description of interventions and control, frequency of interventions, medication adherence scale, definitions of good adherence, and adherence levels. When available, effects of good adherence—such as changes in systolic blood pressure, low-density lipoprotein, and total cholesterol—were obtained.

Data synthesis and analysis

To enable a consistent approach to the meta-analysis and interpretation of findings in this review, effect estimates (expressed as relative risk, RR) for subsequent changes in medication adherence were based on the proportion of participants with good adherence (≥80% adherence), irrespective of the measurement tool used. This proportion is the most widely accepted and reported cut-off for optimum adherence.\(^7\)\(^\text{1}\)\(^3\) Summary RRs were calculated by pooling the study-specific estimates using a random-effects meta-analysis that allows for between-study heterogeneity. All statistical tests were two-
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Studies identified

Our search strategy retrieved 2383 unique citations. Following the initial screening based on titles and abstracts, 241 articles remained for further evaluation. Of these articles, 394 were excluded in the subsequent detailed assessments for reasons shown in Figure 1 or if full texts were not available. The remaining 27 articles that met our inclusion criteria were finally included in the review. Out of these, 14 studies were included in the quantitative synthesis part of our review, which, in aggregate, comprised of 7725 unique individuals.

Adherence achieved by interventions related to education and support

There were 19 studies that evaluated the effects of various education and support strategies. These studies and their individual results are summarized in Table I. The interventions included various pharmacist-, nurse-, and community worker-led programs. Overall, there was a large variability in the methods used, frequency of interventions, and duration of interventions. The interventions were led by pharmacists, nurses, and community health workers, or a combination of them. Interventions were offered for either 6 months or 12 months, with varying frequencies (minimum once, maximum 2 times throughout the study period). The most important components in these interventions were education and behavioral counseling. Out of the 19 articles, 11 did not have a baseline adherence measurement to compare the before and after effects of the interventions. All the articles used usual care as a comparator, except for 4 articles that added educational leaflets or DVDs to the usual care. Differences in the levels of good adherence between the intervention and control arms were more pronounced for interventions lasting 12 months than for those lasting 6 months.

Out of the 19 studies, only 11 articles could be combined in the meta-analysis. We evaluated the overall differences between the two treatment arms for education and support strategies at 6 and 12 months for nonspecific CVD medications (Figure 2 and Figure 3, respectively, page 284). Participants receiving adherence-enhancing education and support programs for 6 months were 1.35 times more likely to achieve good adherence to their CVD medications than those undergoing usual care (6 studies20-25; 1064 participants, RR, 1.35; 95% CI, 1.0-1.67; I²=83%; Figure 2). Patients receiving education and support programs to enhance adherence for 12 months were 1.11 times more likely to be adherent to their CVD medications than those receiving usual care (5 studies17,19,26-28; 3521 participants, RR, 1.11; 95% CI, 1.03-1.21, I²=83%; Figure 3).

Figure 1. Search strategy for the included studies.

Assessing the risk of bias and quality of evidence

We used the Cochrane Collaboration tool to assess the risk of bias in the included studies.14 This tool evaluates seven possible sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

We assessed the quality of evidence of our two main outcomes using the GRADE Working Group framework (Grading of Recommendations, Assessment, Development and Evaluation Working Group). Quality assessment was based on five factors: risk of bias across all studies; indirectness, interventions, and outcomes; outcome reporting; inconsistency among studies; imprecision; and publication bias. The presence of publication bias was assessed using funnel plots, plotting precision against the effect size. Egger’s test was used to quantify asymmetry.18

Results

Assessing the risk of bias and quality of evidence

Table I.

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Methodology</th>
<th>Education/Support</th>
<th>Duration (months)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pharmacist</td>
<td></td>
<td>6</td>
<td>RR 1.35; 95% CI 1.0-1.67, I²=83%</td>
</tr>
<tr>
<td>2</td>
<td>nurse</td>
<td></td>
<td>12</td>
<td>RR 1.11; 95% CI 1.03-1.21, I²=83%</td>
</tr>
<tr>
<td>Intervention</td>
<td>Frequency</td>
<td>Duration</td>
<td>Education counseling</td>
<td>Behavior counseling</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------</td>
<td>----------</td>
<td>----------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>TEAM trial</td>
<td>6</td>
<td>12</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Multifaceted intervention</td>
<td>3 to 6</td>
<td>12</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Follow-up program</td>
<td>3</td>
<td>12</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pharmacy care intervention</td>
<td>3</td>
<td>12</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>STIPT trial</td>
<td>5</td>
<td>12</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Synchronized prescription refill program</td>
<td>12</td>
<td>✔</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Comprehensive pharmacy care program</td>
<td>3</td>
<td>6</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Telephone call reminder</td>
<td>✔</td>
<td>6</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pharmacy Care Intervention</td>
<td>6</td>
<td>6</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Community pharmacists hypertension-care service</td>
<td>6</td>
<td>6</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pharmacist counselling</td>
<td>1</td>
<td>6</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Healthcare education program</td>
<td>4</td>
<td>12</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Motivational interviewing</td>
<td>4</td>
<td>12</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Clinic and home nurse support</td>
<td>6</td>
<td>6</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Self-management intervention program</td>
<td>6</td>
<td>6</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Integrated adherence program for atorvastatin</td>
<td>1</td>
<td>6</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Abbreviations: CMAS, composite medical adherence score; MAT, medication assessment tool for secondary prevention of coronary heart disease; MPR, medication possession ratio; NR, not reported; PDC, proportion of days covered; PRN, as needed; TEAM, Team Education and Adherence Monitoring trial. Values are presented as proportions of good adherence, unless otherwise stated.

a Frequency of intervention throughout the study duration.
b Duration of intervention, presented in months.
c Values are for mean (standard deviation).
d Adherence to all the listed criteria.
e Proportion of medications taken for all chronic medications.
f Presented as proportion of participants missing at least 2 pills per month.

Table I (continued on next page)
Improving Medication Adherence in Cardiometabolic Disease

Therapy-related strategies to improve adherence to cardiovascular medications – Chowdhury and others

Table I. Findings from education and support programs.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention</th>
<th>Control Events</th>
<th>Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhurat 2012</td>
<td>25</td>
<td>33</td>
<td>58</td>
<td>1.19 (0.88-1.62)</td>
<td></td>
</tr>
<tr>
<td>Danush 2016</td>
<td>61</td>
<td>79</td>
<td>139</td>
<td>1.13 (0.92-1.37)</td>
<td></td>
</tr>
<tr>
<td>Fliri-Benedict 2013</td>
<td>84</td>
<td>87</td>
<td>170</td>
<td>1.33 (1.03-1.64)</td>
<td></td>
</tr>
<tr>
<td>Lee 2006</td>
<td>75</td>
<td>77</td>
<td>150</td>
<td>4.48 (1.86-7.02)</td>
<td></td>
</tr>
<tr>
<td>Soosanker 2004</td>
<td>70</td>
<td>110</td>
<td>180</td>
<td>1.15 (0.92-1.43)</td>
<td></td>
</tr>
<tr>
<td>Wald 2014</td>
<td>136</td>
<td>150</td>
<td>286</td>
<td>1.21 (1.09-1.35)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>536</td>
<td>528</td>
<td>1060</td>
<td>1.35 (1.08-1.67)</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2=0.06$, $\chi^2=45.81$, df=5 ($p<0.00001$); $I^2=89$

Test for overall effect: $Z=2.69$ ($p=0.007$)

Abbreviations: CMAS, composite medical adherence score; MAT, medication assessment tool for secondary prevention of coronary heart disease; MPR, medication possession ratio; NR, not reported; PDC, proportion of days covered; PRN, as needed; TEAM, Team Education and Adherence Monitoring [trial]. Values are presented as proportions of good adherence, unless otherwise stated.

$^g$Presented as value of nonadherence.

Figure 2. Good adherence to educational and support strategies for nonspecific cardiovascular medications at 6 months.

Figure 3. Good adherence to educational & support strategies for non-specific CVD medications at 12 months.
Therapy-related strategies to improve adherence to cardiovascular medications – Chowdhury and others

**Improving Medication Adherence in Cardiometabolic Disease**

For adherence to specific CVD medications, while interventions that aimed to improve statin intake were not effective at 6 months, a more significant improvement in adherence was achieved at 12 months (2 studies; 1317 participants; RR, 1.21; 95% CI, 1.05-1.39; I²=72%). There were also a few studies that evaluated adherence to clopidogrel. Education and support strategies, albeit based on 2 trials, appeared to increase clopidogrel adherence significantly (573 participants; RR, 1.26; 95% CI, 1.11-1.42; I²=0%).

**Adherence achieved by technology-based interventions**

Three articles were included in the technology group, with none combined for a meta-analysis. The findings from these studies are summarized in Table II. In general, the interventions were mobile phone–based, and consisted of either automated text messages or phone calls. The frequencies of intervention were also highly variable, ranging from once to 52 times during the study period. As the duration of interventions also varied, we were not able to combine the studies to measure a pooled effect of the interventions in a consistent way. However, when the trial results were appraised individually, there appeared to be significant improvements in adherence between the intervention and control arms within each of the included trials.

**Adherence achieved by using fixed-dose combination pills**

Five trials were identified that sought to evaluate the effects of fixed-dose combination pills use on improving medication adherence (with only 3 available for quantitative synthesis). Their findings are summarized in Supplementary Table II (online only).

In these studies, a fixed-dose combination pill typically contained an angiotensin-converting enzyme inhibitor, an antiplatelet agent, a statin, and either a thiazide diuretic or a β-blocker. A significant overall benefit on adherence was observed with a longer duration of intervention. The use of fixed-dose combination pills did not improve the adherence significantly

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Frequency</th>
<th>Duration</th>
<th>Measurement tool</th>
<th>Baseline adherence</th>
<th>End point adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMS and automated behavioral education response</td>
<td>Once per week</td>
<td>12 months</td>
<td>≥80% PDC</td>
<td>NR</td>
<td>62.8%</td>
</tr>
<tr>
<td>SMS, automated education response and optional interactive personalized message</td>
<td>Once per week</td>
<td>12 months</td>
<td>≥80% PDC</td>
<td>NR</td>
<td>60%</td>
</tr>
<tr>
<td>Automated telephone call followed by education letter</td>
<td>Once</td>
<td>2 weeks</td>
<td>Proportion of dispensed medication</td>
<td>NR</td>
<td>42.3%</td>
</tr>
<tr>
<td>Automated text reminders</td>
<td>Variable</td>
<td>6 months</td>
<td>≥80% medication use</td>
<td>NR</td>
<td>91%</td>
</tr>
</tbody>
</table>

**Table II. Findings from technology-based programs.**

For adherence to specific CVD medications, while interventions that aimed to improve statin intake were not effective at 6 months, a more significant improvement in adherence was achieved at 12 months (2 studies; 1317 participants; RR, 1.21; 95% CI, 1.05-1.39; I²=72%). There were also a few studies that evaluated adherence to clopidogrel. Education and support strategies, albeit based on 2 trials, appeared to increase clopidogrel adherence significantly (573 participants; RR, 1.26; 95% CI, 1.11-1.42; I²=0%).

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</tr>
</tbody>
</table>

**Abbreviations:** NR, not reported; PDC, proportion of days covered.

*Daily for 2 weeks, then alternate days for the following 2 weeks then weekly for 22 weeks.*
in the short term (3 months), but appeared to confer significant improvements in medication adherence at 9 months (1 study, p=0.019) and at 12 months after the intervention (3 studies, 3140 participants; 1898 good adherence events; RR, 1.44; 95% CI, 1.20–1.72; I²=83%) (Figure 4, page 285). Nonetheless, the quality of evidence for the use of fixed-dose combination pills for CVD medication adherence was generally low (Table II).

◆ Assessments of study quality and risk of bias

Only 5 out of the 27 studies included reported a low risk of bias in all 5 domains (Supplementary Table III, online only). The highest risk of bias was reported in 9 out of the 27 included studies. We constructed funnel plots to assess the publication bias of the included studies in the quantitative analysis (Supplementary Figure 1, online only). P values in the Egger’s asymmetry test involving studies that evaluated education and support strategies in relation to CVD medication adherence were 0.17 at 6 months, and 0.46 at 12 months, respectively. We evaluated the overall quality of evidence and presented it in the form of a “summary of findings” table. The quality of evidence for education and support interventions at 6 and 12 months were both graded as very low (Table III).

Discussion

◆ Summary of the key findings

The findings of this review indicate that therapy-related strategies to improve adherence in patients taking CVD medications show a moderate—though significant—benefit. However, significant differences in medication adherence were observed across all types of interventions: education and support, technology-based, and fixed-combination pills. The quality of the evidence reported for education and support as well as polypill strategies was generally very low.

◆ Comparison with other reviews

The combination of educational and behavioral strategies has been recommended to ensure persistence of adherence.33,34 There are three aspects of medication administration that are involved in adherence: initiation of the prescribed medication,

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Risk with usual care</th>
<th>Risk with intervention</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in adherence with 6 months of education &amp; support intervention programs Follow-up: 6 months</td>
<td>64 per 100 (69 to 100)</td>
<td>86 per 100</td>
<td>RR 1.35 (1.08 to 1.67)</td>
<td>1064 (6 RCTs)</td>
<td>VERY LOWa</td>
<td></td>
</tr>
<tr>
<td>Change in adherence with 12 months of education &amp; support intervention programs Follow-up: 12 months</td>
<td>76 per 100 (78 to 92)</td>
<td>84 per 100</td>
<td>RR 1.11 (1.03 to 1.21)</td>
<td>3521 (5 RCTs)</td>
<td>VERY LOWb</td>
<td></td>
</tr>
<tr>
<td>Change in adherence with 12 months of fixed-dose combination pill intervention program Follow-up: 12 months</td>
<td>53 per 100 (63 to 91)</td>
<td>76 per 100</td>
<td>RR 1.44 (1.20 to 1.72)</td>
<td>3140 (3 RCTs)</td>
<td>LOWc</td>
<td></td>
</tr>
</tbody>
</table>

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Abbreviations: CI, confidence interval; RCT, randomized controlled trial; RR, risk ratio.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a Downgraded three levels due to: serious risk of bias (absence of randomization and blinding of outcome assessors in 3 out of the 6 studies); inconsistency (significant heterogeneity between the studies, I²=89%); indireness (indirect measure of the outcome in all studies); and imprecision (large confidence interval).

b Downgraded three levels due to: serious risk of bias (absence of randomization and blinding of outcome assessors in 1 study); inconsistency (significant heterogeneity between the studies, I²=83%); and indireness (indirect measure of the outcome in all studies).

c Downgraded two levels due to: inconsistency (significant heterogeneity between studies, I²=83%); and indireness (indirect measure of the outcome in all studies).

Table III. GRADE Summary of findings table for therapy-related strategies for cardiovascular medication adherence.
The various aspects of medication adherence are strongly influenced by the behavior of the patient. Among the many behavioral change strategies and techniques, motivational interviewing is often administered as a strategy to improve adherence. However, motivational interviewing alone results in a fairly modest improvement in medication adherence.\(^5\,\^6\) When looking at individual CVD medication classes, the highest effect size was seen in antithrombotics (2 studies; 387 participants; RR, 2.32; 95% CI, 1.18-4.56), antihypertensives (6 studies; 1362 participants; RR, 2.21; 95% CI, 1.63-2.96) followed by lipid-lowering medications (3 studies; 404 participants; RR, 2.11; 95% CI, 1.00-4.46).\(^7\) Even though there is no strong evidence of the effectiveness of using text messaging systems to improve adherence to CVD medications, text messaging has been reported to double the level of medication adherence in chronic diseases.\(^8\)

The European Society of Cardiology recommends simplifying treatment regimens to the lowest acceptable level, with repetitive monitoring and feedback.\(^9\) The dosage and number of medications are often automatically increased when there is failure to control symptoms, but this only worsens the rate of nonadherence. Therefore, using fixed-dose combination pills is a potentially useful strategy to improve medication adherence, especially in patients on multiple medications. The use of combination pills has shown a 50%-60% cumulative risk reduction.\(^10\) In a meta-analysis of 32 studies, patients taking twice-daily medications had a 7%-22.6% lower adherence than those on once-daily medications.\(^11\) Simplifying dosing regimens can increase the likelihood of adherence between 8% and 19.6%.\(^12\)

**Strengths and limitations**

The strengths and limitations of this review merit careful consideration. Although we performed an extensive search and systematic synthesis of available evidence by including data from different sources of evidence, there were insufficient numbers of trials for each of the intervention subtypes to meaningfully compare their effects on medication adherence. Additionally, the quality of evidence was limited by the variability of the measurement tools used in the different studies, the indirectness of the methods of adherence assessment, diversity in the components of interventions, and a general insufficiency of high-quality randomized controlled trials. The absence of baseline adherence data in half of the included studies also limited our ability to draw conclusions on the magnitude of change attributed to the intervention.

There is a need for larger-scale and higher-quality studies to assess the efficacy of these methods to improve adherence to CVD medications. Future studies should not only explore medication adherence but also medication persistence, and the period of follow-up should, therefore, be planned accordingly.

**Conclusion**

Adherence to cardiovascular medications is an important component of patient management. Different types of strategies such as education and support, technology, and fixed-dose combination pills, are available but should be tailored to the needs of individual patients. Adherence is a complex and dynamic process; it is, therefore, important for the treating team to thoroughly explore the reasons behind nonadherence and subsequently implement strategies that meet the specific needs of the individual patient.

**References**

Key words: adherence; cardiovascular disease; fixed-combination pill; therapy-related strategy.
Objective: To determine the efficacy of various therapy-related strategies in improving adherence to diabetic medications. Design: Systematic review and meta-analysis of prospective interventional studies. Data sources: Medline, Embase and Cochrane electronic databases, supplemented by searching the reference lists of relevant studies. Study selection: Randomized controlled trials in adults (age >18 years) with either type 1 or 2 diabetes mellitus and on existing diabetic medications (defined as any oral antidiabetic medication and insulin) that evaluated the effects of therapy-related strategies on subsequent changes in medication adherence compared with usual care or equivalent. Data extraction and analysis: Two investigators extracted data and a consensus was reached with involvement of a third. Study-specific effect estimates were combined using random-effects meta-analysis. A systematic narrative review was performed for the studies that could not be quantitatively synthesized. Results: Our search strategy retrieved 1364 unique citations, of which 14 were included in this review. We evaluated 15 different interventions from these 14 studies, including 9 multifaceted interventions and 6 single-intervention programs. The most common intervention was personalized education counseling (10 out of 15 interventions). Other interventions included automated system (2 studies), pictorial (2 studies), and drug labeling strategies (1 study). Adherence was measured using self-report tools in 11 studies, while 3 studies used medication counts–related tools, and 1 used interviews. In the quantitative synthesis, therapy-related interventions significantly improved adherence to diabetic medication (6 trials; 929 participants; 590 events; pooled relative risk, 1.218; 95% CI, 1.07-1.386; I²=0). Since there were significant differences in measurement tools and reporting across the studies, only a subset could, however, be included in the meta-analysis. Among those studies not included in the meta-analysis, a 1-week intervention did not result in a significant difference in adherence between the 2 study groups. However, for interventions lasting at least 6 weeks, a significant difference was reported. Conclusion: Available intervention studies on various strategies to improve adherence to diabetic medications generally show significant positive effects of therapy-related interventions on medication adherence. Similarly, pharmacy- and technology-based strategies also tend to benefit adherence substantially. However, the number of available trials is low and their quality is generally poor.

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IMPROVING MEDICATION ADHERENCE IN CARDIOMETABOLIC DISEASE

Introduction

High diabetes prevalence worsened by a lack of medication adherence

Diabetes mellitus, principally type 2, remains a major public health challenge worldwide. Poorly controlled diabetes mellitus leads to a wide array of complications including diabetes-induced renal dysfunction, retinopathy, and peripheral and autonomic neuropathies as the key microvascular complications of diabetes.1 The overwhelming disease burden and the extensive complications associated with diabetes are further worsened by a lack of medication adherence, which is becoming increasingly common globally. An emphasis on adequate adherence to diabetes therapy is, therefore, crucial given the deaths and poor quality of life brought about by diabetes and its complications.2

Lack of adherence and associated detrimental impact on health

Adherence is defined as “the extent to which a person’s behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider.”3 Adherence includes initiation of the treatment, implementation of the prescribed regime, and discontinuation of the pharmacotherapy.4 Worldwide, a substantial proportion of people do not adhere adequately to oral antidiabetic agents,5,6 with good adherence to sulfonylureas and metformin reported to be only 31% and 34%, respectively.7

Adherence to oral antidiabetic agents has been reported to have an inverse association with glycemic control,8 which subsequently leads to the development of microvascular and macrovascular complications of diabetes and altered lipid metabolism.9 In addition, patients with uncontrolled diabetes demonstrate a higher probability of developing depressive mood disorders.3 A lack of adherence to oral antidiabetic agents has been shown to lead to a 39% increased risk of all-cause mortality and a 38% increased risk of hospitalizations, compared with adherent patients.10 The inverse relationship of medication nonadherence has also been observed with total annual health care costs,12 especially inpatient costs.13

Objective of the present review

Given the widespread problem of nonadherence to oral antidiabetic agents and its likely impact, an earlier World Health Organization statement emphasized that increasing the efficacy of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatment.3 However, existing trial evidence on the benefits of different types of available therapy-related strategies to improve adherence is inconsistent and should be systematically reviewed. Therefore, we aimed to synthesize all available evidence to review the impact of different interventions on improving adherence to diabetic medications.

Methods

Data sources, search strategy, and eligibility criteria

Medline, Embase, and Cochrane Central electronic databases were searched systematically for relevant published articles (date of last search: May 3, 2017). Our search strategy combined terms related to the intervention (eg, oral antidiabetic agents, insulin) and outcomes (eg, medication adherence, compliance), without any language restriction (see Supplementary Table I, online only). We searched for studies that evaluated the effects of adherence-enhancing strategies compared with usual care or equivalent in adult participants (age>18 years) with either type 1 or 2 diabetes mellitus, taking any diabetic medication. Diabetic medications were defined as any class of antidiabetic medications (ie, metformin, sulfonylureas) and insulin.

Study selection

We included randomized controlled trials that (i) followed patients prospectively, (ii) evaluated therapy-related interventions that promoted medication adherence, and (iii) had assessed medication adherence using commonly known measurement tools. Direct measurement tools were defined as directly observed therapy and measurement of levels of medicine, metabolites, or biologic markers in the blood. Indirect measurement tools were defined as patient questionnaires, self-reports, pill counts, rates of prescription refills, and electronic medication monitors.14 Potential eligible articles were identified by two reviewers through screening of titles and abstracts. Full texts were retrieved for articles that satisfied all the selection criteria. The reference lists of the articles selected and of relevant reviews on the topic were searched for additional publications.

Data extraction

A predesigned data extraction form was used to extract relevant information. Two reviewers piloted the data extraction form for a sample of the included papers until an agreement was reached among reviewers. The extracted data included information on study size, study design, baseline population, country of study, duration of follow-up, duration of diabetes mellitus, type(s) of diabetes mellitus medication used, description of intervention and control, frequency of intervention, medication adherence scale, definitions of good adherence, and values of adherence. When available, effects of good adherence—such as changes in HbA1c—were obtained.

Data synthesis and analysis

Effect estimates (expressed as relative risk, RR) were calculated for subsequent changes in medication adherence and were based on the proportion of participants with good adherence (≥80% adherence or equivalent).15,16 irrespective of the measurement tool used. Summary RRs were calculated by pooling the study-specific estimates using a random-effects meta-analysis that allows for between-study heterogeneity. All statistical tests were two-sided and used a significance level of P<0.05. Analyses were performed using the statisti-
Improving medication adherence in cardiometabolic disease

Therapy-related strategies to improve adherence to diabetic medications – Chowdhury and others

Assessing the risk of bias and quality of evidence

The risk of bias in the included studies was assessed using the Cochrane Collaboration tool for randomized controlled trials. Seven possible sources of bias were evaluated with this tool: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The quality of evidence of our outcomes was assessed using the GRADE Working Group framework (Grading of Recommendations, Assessment, Development and Evaluations Working Group) and presented in the form of a “Summary of findings” table. The GRADE working group defined quality of evidence based on five factors: risk of bias across all studies, consistency of the effects across all included studies, directness of the outcome measured, precision of the effect estimates, and publication bias. We assessed the presence of publication bias using funnel plots, plotting precision against the effect size. We performed Egger’s test to quantify asymmetry.

Results

Studies identified

We retrieved 1364 unique citations through our electronic database search. We retained 200 articles for further evaluation following our initial screening based on titles and abstract. Our search flowchart and reasons for exclusion are presented in Figure 1. In total, 14 articles were finally eligible to be included in this review. While a narrative review was performed for all of the included studies, given the substantial methodological heterogeneity and differences in the ways outcomes were reported, only six articles could be combined for quantitative synthesis.

Adherence achieved by therapy-related strategies

There were fourteen studies that evaluated the effects of therapy-related strategies on diabetes medication adherence. The baseline characteristics of the included studies are presented in Table I and there were no significant differences. The
## Improving Medication Adherence in Cardiometabolic Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Name of intervention</th>
<th>Components of intervention</th>
<th>Face-to-face education</th>
<th>Phone counseling</th>
<th>Behavior counseling</th>
<th>Medication assessment</th>
<th>Group workshop</th>
<th>Toolkits</th>
<th>Reminder system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Mazroui et al.</td>
<td>Pharmaceutical care</td>
<td>The research pharmacist had discussions with their physicians regarding drug therapy and, if necessary, treatment modification was recommended, education on their illness and their medication in a structured fashion, printed leaflet to assist the education program, leaflets containing information about hypertension and hyperlipidemia, advice on the following: self- monitoring of glycemic control, physical exercise, diet, medication adherence, and smoking cessation</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acra et al.</td>
<td>Text message-based mHealth in Emergency Department Patients With Diabetes (TExT-MED)</td>
<td>Patients received 2 messages (9 AM and 5 PM) delivered to their mobile telephone daily. The TExT-MED curriculum contains messages in the following 4 categories: 1. Educational/motivational (1 per day) 2. Medication reminders (3 per week) 3. Healthy living challenges (2 per week) 4. Trivia (2 per week)</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babamoto et al.</td>
<td>Amigos en Salud (Friends in Health)</td>
<td>Community health workers conducted individual educational sessions based on ADA standards with participants and their family members. Education sessions were tailored to the participants' needs, such as knowledge, identified problems, goals, and level of progress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butt et al.</td>
<td>Patient Education by Pharmacist Program</td>
<td>Not clearly stated</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chow et al.</td>
<td>Home-based intervention</td>
<td>Two home visits: 1. Focused on the proper use of medications, including medication indications, dosage, administration frequencies, side effects and side effect management, storage and disposal of the medications and the importance of medication adherence; 2. Focused on T2DM, which included pathophysiology, risk factor, types of diabetes, sign and symptoms, diabetes complications, meal planning, lifestyle modifications and self-care. Patients were also given an information booklet on T2DM and a food pyramid chart prepared by the Ministry of Health</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jahangard-Ratjbar et al.</td>
<td>Diabetes Education Program</td>
<td>1. Phone call in between visits to reinforce therapy adherence and resolve any therapy-related issues 2. Individualized counseling on diet management, physical activity and diabetes complications during the interventions 3. Self-monitoring blood glucose 4. Logbook and education pamphlets on diabetes medications</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Medicographia 133 Chowdhury bis(6)_Mise en page 1*
The median follow-up of the included studies was 6 months (minimum 1 week, maximum 12 months). While all the included studies included participants with type 2 diabetes mellitus, none of the studies targeted solely participants with type 1 diabetes mellitus.

There were 15 different therapy-related interventions in the 14 included studies (Table II), of which 9 were multifaceted interventions and 6 were single intervention programs. The most common intervention was personalized education counseling (10 out of 15 interventions). Ten studies included health care professional interventions that were mostly led by a pharmacist, two involved automated system interventions, two were based on pictorial and one on drug labeling strategies to improve medication adherence.

Eleven studies measured adherence using self-report tools, three used medication counts-related tools, and one used interviews (Table III, page 295). The adherence rates of the two study arms are presented in Table III. In three studies, baseline adherence was not reported. In the quantitative synthesis, therapy-related interventions significantly improved adherence to diabetic medication (6 trials; 929 participants; 590 events; pooled relative risk, 1.218; 95% CI, 1.07-1.386; I²=0) (Figure 2, page 295). The quality of evidence was moderate.

### Assessments of study quality and risk of bias

None of the included studies had a low risk of bias in all seven domains (Supplementary Table II, online only). Participant bias was not clearly reported in all of the included studies. There was also unclear demonstration of reporting bias in all of the included studies. Funnel plotting for the studies included in the meta-analysis produced a symmetrical funnel plot (Supplementary Figure 1, online only). However, in view of the rather small number of studies included in the funnel plot (n=6), this may be inadequately powered to distinguish chance from true asymmetry. Egger’s asymmetry test of associa-

<table>
<thead>
<tr>
<th>Study</th>
<th>Name of intervention</th>
<th>Components of intervention</th>
<th>Face-to-face education counseling</th>
<th>Phone counseling</th>
<th>Behavioral counseling</th>
<th>Medication assessment</th>
<th>Group workshop</th>
<th>Toolkits</th>
<th>Reminder system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katalenich</td>
<td>Diabetes Remote Monitoring and Management System</td>
<td>1. Automated text messages to phone calls to remind patients to their blood glucose and report results via an automated system 2. Made adjustments to insulin doses based on validated algorithms</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolf</td>
<td>Patient-centered drug label strategy</td>
<td>Labeling includes specific time of intake, visual display of the dose, and highlights the medication name, indication, dose and instructions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Mohan</td>
<td>Picture Rx Medication List</td>
<td>Illustrated aid on the medication, indication, and dosing instructions, accompanied by plain language bilingual text</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Negaranesh</td>
<td>Teach back method</td>
<td>Individualized and private teaching sessions - exploring the participant’s understanding then only providing relevant diabetes education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Pictorial image method</td>
<td>Individualized and private session using simple, realistic pictures with limited content using familiar objects and symbols</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>O’Connor</td>
<td>Telephone outreach program</td>
<td>Single protocol structured telephone call - positive re-enforcement &amp; exploration of reasons for nonadherence to identify and resolve them</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Phum-Phum</td>
<td>Extra pharmacist service</td>
<td>Scheduled meetings with pharmacist together with routine follow-up visits - refill prescriptions, discussed uses of medications and education on lifestyle and diet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Xie</td>
<td>Pharmacuetical care program</td>
<td>1. Individualized education 2. Educative group activities 3. Telephone counseling</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table II. Details of the interventions of the included studies.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Population</th>
<th>Method of assessment</th>
<th>Duration of intervention</th>
<th>Intervention</th>
<th>Control</th>
<th>Adherence&lt;sup&gt;c&lt;/sup&gt;</th>
<th>P value&lt;sup&gt;d,e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al Mazroui et al.</td>
<td>2009</td>
<td>United Arab Emirates</td>
<td>117</td>
<td>Interview</td>
<td>12</td>
<td>51.70%</td>
<td>78.60%</td>
<td>50.90%</td>
<td>67.50%</td>
</tr>
<tr>
<td>Arora et al.</td>
<td>2014</td>
<td>USA</td>
<td>47</td>
<td>Text message-based</td>
<td>6</td>
<td>4.5 (2.4)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.9 (2.0)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>5.2 (2.0)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.1 (2.5)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Babamorad et al.</td>
<td>2009</td>
<td>USA</td>
<td>75</td>
<td>Morisky Self-Reported Medication Behavior Scale</td>
<td>6</td>
<td>69%</td>
<td>79%</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td>But et al.</td>
<td>2016</td>
<td>Malaysia</td>
<td>33</td>
<td>8-item Morisky Medication Adherence Scale&lt;sup&gt;g&lt;/sup&gt;</td>
<td>6</td>
<td>5.83 (1.84)</td>
<td>6.77 (1.76)</td>
<td>5.95 (1.51)</td>
<td>5.98 (1.50)</td>
</tr>
<tr>
<td>Chow et al.</td>
<td>2015</td>
<td>Malaysia</td>
<td>50</td>
<td>Home-based intervention (pharmacist)</td>
<td>3</td>
<td>3.53 (NR)</td>
<td>6.90 (NR)</td>
<td>3.49 (NR)</td>
<td>4.05 (NR)</td>
</tr>
<tr>
<td>Jahangardi-Rafsanjani et al.</td>
<td>2015</td>
<td>Iran</td>
<td>45</td>
<td>8-item Morisky Medication Adherence Scale&lt;sup&gt;h&lt;/sup&gt;</td>
<td>5</td>
<td>49%</td>
<td>76%</td>
<td>54%</td>
<td>51%</td>
</tr>
<tr>
<td>Jarab et al.</td>
<td>2012</td>
<td>Jordan</td>
<td>77</td>
<td>Pharmaceutical care program (pharmacist)</td>
<td>6</td>
<td>23.90%</td>
<td>71.40%</td>
<td>29.10%</td>
<td>35.40%</td>
</tr>
<tr>
<td>Katalenich et al.</td>
<td>2015</td>
<td>USA</td>
<td>50</td>
<td>Diabetes Remote Monitoring and Management System (automated system)</td>
<td>6</td>
<td>28%</td>
<td>37.21%</td>
<td>12.50%</td>
<td>20.51%</td>
</tr>
<tr>
<td>Mohanty et al.</td>
<td>2014</td>
<td>USA</td>
<td>99</td>
<td>Picture Rx Medication List</td>
<td>1 week</td>
<td>8-item Adherence to Refills &amp; Medications Scale</td>
<td>NR</td>
<td>10.3</td>
<td>NA</td>
</tr>
<tr>
<td>Negrurindle et al.</td>
<td>2013</td>
<td>Kurdistan</td>
<td>43</td>
<td>Teach back method (community health nurse)</td>
<td>6 weeks</td>
<td>4.37 (1.48)</td>
<td>7.03 (0.99)</td>
<td>4.52 (1.74)</td>
<td>4.32 (1.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>44</td>
<td>Pictorial image method (community health nurse)</td>
<td>6 weeks</td>
<td>4.33 (1.62)</td>
<td>6.73 (1.52)</td>
<td>4.33 (1.62)</td>
<td>6.73 (1.52)</td>
</tr>
<tr>
<td>O’Connor et al.</td>
<td>2014</td>
<td>USA</td>
<td>529</td>
<td>Telephone outreach program (nurse health manager/diabetes educator/pharmacists)</td>
<td>6</td>
<td>0.802 (0.22)</td>
<td>0.793 (0.24)</td>
<td>0.903</td>
<td></td>
</tr>
</tbody>
</table>
Improving medication adherence in cardiometabolic disease

Therapy-related strategies to improve adherence to diabetic medications – Chowdhury and others

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lations, nonetheless, was not significant (P=0.164). The quality of evidence of the association between therapy-related strategies and medication adherence was presented in the form of a “Summary of findings” table (Supplementary Table III, online only). The overall quality of evidence was graded as moderate. The quality of evidence was downgraded two levels because of: (i) serious risk of bias (blinding of outcome assessors was not reported in 3 out of 6 studies and absent in 2 out of the 6 studies; and the method of randomization was unclear in 2 studies); and (ii) indirectness (indirect measure of the outcome in all studies).

Discussion

SUMMARY OF THE KEY FINDINGS

The current review of available intervention studies on various strategies to improve adherence to diabetic medications demonstrates a moderate, but significant, effect of therapy-related interventions in improving medication adherence.

Similarly, other interventions (such as pharmacy- and technology-based programs) also improved the level of adherence to diabetic medications substantially, but these benefits were particularly observed in interventions lasting more than

Table III. Table of characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Population</th>
<th>Method of assessment</th>
<th>Adherence</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Baseline</td>
<td>End</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pill count (%)</td>
<td>Pill count</td>
<td>81.80 (17.0)</td>
<td>88.6 (11.9)</td>
</tr>
<tr>
<td></td>
<td>2016</td>
<td>USA</td>
<td>220</td>
<td>229</td>
<td>Patient-centered drug label strategy</td>
<td>OR: 1.59 (0.93-2.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pill count</td>
<td>OR: 1.13 (0.75-1.71)</td>
</tr>
<tr>
<td></td>
<td>2015</td>
<td>China</td>
<td>114</td>
<td>113</td>
<td>Pharmaceutical care program (Pharmacist)</td>
<td>Dispensed drug history</td>
</tr>
</tbody>
</table>

Figure 2. Effect of therapy-related strategies on improving adherence to diabetic medication.
6 weeks. Nonetheless, the overall number of trials available in each of these intervention groups and their quality were generally inadequate.

**Comparison with other reviews**
A number of reviews have evaluated different types of interventions to improve medication adherence, but a measure of true effect could not be established. Although education counseling is potentially important for optimal adherence, studies linking education counseling to improved adherence in literature are also generally scarce and often inconclusive, with an earlier review reporting significant improvements in adherence in only 2 intervention studies.

Pharmacological intervention remains a key component of effective diabetes management, which perhaps explains why a large number of trials are based on pharmacist-based interventions. Pharmacists can educate their patients about the proper use of medications, screen for drug interactions, explain monitoring devices, and make recommendations for ancillary products and services. This also enables them to potentially increase the communication between health care providers and patients, implement multidisciplinary programs, and recommend treatment regimens with easier dosing. With their clinical training, pharmacists have been seen to positively impact health outcomes and empower patients to actively manage their health. While patient counseling remains the most common form of pharmacist-based intervention to improve medication adherence, there are various forms of pharmacist-based interventions, and there seems to be no conclusive evidence of any specific intervention being superior to the rest (principally owing to the somewhat poor quality of existing studies). A recent review reported generally significant improvements in adherence rate with pharmacist interventions in 5 studies.

Furthermore, an earlier small prospective cohort study reported an improvement in medication adherence with the additional support of a diabetes nurse educator (29 participants; odds ratio, 6.6; 95% CI, 1.0-55.7). Other interventions, such as intense monitoring and sending of periodic cell phone messages, did not show any statistically significant impact on improving medication adherence (8 interventions; standardized mean difference, 0.22; 95% CI, 0.05-0.49). Multifaceted interventions (ie, those addressing more than one adherence factor) were comparatively more effective in improving adherence to diabetic medications and overall glycemic target in patients with type 2 diabetes mellitus compared with single strategies.

**Strength and limitations of the current review**
The strengths and limitations of the present review deserve careful consideration. Although the present review is based on an extensive literature search and systematic synthesis of available evidence, as for any systematic review, publication bias remains a possibility. This is of particular concern for a number of articles in which full texts were not available and for the grey literature, which could not be searched. Additionally, the quality of evidence in the retrieved studies was generally poor, owing principally to the variability of measurement tools used in the different studies, the indirectness of the methods of adherence assessment, the multiple components of the interventions, and the insufficient quality of studies in general. Self-report was the most commonly used tool to evaluate medication adherence, making interpretation of the findings complicated since patients often tend to underreport a lack of adherence in order to avoid disapproval from their health care providers. Therefore, findings from studies measuring adherence with self-reporting instruments should be considered with some caution.

**Implications for future research and practice**
There is a clear need for standardized methods of adherence assessment and reporting, as well as larger scale and better quality studies to assess the efficacy of these methods to improve diabetic medication adherence reliably. To reduce the possibility of reporting bias, the study protocols of all new trials should be published. It is also essential that randomized trials clearly state the presence or absence of blinding—with reasons—involving various parties in the study. Since there appears to be no clear ideal instruments to reliably measure medication adherence, using multiple tools might capture individual adherence levels to diabetic medications with greater precision. Additionally, future studies should also explore medication persistence to diabetic medications, which remains largely underaddressed in the prevailing literature. Finally, although these methods have a generally significant positive effect on adherence, individual patient needs should still be considered when formulating an intervention plan to improve adherence.

**Conclusion**
Available intervention studies on various strategies to improve adherence to diabetic medications show generally significant positive effects of therapy-related interventions on improving medication adherence. Similarly, pharmacy- and technology-based strategies also tend to benefit adherence substantially. However, the number of available trials is low and their quality is generally poor.

**Acknowledgements.** The authors would like to thank the Department of Public Health & Primary Care at the University of Cambridge and the Director General Of Health Malaysia.

**Keywords:** adherence; diabetes; systematic review; therapy-related strategy
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References


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Immune-inflammatory diseases • Neurodegenerative diseases

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Is enough being done to tackle medication nonadherence?

1. B. Afandi, *United Arab Emirates*
2. A. Almansari, *Saudi Arabia*
3. J. Boavida, *Portugal*
4. A. Chaib, *Morocco*
5. G. S. Stergiou, *Greece*
6. K. Tan Eng Kiat, *Singapore*
7. O. Yavuzgil, *Turkey*
Is enough being done to tackle medication nonadherence?

1. B. Afandi, United Arab Emirates

Is enough being done to tackle medication nonadherence? A recent audit of 572 patients with diabetes from our practice showed that only 33% of participants were rated as having a good knowledge of their illness. A second audit of 100 elderly women reported an illiteracy rate of 48%. One-half of the participants needed assistance understanding written medical information and one-third needed assistance on how to measure blood glucose. In addition, 43% reported the need for more medical information to manage their disease when they fast during the holy month of Ramadan. More than 60% of participants preferred the one-to-one medical teaching format.

The health authorities must bridge the widening gap between the advances in pharmaceuticals and the development of strategies to promote patient adherence. The cornerstone must be endorsing empathic patient-physician partnerships with effective communication and social support from other health care professionals. Effective interventions for improving patient adherence must be individualized and tailored to the patients’ cultural backgrounds, specific conditions, and treatment protocols. Institutional programs to increase patients’ awareness about cardiovascular diseases are essential. The preventive mechanism of cardiovascular medications that do not necessarily relieve symptoms must be fully addressed to improve understanding and compliance. In order for patients to take responsibility, they must understand their medical conditions in their own words. They should be fully motivated to participate actively in the decision-making process to create their treatment plans.

Health care system investment in comprehensive patient education programs must parallel the huge investments made by pharmaceutical manufacturers. This investment is achievable and cost-effective, which will ultimately lead to better health care outcomes.

References
2. A. Almansari, Saudi Arabia

Patient education on the long-term complications of the disease, the benefits of adherence, and the effectiveness of the treatment creates a sophisticated patient who is able to weigh the risks and benefits of treatment adherence. Patient education should include the concept of the therapeutic action of medicines and show that nonadherence might lead to subtherapeutic doses.

The role of technology in the development of innovative methods for drug delivery is essential to overcome the problem of nonadherence. Continuous delivery systems, which can be implanted subcutaneously and release a drug over a long period of time in a calculated manner, would certainly improve treatment adherence, although they have not yet been tested clinically. Advanced delivery systems are required not only to manage the disease, but also to give patients the confidence that they are receiving their treatment in an optimal way, which will also be reflected on their psychology.

Therefore, increasing the effectiveness of adherence interventions may have a far greater impact on the health of a population than any improvement in specific medical treatments, and it is worthwhile spending time and energy on strategies to promote treatment adherence for cardiometabolic diseases.

References
According to the constitution of the World Health Organization,1 which was signed by the representatives of 61 states on July 22, 1946, “Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.” This statement can almost be a utopia due to the complexity of all the implied factors.

Science, technology, and knowledge have helped in the discovery and production of medications that are designed to fight chronic diseases, such as diabetes. These medications intend to decrease the cost to society of certain diseases by avoiding complications and increasing quality of life and access to them is being expanded to a wider population. However, people’s adherence to medication is far from desirable, with the outcomes being far from those expected.2 Diabetes and other cardiovascular diseases have a growing prevalence due to longer life expectancies and unhealthy lifestyle habits.

So, what is missing? Should science and society invest in new, more efficient (and cost-effective) medications to overcome the gap between what is happening and the initial objective? Should we try to understand why patients do not follow their prescription and what their doctors say? Why do people not do what they should, despite what they are told, and even after they recognize that they should do what they are told?

The complexity and specificity of each individual makes it impossible to reduce human beings into categories, such as diabetics or hemophiliacs, with a solution, eg, the prescribed medication. Instead, each person with diabetes is unique; therefore, they should be listened to, asked for their beliefs, and motivated to play an active role in the treatment of their disease.

Doctors still have an important role because they must contribute their biomedical knowledge and make decisions on which medication is more adequate to the specificities of the disease, but above all, which medication is more adequate to the specificities of the person with the disease. It is no longer sufficient to just analyze the symptoms with the view of getting a diagnosis and, consequently, prescribe a drug. The person with the disease should be considered as a variable in the equation, and is probably one of the most important variables since they can determine the success or the failure of the treatment.

In 2008, Jean-Philippe Assal3 defined therapeutic education as a tool designed to

“train patients in the skills of self-managing or adapting treatment to their particular chronic disease, and in coping processes and skills. It should also contribute to reducing the cost of long-term care to patients and to society. It is essential to the efficient self-management and to the quality of care of all long-term diseases or conditions, though acutely ill patients should not be excluded from its benefits. Therapeutic patient education is education managed by health care providers trained in the education of patients, and designed to enable a patient (or a group of patients and families) to manage the treatment of their condition and prevent avoidable complications, while maintaining or improving quality of life.”

The important conclusion is that, in addition to producing new medications, efforts should be made to spread and implement therapeutic patient education as a key concept in the self-management of chronic diseases to improve the quality of life.

References
The prevalence of cardiometabolic diseases is steadily increasing worldwide. The long-term management of these diseases remains a challenge despite the many drugs used. The efficacy might be appreciated using some parameters (ie, blood pressure, glycemia, and lipidaemia) that even the patients may follow. Cardiometabolic diseases usually involve a lifelong treatment, which eventually becomes difficult to adhere to, especially if the patient finds the results disappointing. At the same time, research and pharmaceutical industries continue to produce new drugs that promise to have a better impact on morbidity and mortality. However, the results obtained in real life by the new molecules are frequently below those obtained in randomized controlled trials. One of the causes for this difference in results is patients’ non-adherence to their long-term treatments. In fact, the most optimistic investigations evaluate treatment adherence to be less than 50%, with all that this involves, such as costs for medical consultations, disease aggravation, and repeated hospitalizations. The cost of non-adherence vs the production of new drugs should be assessed mainly in emergent countries, where the cost of treating cardiovascular disease and providing access to new drugs is a burden on public health. In the meantime, there are many ways to improve treatment adherence and these should be encouraged. Several proposals will make it possible to provide better and less costly treatments, such as a simplified educational message and the use of supports and diagrams that even an illiterate patient can understand.

As patients now have access to different mobile applications, it will be wiser to use smart devices (phones, tablets, etc) as reminder and surveillance tools that can simulate the strict monitoring of randomized controlled trials, which will improve treatment adherence.

Another way to motivate patients to be more adherent to their treatment will involve sensitizing and making them more responsible for their disease, the issues surrounding their treatment, and the assessment of the risks of cardiometabolic disease. Therefore, treatment adherence is not only a health issue, but also a budgetary one. Its improvement necessitates a broad mobilization of actors around targeted programs and specific objectives. The involvement of trained staff, not necessarily health care professionals, would be more advantageous and less expensive.

In return, the production of new drugs will certainly add value both for therapeutic efficacy and for reducing the morbidity and mortality of these chronic pathologies. However, there is no guarantee that adherence to these new products will be better than the old ones. Therefore, the production of new drugs will have to bring innovations that will ensure good treatment adherence, ie, once-daily dose regimens, fixed-dose combinations, or even new routes of administration. These innovations will certainly entail added cost, but it may be worthwhile if treatment adherence can be improved.

**References**

In the management of cardiovascular risk factors, such as hypertension, hypercholesterolemia, and diabetes, there is considerable discrepancy in the control rates achieved in research trials and clinical practice. Recent long-term outcome trials showed that optimal control of hypertension is feasible in the vast majority of patients. In contrast, population studies in several developed countries showed that only about 50% of treated hypertensive patients achieved effective blood pressure control. These data suggest that human factors (doctor-patient cooperation), rather than treatment-related factors (lack of efficacy or adverse effects), are mostly responsible for the failure to control hypertension in clinical practice. Indeed, poor patient adherence with drug treatment is recognized as the number one reason for resistant hypertension. Poor treatment adherence results in incomplete control of hypertension, which leads to an increased risk of cardiovascular events and increased health care costs. Thus, for the vast majority of patients with uncontrolled hypertension, a more efficient application of the currently available drugs is needed rather than the development of new drugs.

To improve hypertension control rates, the scientific community needs to focus its attention and direct energy and resources into improving treatment adherence; however, this will require initiatives directed at both the patients and the doctors. Patient education is essential and requires time to be devoted by the doctor, particularly at the initial in-office visits when treatment decisions are made. Patients should understand the risks of elevated blood pressure, the principles of long-term drug therapy for hypertension, and the benefits of long-term treatment adherence and blood pressure control.

References
Medication adherence or nonadherence is a complex matter that is influenced by physician-, patient-, and medication-related factors. Physician-related factors include the ability to communicate and motivate patients to enhance the concordance of views between doctors and patients, individualization of therapy and targets, and minimizing dosing complexities. Then, there are a whole host of patient-related factors, including concordant or discordant views with their doctor; attitudes toward Western medications and the disease that may be influenced by friends and family, media, previous experiences, and cultural beliefs; economic status; and remembering to take their medication. Finally, commonly known medication-related factors that influence compliance include cost, side effects, efficacy, ease of dosing, method of administration, and pill size.

We have to admit that inherent to the development of new therapies has been an improvement in efficacy, reduction in side effects, and ease of administration and dosing regimens. This also applies to existing therapies. The following list contains a few examples of these improvements:

- Incretin-based therapies in diabetes introduced a decade ago addressed the concerns of the efficacy of lowering blood glucose being accompanied by weight gain and hypoglycemia.
- The oral dipeptidyl peptidase-4 inhibitor agents have almost zero side effects, and they lower blood glucose with a weight neutrality and hypoglycemia that is comparable with placebo.
- For greater efficacy and weight reduction, there are injectable glucagon-like peptide-1 analogs. These should be compared best with insulin, the historic injectable therapy for diabetes. They provide blood glucose–lowering efficacy without the weight gain and hypoglycemia of insulin therapy and indeed with the advantage of weight loss. There is no titration of blood glucose required; the administration has moved from once/twice daily to once weekly, and, now, potentially to once every 6 months or longer. The devices that deliver glucagon-like peptide-1 analogs have also become simpler to use.
- The orally administered sodium-glucose cotransporter 2 inhibitors are an alternative for the efficacy of blood glucose–lowering with weight reduction and minimal hypoglycemia with additional benefits on lowering blood pressure, uric acid, and triglycerides.

If these options are not enough, fixed-dose, single-pill combinations further enhance compliance by reducing pill load and simplifying dosing regimens, for example, moving from the twice-daily dipeptidyl peptidase-4 inhibitor/metformin immediate release preparations to the once-daily dipeptidyl peptidase-4 inhibitor/metformin XR preparations, with a similar move for the sodium-glucose cotransporter 2 inhibitor/metformin preparations. In most cases, there is also a cost-saving benefit with the fixed-dose, single-pill combinations. Glitazide is a second generation sulphonylurea introduced in the 1970s, reformulated into a modified-release preparation (Diamicron MR 30 mg) in the early 2000s with better compliance as a once-daily administered pill and with lower hypoglycemia, and then, a decade later, introduced as its current MR 60 mg preparation to further enhance patient compliance at its most efficacious dosing.

In conclusion, it is reassuring that we can see, in the last decade, the introduction of new therapies combined with measures to improve treatment adherence to the new and existing therapies.
As the elderly population is gradually increasing, coping with chronic illnesses has become increasingly complex. The challenge against both cardiovascular disease and its cardiometabolic precursors should have a comprehensive medical perspective covering many fundamental factors.

In the US, where almost 800,000 cardiovascular deaths occur annually, the rate of death due to "age-related heart disease (per 100,000 population) declined from 412 in the 1980s to 191 in 2012. Stroke, which was the third or fourth leading cause of death in the last 50 years, dropped to fifth place." Lifestyle and behavior changes undoubtedly had an effect on these positive changes. However, it is generally accepted that medicines that have effects on cardiovascular mortality are the most important contributors to this development. There are about 200 new medicines under development for cardiovascular disease and stroke, with clinical trials conducted and reviewed by the US Food and Drug Administration. Although it is not difficult to predict that these new agents, which are currently being developed in the treatment of many chronic diseases, such as atherothrombosis, lipid disorders, heart failure, and hypertension, will further reduce cardiovascular mortality rates in the future, it is not entirely clear whether randomized trial data actually reflects real-life data for all disease subgroups.

Suboptimal drug adherence appears to be the most important barrier between real-life data and randomized study outcomes, which has also been described by the World Health Organization as a serious problem worldwide. Even in developed countries, it is known that almost one in two patients do not show adequate adherence to long-term treatments, which leads to worsening of the disease at the population level, an increased mortality rate, and serious financial loss in the long term. Statins, antihypertensives, and antithrombotics, which have a particularly wide primary and secondary area of use, are of the greatest interest in this subject area. In the Heart and Soul study, a study that is investigating the importance of self-reported adherence, cardiovascular events are twice more frequent in participants without good treatment adherence; this condition remains an independent risk factor for subsequent adverse cardiovascular events after adjustment for baseline features. A study showed that maintaining good adherence to statins for at least 2 years resulted in a 30% reduction in the risk of acute myocardial infarction; this result is even better than in patients receiving higher doses of statins. More striking scientific evidence for the importance of drug adherence came from the CHARM study (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity). In this study, the risk reduction resulting from good treatment adherence was more prominent than the benefit obtained with the study drug.

In summary, given the magnitude of the problems with drug adherence, it appears that the drugs that are currently available to treat cardiovascular diseases are not used with sufficient levels of adherence. Therefore, ensuring that the available drugs are used with appropriate adherence in the general population is perhaps more important than the development of new agents, and may in fact bring positive effects faster.

References
Monitoring of Drug Adherence in Hypertension – Burnier

It is today well accepted that poor adherence is a real concern in hypertension. With the absence of new drugs to treat hypertension, it is crucial to improve blood pressure control with available antihypertensive agents by working on adherence. Unfortunately, nonadherence to therapy remains largely underdiagnosed in clinical trials, despite the availability of adequate new noninvasive methods, and it is almost never measured in clinical practice. In order to make good therapeutic choices about the treatment of resistant hypertension, it is vital to systematically assess adherence in patients who fail to respond adequately to blood pressure–lowering medication. The emergence of new, less expensive, and less complicated ways of monitoring adherence (eg, adherence apps) should help in this objective. It is of the utmost importance to remember that hypertensive patients on therapy, but with inadequate adherence are at greater cardiovascular risk. Conversely, good adherence to antihypertensive medication is associated with a lower incidence of cardiovascular and renal complications. Lastly, poor adherence has an enormous negative impact on health care costs. All efforts made toward improving drug adherence therefore represent a win-win situation that satisfies all parties in the health care network, ie, patients, physicians, other health care providers, and payers.
Drug adherence in hypertension

It is obvious that adherence to antihypertensive therapy is an important determinant of the blood pressure response to treatment. In the last two decades, drug adherence has been measured in many studies. These have not only aimed to characterize drug adherence in hypertension, but also to investigate how adherence could be enhanced or supported. Lessons learned from these studies are that adherence is highly variable, but relatively high when quantified in hypertension. This latter observation was rather surprising, but these instances of high adherence may be due to measurement bias. Indeed, as soon as patients are told that their adherence will be monitored, their assiduity in taking their pills regularly improves substantially, at least during the first months of monitoring. With the use of devices that enable us to obtain a dosing history, many interesting aspects of the adherence process have come to light. The first and probably the most important one is that drug adherence is a dynamic process that is hard to summarize with a single number. Patients may be adherent at certain periods and less so at other times, for example, during weekends, holidays, or when problems associated with family life or work occur.

Because of the variability and difficulty in quantifying adherence, establishing a cut-off level for acceptable treatment adherence is not easy. In medical literature, the cut-off arbitrarily chosen to define “good” adherence is 80%. This cut-off can be obtained by missing one day’s treatment every five days or equally by missing one week’s treatment every five weeks; however, the clinical consequences of the missed treatment in these two scenarios are unlikely to be the same. It should be noted that the impact of different antihypertensive drugs on blood pressure control and cardiovascular risk reduction depends on their individual pharmacological profiles, with long-acting drugs preferable for patients who find adherence problematic.

At an individual study level, some studies have been unable to demonstrate a relationship between adherence and blood pressure level achieved with treatment while, in others that have shown a relationship to exist, it was weak. One reason for this weakness is that high on-treatment blood pressure values may also be caused by unsuitable treatment or too low a dosage of an appropriate medication. Large-scale analyses have, however, concluded that patients with good adherence do have better blood pressure control and a reduced cardiovascular risk. The risk of coronary heart disease, heart failure, and cerebrovascular disease is reduced in hypertensive patients who adhere well to treatment.

The recent revival of drug adherence

In the field of hypertension, the problem of poor adherence to drug therapy has not received much attention in the past and, hence, has been rather overlooked. For several decades, physicians and researchers focused on the development of new drugs and combination therapies that were supposed to improve blood pressure control in hypertensive populations. This is no longer the case. Adherence has recently come back to the forefront of hypertension research with the development of interventional therapies, such as renal denervation or carotid baroreflex stimulation, for the management of patients with apparent resistant hypertension.

Determining whether a patient with resistant hypertension is taking their antihypertensive medication as prescribed is critical. If antihypertensive medication fails to reduce blood pressure, two explanations are possible: the patient is nonresponsive to therapy; or the patient is nonadherent and not taking his medication as advised. Up until recently, patients with resistant hypertension would have automatically been categorized as nonresponders rather than nonadherent because of the lack of means of and great difficulty in assessing medication adherence. This automatic categorization as “nonresponsive” would have then led to the addition of other antihypertensive agents and/or an increase in dosage. Neither of these measures would have any effect in a patient whose true problem was nonadherence, and this absence of effect would be incorrectly attributed to “resistance” rather than nonadherence, further complicating an already muddled situation. Moreover, before intervening with an expensive procedure, it is important to be sure that candidates for renal denervation are truly resistant. When potential causes of apparent resistance to drug therapy in hypertension were investigated, poor drug adherence was identified as one of the most important factors of pseudoresistance. Despite its importance, the true incidence of poor adherence in resistant hypertension remains imprecise because adherence has rarely been measured adequately. Published figures range between 10% and 50%.

Monitoring drug adherence: a clinical challenge

Measuring drug adherence in clinical practice has never been a simple issue, whereas in clinical trials measurement is standardized: assessment of adherence is essentially based on pill counts and the return of unused pills. In fact, there are many other published techniques that can be used in different clinical contexts. Physicians use some of them, but we ought to acknowledge that the majority of physicians dedicate very little time to this issue even though they recognize that adherence is an important parameter to assess in chronic diseases.
Interviewing a patient about his or her medication and treatment adherence is not particularly accurate (<30% chance of detecting nonadherence), but it is easy and relatively quick. A quick interview is particularly valuable as a prompt in patients looking for an opportunity to engage in discussion; for example, it will induce certain patients—those who never started treatment or those who stopped treatment—to explain why they decided to do what they did. That said, a physician’s intuition by itself is unfortunately not a reliable gauge of adherence, nor are other indirect markers of treatment adherence, like drug-induced adverse events, clinical response, or consultations attended. Nonetheless, a careful, nonjudgmental discussion about adherence to therapy should remain the first step in any investigation on drug adherence. Physicians should be better trained on how to formulate their questions in order to leave the patient space and time to eventually communicate their problems with drug therapy. Table I shows examples of questions that can be used by physicians, as suggested by Brown et al. 24

### Table I. Types of question that physicians could ask in order to assess a patient’s medication adherence.

<table>
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<td>“I know it must be difficult to take all your medications regularly. How often do you not take them?”</td>
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<tr>
<td>“Of the medications prescribed to you, which ones are you taking?”</td>
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<tr>
<td>“Of the medications you listed, which ones are you taking?”</td>
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<tr>
<td>Alternatively, “Of the medications you listed, which ones did you forget this week?”</td>
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<tr>
<td>“Have you had to stop any of your medication for any reason?”</td>
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<tr>
<td>“How often do you not take medication X?”</td>
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<tr>
<td>“When was the last time you took medication X?”</td>
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<tr>
<td>“Have you noticed any adverse effects from your medications?”</td>
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Several questionnaires have been created to assess adherence. These questionnaires are generally used in clinical studies, but they could also be used in clinical practice. Their results tend to overestimate adherence, as patients often forget the episodes when no medication was taken. The most popular questionnaire is the Morisky questionnaire, 25 which is easy and rapid to use in its simplified version. The four items of the simplified questionnaire are: (i) Do you ever forget to take medications? (ii) Are you ever careless in taking your medications? (iii) Do you ever miss taking your medications when you are feeling better? and (iv) Do you ever miss taking any of your medications because you are feeling sick? Each item has a yes/no response option and one “yes” provides one point. A score of ≤2 is indicative of low adherence to drug therapy. When compared to electronic measurements of adherence that provided a dosing history, the Morisky questionnaire was found to overestimate drug adherence.

Pill counting, a favorite and generally effective method of assessing drug adherence in clinical trials, overestimates adherence to treatment too because patients tend to give back empty boxes. For calculating long-term treatment adherence in epidemiological studies, the percentage of days covered by prescriptions can be determined by regular checking of prescription refills using the records from electronic pharmacy dispensing systems. 26 This type of continuous registry is useful for estimating persistence with therapy and establishing risk factors associated with poor adherence. 27,28 Weaknesses of this method, however, are the assumptions that patients take their medicine as they should and that patients always use the same pharmacy. Patient education and comprehensive monitoring of all medication distribution channels could help address these weaknesses.

In the future, drug adherence monitoring in clinical trials might be performed using a new system of ingestible sensor included in every single pill. The Food and Drug Administration has accepted this system, developed by Proteus Digital Health, as a new approach to monitor adherence in clinical studies. 29 It has the advantage of proving drug ingestion has occurred, but it still relies on patient compliance: the patient has to apply a patch to his or her skin in order for data to be transmitted (Figure 1, page 310).

Continuous electronic pill-box monitoring as well as intermittent direct measurements of plasma or urinary drug levels can also provide relevant and trustworthy information about drug adherence. In the first instance, if the pill box is opened it is assumed the drug is ingested. I believe that some researchers worry unduly about the ability to prove that medication has actually been taken with electronic systems. Over the long term (several months), a patient is unlikely to routinely open an electronic pill box for the express purpose of systematically discarding his or her medication, so perhaps this worry is misplaced or at least not as great as one might believe. Long-term monitoring is likely to be dependable.

In the second instance, with plasma and urine drug monitoring, a positive result proves that a drug was ingested, but not when or how often or how many doses were forgotten. A negative result is easy to understand: the medication was simply not taken. Direct measurement of drug levels, though expensive and arduous, is becoming more popular in resistant hypertension, 30,31 but white-coat adherence bias can exaggerate the real level of adherence. Clinical trial investigators are normally obliged to inform patients that they will be taking blood or urine samples for testing and some patients, in anticipation of the tests, will become more adherent just before and after a planned visit. 30

In studies where patients were not informed of blood and urine testing, treatment adherence in patients with resistant hypertension has been found to be especially limited. 30,31,32
About half of resistant hypertension patients and about a quarter of renal denervation candidates are nonadherent (partially or completely). Our study of electronic monitoring of drug adherence showed adherence problems affected approximately one in three patients with resistant hypertension. Yet, measuring drug levels and communicating the results to patients may have a favorable impact on adherence, as was observed in one clinical trial involving patients with resistant hypertension. In a recent analysis, Schmieder et al have clearly shown that some patients change from being adherent to being partially or totally nonadherent after renal denervation. Finally, in recent studies, some investigators have used directly observed treatment (DOT), or “tablet feed,” which is commonly used in the management of tuberculosis, to evaluate the role of poor adherence in mediating uncontrolled blood pressure. Although a small number of patients were enrolled in some of these studies, these clearly showed that blood pressure actually normalized in many patients when the treatment was given under controlled conditions. The strategy used was to couple directly observed treatment with the measurement of 24-hour ambulatory blood pressure. Patients were asked to come to the unit with their drugs. These were taken under supervision and blood pressure was monitored thereafter over 24 hours. In some cases, this approach may be useful and may avoid the use of drug level measurements, which are more costly. As mentioned in a recent review, the ideal method to assess drug adherence in clinical practice should “provide a reliable capture, storage, analysis, and communication of dosing history data in ways that make it difficult or impossible for patients or trial staff to censor or otherwise manipulate the data.” Nowadays, three methods are close to fulfilling these criteria: the retrospective analysis of prescription refill records for epidemiological studies, the analysis of chemical markers of drug exposure, and the automatic electronic monitoring of adherence. The future of drug adherence monitoring will certainly include the use of mobile health technologies and apps, connecting patients with their physicians or with other members of the health care team. Today, several apps are available on the market, but so far none of them has really been convincing in terms of diagnosing poor adherence. They might be rather more useful in supporting adherence in the long-term management of hypertensive patients. Today, a large clinical trial is ongoing with an app, the Eurohypertension app, developed in part by the European Society of Hypertension. Preliminary results with this approach have suggested an improvement in blood pressure control, implying better adherence to therapy among patients using the app. Conclusion New antihypertensive drugs are lacking so making the best use of those we already have, which includes optimizing adherence to therapy, is a logical move. Though nonadherence is underdiagnosed in clinical trials and rarely measured in prac-
tice, it is a real and costly challenge in hypertension. Tensive patients who take their treatment irregularly are at greater cardiovascular risk,10 while those with good adher-
ence see their risk of outcomes diminish.10,12,14 In patients with resistent hypertension who respond unsatisfactorily to blood pressure-lowering medication, the systematic assessment of adherence is particularly crucial.20 The ongoing development of modern, inexpensive, and simple instruments for mon-
toring adherence promises to benefit patients, physicians, and health care payers.

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Keywords: adherence; adherence app; adherence monitoring; directly observed treatment; drug monitoring; electronic pill box; hypertension; ingestible sensor; Morisky questionnaire; pill counting; resistant hypertension

Monitoring of drug adherence in hypertension – Burnier

MEDICOGRAFIA, Vol 39, No 4, 2017 311
The impact of new technology on medication adherence: finally breaking the nonadherence barrier?

by J. Brguljan, Slovenia

In the treatment of hypertension, good medication adherence is crucial to achieve optimal blood pressure control and reduce the risk of cardiovascular events and the costs related to antihypertensive treatment. Medication adherence is a complex issue that goes beyond pill consumption and is actually a reflection of a patient’s overall behavior toward his/her health. However, adherence is not exclusively the responsibility of the patient as it is an interplay between the various components of the treatment process: patients, doctors, pharmacists, and health care systems. The use of modern technology to improve adherence is an interesting and promising concept, especially as technological interventions can be implemented at all stages of the treatment process. Technical solutions include the use of mobile phones and the internet to communicate with patients and share information, medication event monitoring systems, text messaging, home telemonitoring, mobile devices, electronic health records, electronic blisters, ingestible biosensors, long-acting medications, and fixed-dose combinations. While technological interventions have the potential to improve adherence, their use calls for an evolution of the physician’s role in advocating for and educating patients. Ultimately, nothing can replace the relationship between doctor and patient, which should be at the center of any effort to improve adherence using technological interventions.

Medicographia. 2017;39:312-318

Medication adherence is not a simple process. It is an interplay between patients, their habits, their awareness of their illness, their doctor’s awareness and medical knowledge; the health care system, and finally, medications themselves. Medications are usually prescribed to recover homeostasis. History taking and clinical examination are fundamental processes that influence treatment decisions and medication prescription.

Blood pressure control and adherence

The sphygmomanometer is a very useful tool that was first introduced into clinical practice some 120 years ago, followed decades later by the concept of high blood pressure as a disease. It took several more decades before antihypertensive medications became available, and today there are several classes of blood pressure–lowering drugs. Yet, despite having the basic tools to diagnose and treat hypertension at our disposal for over half a century, high blood pressure remains one of the leading contributors to morbidity and mortality worldwide. Many people with
Many people now use mobile phones. In addition to being used for educational purposes, but are more useful in monitoring a patient’s blood pressure and its response to antihypertensive treatment. A Korean study evaluated the benefits of mobile phones in helping patients to monitor their blood pressure and bodyweight using a weekly web-based diary along with remote support. Participants were recruited from the family medicine outpatient department of a tertiary care hospital located in an urban city of South Korea. Twenty-eight patients were assigned to an intervention group and 21 to a control group. The intervention’s goal was to bring blood pressure, body weight, and serum lipid levels close to normal ranges. Patients in the intervention group were requested to record their blood pressure and body weight in a weekly web-based diary or by using their mobile phones. The researchers sent weekly recommendations to each patient by SMS and Internet. The intervention took place over 8 weeks. After 8 weeks, the systolic and diastolic blood pressure in the intervention group decreased significantly from the baseline by 9.1 mm Hg and 7.2 mm Hg, respectively (P<0.05); in contrast, there was no significant change in the control group.²

In a pragmatic, single-blind, 3-arm, randomized trial (SMS-Text Adherence Support [STARS]) undertaken in South Africa, patients treated for high blood pressure were randomly allocated in a 1:1:1 ratio to information-only SMS text messaging, interactive SMS text messaging, or usual care. The number of patients included was 457:458:457. A slight reduction in systolic blood pressure was found for the patients getting text messages compared with usual care at 12 months. There was no evidence that an interactive intervention increased this effect.³

In their study, Kissel and colleagues included 97 hypertensive patients under active ambulatory care management—including SMS and mobile phone technology—and 102 patients under traditional ambulatory care management. The blood pressure, body mass, and smoking history of patients were analyzed in the study, which lasted 1 year. In the active ambulatory care management group, 36% of patients were withdrawn from the study. At the end of the study, 77% of patients from the active care management group had achieved the blood pressure level goal, which was over 5 times more than in the traditional ambulatory care management group (P<0.001). The risk ratio of achieving and maintaining the goal blood pressure in the active care management group was 5.44, (CI, 3.2-9.9; P<0.005). It was concluded that active ambulatory care management supported by SMS and mobile phone technology improves the quality of ambulatory care for hypertensive patients.⁴

Today, innovative digital technologies have the potential to redefine blood pressure management, eliminating not only the cuff, but also the century-old approach that necessitates monitoring, decision-making, education, and treatment to be tied to a visit to the doctor. A wide variety of devices ranging from

**Use of mobile phones**

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Today, innovative digital technologies have the potential to redefine blood pressure management, eliminating not only the cuff, but also the century-old approach that necessitates monitoring, decision-making, education, and treatment to be tied to a visit to the doctor. A wide variety of devices ranging from
handheld devices, to wristbands and weighing scales are currently being developed to simplify and improve blood pressure measurement. These emerging technologies use techniques such as photoplethysmography (the optical sensing of changes in light absorption with each heartbeat, as in pulse oximetry) or radar to measure blood pressure. Probably the greatest advancement these non-cuff sensing technologies will bring is in enabling the development of wearable sensors for continuous and noninvasive measurement of blood pressure, but they still need to be tested in real practice.

◆ Medication Event Monitoring Systems (MEMS)

A medication event monitoring system (MEMS) consists of a conventional medicine container fitted with a special closure that records the time and date each time the container is opened and closed. It is generally acknowledged that electronic monitoring of adherence to treatment improves blood pressure control by increasing patients’ awareness of their treatment; however, the effect is questionable in the long-term. In their observational study of 470 patients with mild-to-moderate hypertension, van Onzenoort et al measured adherence in 228 patients by means of both a MEMS and pill count (intervention group), and in 242 patients by means of pill count alone (control group). During a follow-up period of 1 year consisting of seven visits to the physician’s office, blood pressure measurements were performed and medication was adjusted based on the blood pressure achieved. In addition, adherence to treatment was assessed at each visit. Based on pill counts, median adherence to treatment did not differ between the intervention group and the control group (96.1% vs 94.2%; P=0.97). In both groups, systolic and diastolic blood pressure decreased similarly: 23/13 mm Hg vs 22/12 mm Hg in the intervention and control group, respectively. In this study, the use of a MEMS did not lead to better long-term blood pressure control, nor did it result in fewer drug changes and the use of fewer drugs. Recently, it was shown that patients are more inclined to take their drugs as prescribed when they are faced with an upcoming consultation. This phenomenon—known as white coat compliance—emphasizes the importance of clinical visits for patients with hypertension. So, in the study of van Onzenoort et al, the absence of an effect on blood pressure control of the MEMS intervention and the high adherence may be explained by the frequent visits that the patients participating in the study had to attend.9

Health care system organization

The use of mobile computing and communication technologies in health care and public health—known as mobile health—is a rapidly expanding area of e-health. The potential of mobile-health interventions to have beneficial effects on health care and health care service delivery processes is huge, especially in resource-poor settings. Understandably, there is considerable enthusiasm for these interventions.

◆ Text messaging

Missed appointments are one of the important problems in daily practice. The effectiveness of mobile health technology in improving health care service delivery processes was assessed in a systematic review and meta-analysis. The pooled effect on appointment attendance using text message (SMS) reminders versus no reminder was increased, with a relative risk (RR) of 1.06 (95% confidence interval [CI], 1.05-1.07; I²=6%). The pooled effect on the number of cancelled appointments was not significantly increased (RR, 1.08; 95% CI, 0.89-1.30). There was no difference in attendance using SMS reminders versus other reminders (RR, 0.98; 95% CI, 0.94-1.02, respectively).10

◆ Home telemonitoring

Home telemonitoring of blood pressure has been proven to be effective in regulating blood pressure. Using this technique would be useful in the future even though, as shown in 401 primary care patients aged 29-95 years with uncontrolled daytime ambulatory blood pressure (≥135/85 mm Hg, but <210/135 mm Hg), it costs significantly more than usual care (mean difference per patient £115.32 (95% CI, 83.49-146.63; P<0.001). Increased costs were due to telemonitoring services, patient training, and additional general practitioner and nurse consultations. The mean cost of systolic blood pressure reduction was £25.56/mm Hg per patient (95% CI, 16.06-46.89). Over the 6-month trial period, supported telemonitoring was more effective at reducing blood pressure than usual care, but also more expensive. If clinical gains were maintained, these additional costs would be very likely to be compensated for by reductions in the cost of future cardiovascular events. Longer-term modeling of costs and outcomes is required to fully examine the cost-effectiveness implications.11

◆ Use of mobile devices

Topol and Steibuhel have done a lot of investigations and work on the development of electronic possibilities to follow patients remotely to achieve better health outcomes, improve communication, and decrease hospital admissions. They conducted a prospective randomized controlled trial of adults who had submitted a 2012 health insurance claim associated with hypertension, diabetes, and/or cardiac arrhythmia. The intervention involved receipt of one or more mobile devices that corresponded to their condition(s) (hypertension, Withings Blood Pressure Monitor; diabetes, Sanofi iBGStar Blood Glucose Meter; arrhythmia, AliveCor Mobile ECG) and an iPhone with linked tracking applications for a period of 6 months. The control group received a standard disease management program. In addition, participants in the intervention group received access to an online health management system that provided them with detailed device tracking information over the course of the study. They also examined health self-management. Surprisingly, there was little evidence of differences in health care costs or utilization as a result of the intervention. They even found evidence that the control and in-
Electronic health records
Establishing electronic health records is another option that offers better treatment control and adherence and also gives useful information for further treatment. In their recent study, Ravindrarajah et al examined the primary care electronic health records from 2001 to 2014 of 265,225 participants aged 80 years and over from the UK Clinical Practice Research Datalink, and found that, in octogenarians, blood pressure treatment had intensified, and that blood pressure values had declined, with a substantial increase in the proportion of patients achieving conventional blood pressure targets. However, we need to be very careful regarding data protection, because distrust in the use of personal information may render patients reluctant to visit their doctor.

Doctors
Doctors are at the center of the medical team, and as such, keep the “treatment circle” going. It is important that doctors are highly educated and keep themselves up-to-date with all the possible treatments, as they are developing really fast. First of all, doctors need to be absolutely positive about the treatments and procedures they recommend to their patients. Due to lack of time and financial support, attending congresses is not always possible. However, thanks to new technology, doctors can now benefit from e-learning and can “attend” webinars. There is a wide range of continuing medical education courses available, but due to lack of time, doctors often do not make the most of what’s on offer. In any case, even though we can read about all the biggest medical achievements on the internet, nothing can replace personal communication and the sharing of personal clinical experience.

Medications
Electronic medication blisters were tested in a randomized single-blinded (doctor-blinded), controlled, single-center study with a crossover design performed on 53 patients with increased cardiovascular risk—defined as the presence of at least two out of three health risks such as type 2 diabetes, hypertension or hypercholesterolemia. To objectively track the dosage and timing of medication intake, electronic medication blister packs (OtCM, DSM TCG B.V., Mauritshuis, the Netherlands) were used as add-ons to standard medication blister packs. Labels with printed circuitry were applied to the aluminum foil cover of the blister (bottom side) and were linked to a small printed circuit board (positioned on the blister’s upper side). Taking out a pill broke the conductive track inside the label directly underneath that pill. This event was recognized and led to the storage of the corresponding data (position and time) in the microcontroller’s internal memory. These data could be interrogated wirelessly by a near-field communication (NFC)–enabled reader device (Figure 1). Although a statistically significant difference ($P=0.04$) between the monitoring and control phase was observed for the diabetes medication only, the results indicate that mHealth-based adherence management is feasible and well accepted by patients with increased cardiovascular risk. It may help to increase adherence, even in patients with high baseline adherence and, subsequently, lead to improved control of indicators, including blood pressure and cholesterol concentrations.

Ingestible biosensor systems
Another medication-based approach to assess drug adherence is the use of ingestible biosensor systems, such as radio-frequency identification (RFID)-tagged gelatin capsules. Once the capsule dissolves in the stomach, the RFID tag activates to transmit a unique signal to a relay device, which transmits a time-stamped message to a cloud-based server that functions as a direct measure of medication adherence.

Fixed-dose combinations
To date, the most important achievements in medication-based technologies are fixed-dose combinations and long-acting medications. The use of single-pill combinations of two antihypertensive agents is associated with substantially better adherence than the same two drugs given separately. In addition, single-pill combinations are much more effective at lowering blood pressure. We are still waiting for long-lasting medications (ie, 1 month or more) for the treatment of hypertension.

The impact of new technology on medication adherence – Beguljan
Where are we today?
The ACCOMPLISH trial (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Syoptic Hypertension) achieved the best blood pressure control ever attained in a large outcome trial in hypertension, with more than 80% of the 11 440 patients getting to their blood pressure target. Various motivation items routinely used in outcome trials, including clearly marked pill boxes and blister packages, may have contributed to better adherence and blood pressure control in white patients or in African-American patients as shown in the meta-analysis of Ruppar et al. Efforts to improve adherence to antihypertensive medications is extremely important and may involve multiple methods.

Therapeutic drug monitoring is an evolving and useful tool for detecting and reducing nonadherence, and leads to effective blood pressure control. Therapeutic drug monitoring is a cost-effective health care intervention in patients diagnosed with apparent treatment-resistant hypertension, and this finding is valid for a wide range of patients, independent of sex and age. In general, therapeutic drug monitoring enables objective surveillance of patient adherence by repeatedly measuring concentrations of antihypertensive drugs in blood and urine. Moreover, a retrospective study looking at the impact of therapeutic drug monitoring on adherence found that when nonadherent patients were confronted with low or undetectable drug levels and were given additional counseling to overcome barriers to adherence, blood pressure control improved considerably without intensification of drug therapy. During the follow-up, systolic blood pressure was reduced by 46±10 mm Hg in nonadherent patients, and only by 12±17 mm Hg in adherent patients, without intensification of the antihypertensive therapy. An essential benefit of therapeutic drug monitoring is that it identifies the source of the problem and may lead to its resolution, ie, getting patients to take the drugs they were prescribed.

Influence of medication nonadherence on patient prognosis
As far as target organ damage is concerned, nonadherence to medications is associated with a high risk of cardiovascular events in the general hypertensive population. In a survey of 18 806 newly diagnosed hypertensive patients in whom drug adherence was assessed using data from a medical database, it was shown that high drug adherence was associated with a long-term reduction in acute cardiovascular events (hazard ratio: 0.62; 95% CI, 0.40-0.96; P=0.032, vs low drug adherence).

In other retrospective studies that used the same methodology to assess adherence, it was also shown that compared with patients with low drug adherence (medication possession ratio [MPR] <80%), patients with high drug adherence (MPR>80%) showed a relative risk (RR) reduction of 11% in chronic heart failure (RR, 0.89; 95% CI, 0.80-0.99), 10% in coronary events (RR, 0.90; 95% CI, 0.84-0.95), and 22% in cerebrovascular events (RR, 0.78; 95% CI, 0.70-0.87).

Interestingly, a recent meta-analysis of 44 individual studies, involving nearly 2 million participants, showed that high adherence to antihypertensive treatment was associated with a 29% RR reduction in all-cause mortality (RR, 0.71; 95% CI, 0.64-0.78). Taken together, these results indicate that nonadherence is an important factor that leads to drastically worse clinical outcomes in hypertension.

Practical conclusion
Good medication adherence is crucial to achieve optimal blood pressure control and reduce the risk of cardiovascular events and the costs related to antihypertensive treatment. Doctors worry about target organ damage and end point events of untreated hypertension, whereas patients only worry about the possible drug side effects that they may experience in the short term.

Doctors need to be convinced that they are prescribing the right treatment, should be up-to-date with the latest medical achievements, have enough time to talk to their patients, and be interested in getting their patients to the blood pressure goal. Patients need to be aware of the harmful impact of elevated blood pressure and have a trustful connection with their doctor. They also need to be able to contact their doctor as soon as they have any doubt about their treatment or feel that they are experiencing side effects, so that they have an opportunity to discuss the problem rather than stopping the treatment of their own accord.

Health care systems need to be organized in a way that offers a close relationship between doctors and patients, and also between family physicians and hypertension specialists so they can join their forces in the battle against the silent killer that is hypertension. The way health care systems are organized is heavily dependent on government policies, so politicians should consult with health care professionals and listen to their professional advice before making decisions.

♦ New technologies
New technology is useful and in permanent development. It is clear from both consumer-level pricing and marketing that many wearable medical devices are being marketed directly to patients themselves. Whether this technology can really empower patients or is simply another market for medical device manufacturers remains to be seen. However, it is undeniable that the growth of technology calls for an evolution of the physician’s role in advocating for and educating patients. In such a fast-moving field it is more important than ever for physicians to stay up-to-date with what devices manufacturers are offering—not only to advise patients on what works, how to access it, and how to get the best out of it, but also
to evaluate the effectiveness and cost-efficiency of these devices, to push device companies to deliver the best possible product, and to ensure that government regulations protect patients as consumers.31

Waking up in a smart house (Figure 2),32 where all the sensors in the house would, each morning, detect our temperature, blood pressure, heart rate, analyze our urine and feces, and analyze our mood when we look in the mirror could be nice as we would get all the possible medical analyses performed every morning. But is this really how we want to live?

◆ The patient-doctor relationship

Although self-blood pressure measurement as an adjunct to office blood pressure measurement was shown to lead to somewhat better adherence in the study of van Onzenoort et al, the difference was only small and not clinically significant. The time relative to a visit to the doctor actually seemed to be a more important predictor of adherence.9

In her book What Patients Say, What Doctors Hear, in which she analyzes the complexities and miscues of the patient–doctor exchange, Danielle Ofri argues that “For all the sophisticated diagnostic tools of modern medicine, the conversation between doctor and patient remains the primary diagnostic tool.”33,34 Only based on this conversation and personal contact can we apply new technology to improve adherence to medication.

As Hippocrates said “it is far more important to know what person the disease has than what disease the person has.”

References

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