



# Enhancing Prescription Medicine Adherence: A National Action Plan

National Council on Patient Information and Education

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# Preface

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

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

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

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

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# Executive Summary

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

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

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

Over a decade ago, the National Council on Patient Information and Education (NCPIE) recognized the need for such a coordinated approach to improved medication adherence and issued a report

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

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

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

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

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

2. **Agree on a common adherence terminology that will unite all stakeholders.**

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

3. **Create a public/private partnership to mount a unified national education campaign to make patient adherence a national health priority.**

To motivate patients and practitioners to take steps to improve medication adherence, compelling, actionable messages must be communicated as part of a unified and sustained public education campaign.

A foremost priority is creating the means by which government agencies, professional societies, non-profit consumer groups, and other affected stakeholders can work together to reach public and professional audiences on a sustained basis. Even as NCPIE and various government agencies, professional societies, and voluntary health organizations work to provide information about medication adherence, there needs to be a national clearinghouse, serving as the catalyst and convener so that all stakeholders can speak with one voice about the need for improving patient adherence. NCPIE, a professional society, or academic institution could manage this clearinghouse effectively.

4. **Establish a multidisciplinary approach to adherence education and management.**

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

5. **Immediately implement professional training and increase the funding for professional education on patient medication adherence.**

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

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

**6. Address the barriers to patient adherence for patients with low health literacy.**

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

**7. Create the means to share information about best practices in adherence education and management.**

Today, stakeholders have access to more than 30 years of research measuring the outcomes and value of adherence interventions. Building on this foundation, a critical next step is for the federal government -- through the Adherence Research Network -- to begin collecting data on best practices in the assessment of patient readiness, medication management and adherence interventions, incentives that produce quality outcomes from adherence interventions, and measurement tools so that this information can be quantified and shared across specialties and health care facilities. Just as federal and state registries collect and share necessary

data on different disease states, a shared knowledge base regarding systems change, new technologies, and model programs for evaluating and educating patients about adherence will significantly improve the standard of adherence education and management.

**8. Develop a curriculum on medication adherence for use in medical schools and allied health care institutions.**

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

**9. Seek regulatory changes to remove road-blocks for adherence assistance programs.**

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

importance of adhering to their prescribed therapy.

**10. Increase the federal budget and stimulate rigorous research on medication adherence.**

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

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

# Introduction

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

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

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

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

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

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

and rebound effects (e.g., with hypertension and depression therapy) when medication is interrupted.<sup>(3)</sup> Because of this impact, adherence has been called “the key mediator between medical practice and patient outcomes.”<sup>(7)</sup>

## A TIME FOR ACTION

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

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

- + Using a verbal discussion reinforced with appropriately designed written materials to help the patient understand the medical condition, the need for the treatment, and the value of the treatment;
- + Offering verbal counseling from both the prescribing health care provider and the pharmacist that the prescription should be filled and taken as prescribed. While written instruction sheets can reinforce these instructions, they should never be used as a substitute for counseling;
- + Providing useful written information in “patient language” that clearly explains

how the patient can correctly manage his/her medications. This information includes details on how to administer the medication, the exact time the medicine should be taken and why, how long to take the medicine, recognition and management steps for common side effects, special precautions, and how to monitor the progress of the therapy;

- + Making patients aware of the various medication adherence aids and devices available, such as dosing reminders, pill boxes and refill reminder programs;
- + Monitoring patient adherence with every visit to the prescribing health care provider or pharmacist; and
- + Instructing patients and caregivers on home monitoring activities (such as home blood pressure monitoring) and home monitoring records that should be maintained for use during future medical and pharmacy visits.

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

“Maximum use of strategies to enhance compliance must be made. Application of these strategies is particularly important now, when there is great pressure to decrease costs and improve quality and patient outcomes.”<sup>(9)</sup>

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

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

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

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

Another major development since the publication of NCPIE's report is new technology that makes available a number of useful mechanisms for fostering adherence. For example, patients can receive pharmaceutical information and refill reminders via letter, fax, telephone, e-mail and pager messages. There are also electronic reminder devices, which can be programmed for multiple

daily alarms and may permit the user to record brief dosing instructions. Moreover, a number of medication organizers now incorporate electronic alarms to alert patients when doses are due.

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

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

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

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

## LACK OF A STANDARD DEFINITION AND CONSISTENT TERMINOLOGY LIMITS CONSENSUS

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

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

Yet to many researchers, “compliance” connotes a passive role for the patient and appears to blame and stigmatizes the patient’s independent judgment

as deviant behavior. Thus, many stakeholders prefer the term “adherence,” which implies a more collaborative relationship between patients and clinicians and is more respectful of the role that patients can play in their own treatment decisions. Thus, the NCPPIE definition proposed in 1995 was intended to encompass the concept of adherence, including two-way communication, patient-centered treatment planning, and agreement upon the medication and dosing requirements.

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

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

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

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

## THE EXTENT OF THE PROBLEM

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

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

- + Between 12 percent and 20 percent of patients take other people’s medicines;<sup>(11)</sup>
- + In developed countries like the U.S., adherence among patients with chronic conditions averages only 50 percent;<sup>(3)</sup>
- + Other studies show that about one-third of patients fully comply with recommended treatment while another third sometimes comply and one-third never comply;<sup>(12)</sup>
- + The World Health Organization reports that only about 43 percent of patients in developed nations take their medicines as prescribed to treat asthma and between 40 percent and 70 percent follow the doctor’s orders to treat depression;<sup>(3)</sup>
- + Although hypertension increases the risk of ischemic heart disease three- to four-fold and increases the overall cardiovascular risk by two- to three-fold, just 51 percent of patients take their prescribed doses of drugs to manage this condition;<sup>(13)</sup>
- + Among 17,000 U.S. patients prescribed beta blocker drugs following a heart attack, a major study conducted by Duke University Medical Center reported that only 45 percent regularly took these medications during the first year after

leaving the hospital, with the biggest drop in adherence occurring during the initial months after hospital discharge;<sup>(13)</sup>

- + Less than 2 percent of adults with diabetes perform the full level of care, which includes self-monitoring of blood glucose and dietary restrictions as well as medication use, that is recommended by the American Diabetes Association;<sup>(14)</sup>
- + Although adherence with short-term therapy is generally considered to be higher than for long-term treatments, rapid declines occur even in the first ten days of use;<sup>(15)</sup> and
- + Even among health care professionals, self-reported adherence with prescribed therapies averaged only 79 percent in one study.<sup>(16)</sup>

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

## SPECIAL POPULATIONS AT RISK

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

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

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

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

## **PAYING THE PRICE FOR POOR ADHERENCE**

Who is paying the price for the epidemic of poor medication adherence? We all are -- and the costs are substantial. Researchers have calculated that non-adherence costs the U.S. health care system about \$100 billion annually,<sup>(22, 23, 24)</sup> including approximately \$47 billion each year for drug-related hospitalizations.<sup>(25)</sup> Moreover, not taking medicines as prescribed has been associated with as many as 40

percent of admissions to nursing homes<sup>(26)</sup> and with an additional \$2,000 a year per patient in medical costs for visits to physicians' offices.<sup>(26)</sup> The total direct and indirect costs to U.S. society from prescription drug non-adherence are about \$177 billion annually.<sup>(27)</sup>

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

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

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

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

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

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

## MEDICATION-RELATED FACTORS

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

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

order to take their medication, such as using devices to test blood levels as part of a treatment protocol, using inhalers, or self-administering injections.<sup>(36)</sup>

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

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

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

## PATIENT-RELATED FACTORS

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

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

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

1. Perceptions about the nature and severity of their illness;
2. Denial of illness and the need to take medicines;
3. The assumption that once the symptoms improve or the person "feels better," he or she can discontinue use of the medication;
4. Limited appreciation about the value of medicines when properly used;
5. Beliefs about the effectiveness of the treatment;
6. Acceptance of taking medications for preventive purposes and for symptomless conditions (e.g. statins to lower blood cholesterol levels);
7. Worries about the social stigma associated with taking medicines;
8. Fear of side effects or concern about becoming drug dependent;
9. Fear of needles and the need for self-injections;

10. Lack of confidence in the ability to follow the medication regimen;
11. Media influence regarding safety or risk issues associated with particular medicines; and
12. Lack of positive motivations and incentives to make necessary changes in behavior.

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

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

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

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

## **PRESCRIBER-RELATED FACTORS**

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

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

At the same time, the WHO report attributes lack of adequate medication counseling to the outdated belief that adherence is solely the patient's responsibility.<sup>(3)</sup> Practical issues such as lack of time and lack of financial reimbursement for education

and counseling also represent persistent barriers to health care provider adherence interventions.<sup>(48)</sup>

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

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

## **PHARMACY-RELATED FACTORS**

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

for adjusting patients' drug regimens as well as identifying and preventing drug-related problems.<sup>(52)</sup>

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

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

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

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

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

## GOVERNMENT IMPEDIMENTS

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

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

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

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

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

With these concerns in mind, the National Consumers League (NCL) created voluntary performance-based Best Practice Principles that build on the requirements contained in the HIPAA privacy rule.<sup>(58)</sup> Developed by a Working Group of representatives from public interest groups, health professional societies, the consumer/privacy movement, pharmacy industry trade groups, pharmacy vendors, retail chains, and the pharmaceutical industry, the Best Practices

Principles are intended to bridge the gap between the protections afforded by HIPAA and fair information practices that define the degree of control that consumers should have over the ways their health information is used. Accordingly, the Best Practices Principles include:<sup>(58)</sup>

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

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

<sup>1</sup> 42 C.F.R. Part 1001.

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

<sup>3</sup> Pub. L. No. 104-191.

<sup>4</sup> 45 C.F.R. § 164.506(a) and (c).

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

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

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

## LIMITED FEDERAL SUPPORT FOR ADHERENCE RESEARCH

Besides federal and state laws and policies that impact the availability of adherence assistance programs, insufficient federal funding for adherence research is another impediment to improving medication use. Although created the Adherence Research Network to identify research opportunities at its 18 Institutes and Centers, the Network has been inactive since 2002. Moreover, in 2000, when the Network was funding adherence research, the actual NIH dollars earmarked

for testing interventions to improve medication-taking behavior was only \$3 million in a budget of nearly \$18 billion.<sup>(59)</sup> The overall NIH budget in 2000 was \$17.8 billion.

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

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

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

<sup>1</sup> Cal. Civ. Code § 56.10(d), as amended by A.B. 715.

<sup>2</sup> Cal. Civ. Code § 56.05(f)(3).

# Strategies for Improving Patient Adherence

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

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

## RECOGNIZING THE DISEASE CHARACTERISTICS OF NONCOMPLIANCE

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

- + Non-adherence can lead to increased morbidity and mortality;

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

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

## INCREASING PUBLIC AWARENESS THROUGH EDUCATION

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

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

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

## PATIENT INFORMATION STRATEGIES

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

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

- + Serious adverse effects to look out for and what to do if they occur.
- + What action to take when the prescription is about to run out.

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

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

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

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

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

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

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

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

## BEHAVIORAL REINFORCEMENT AND PATIENT SUPPORT

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

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

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

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

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

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

Along with these strategies, specialists in the field are advocating for broader awareness and adoption of new technologies that make it possible to engage patients more effectively about medication adherence. For example, prescribers can use email to communicate directly with patients who are encouraged to ask questions electronically. Pharmacies can use adherence-messaging programs to reach patients using letters, newsletters, brochures, telephone calls, e-mails, faxes and even pagers. These programs can be triggered by

automated pharmacy dispensing records, based on estimates of when the patient may run out of the medication. These communications not only remind the patient to refill the prescription but also emphasize the importance of following their health care provider's instructions and keeping follow-up visits.

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

## STRATEGIES DIRECTED AT HEALTH PROFESSIONALS

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

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

professionals, studies find that lack of medication adherence is a problem.<sup>(16)</sup>

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

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

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

At the same time, more initiatives like the "Asheville Project," the longest-running test using pharmacist interventions to improve patient adherence with diabetes and asthma regimens, are needed to improve health outcomes.<sup>(71)</sup> Featuring patient counseling, the Asheville Project

provides pharmacists with intensive training in managing the target disease and then pays them for monthly consultations with patients, during which they encourage those patients to adhere to the recommended lifestyle changes and prescribed medication regimen. Currently, the American Pharmacists Association (APhA) Foundation has launched the Diabetes Ten City Challenge modeled after the Asheville Project to improve medication adherence among people with diabetes.<sup>(72)</sup> This demonstrates that matching patients with specially trained pharmacists is a useful strategy to help patients learn how to manage their disease more effectively while lowering the costs of health care.

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

## **THE NEED FOR A MULTIDISCIPLINARY APPROACH TO IMPROVE ADHERENCE**

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

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

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

## **THE NEED FOR SUPPORTIVE GOVERNMENT POLICIES**

At a time when the number of prescriptions dispensed in the U.S. is expected to grow to 4.5 billion by 2010,<sup>(74)</sup> enabling pharmacists to use the most modern technologies to conduct adherence assistance programs would seem obvious.

However, as noted previously, there are a variety of impediments, including limitations by a number of federal and state laws. An immediate need is to resolve ambiguities about whether sponsored programs fall within the scope of the federal anti-kickback statute, and to ensure that federal and state medical privacy laws make clear that pharmacies may communicate with patients about the importance of adherence to prescribed courses of therapy, as long as such compliance programs address privacy-related concerns.

## **THE NEED FOR RESEARCH SUPPORT AND RESEARCH RIGOR**

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

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

# Advancing Adherence: A National Action Agenda

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## 10 PRIORITIES FOR ACTION

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

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

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

Because the stakes are so high, NCPIE has become a convener and catalyst for promoting a dialogue on new ways to advance patient medication adherence across the continuum of care -- from diagnosis through treatment and follow-up patient care and monitoring. Accordingly, NCPIE convened a panel

of experts to create consensus on ten national priorities that may have the greatest impact on improving the state of patient adherence in the U.S. Ultimately involving the support and active participation of many stakeholders -- the federal government, state and local government agencies, professional societies and health care practitioners, health educators, and patient advocates -- this platform calls for action in the following areas:

### 1. **Elevate patient adherence as a critical health care issue.**

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

### 2. **Agree on a common adherence terminology that will unite all stakeholders.**

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

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

3. **Create a public/private partnership to mount a unified national education campaign to make patient adherence a national health priority.**

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

4. **Establish a multidisciplinary approach to compliance education and management.**

There is a growing recognition that a multidisciplinary approach to medication taking behavior is necessary for patient adherence to be sustained. This has led NCPPIE to promote -- the "Medication Education Team" -- in which the patient and all members of the patient's health care team work together to treat the patient's condition, while recognizing the patient's

key role at the center of the process. Looking to the future, this model has the potential to improve adherence rates significantly by changing the interaction between patients and clinicians and by engaging all parties throughout the continuum of care.

5. **Immediately implement professional training and increase the funding for professional education on patient medication adherence.**

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

6. **Address the barriers to patient adherence for patients with low health literacy.**

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

format to address the patient's individual capabilities.

7. **Create the means to share information about best practices in adherence education and management.**

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

8. **Develop a curriculum on medication adherence for use in medical schools and allied health care institutions.**

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

9. **Seek regulatory changes to remove road-blocks for adherence assistance programs.**

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

10. **Increase the federal budget and stimulate rigorous research on medication adherence.**

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

## THE TIME IS NOW

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

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

# Table 1

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

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

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

## Table 2

### STRATEGIES FOR IMPROVING ADHERENCE TO A MEDICATION REGIMEN\*

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

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

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

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

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A stylized graphic of a human figure in shades of purple, composed of a circle for the head and three curved shapes for the arms and legs, set against a solid purple background.

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