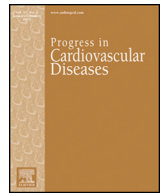




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Review Article

## Medication adherence: Importance, issues and policy: A policy statement from the American Heart Association



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ABSTRACT

Medications do not work in patients who do not take them. This true statement highlights the importance of medication adherence. Providers are often frustrated by the lack of consistent medication adherence in the patients they care for. Today with the time constraints that providers face, it becomes difficult to discover the extent of non-adherence. There are certainly many challenges in medication adherence not only at the patient-provider level but also within a healthy system and finally in insurers and payment systems. In a cross-sectional survey of unintentional nonadherence in over 24,000 adults with chronic illness, including hypertension, diabetes and hyperlipidemia, 62% forgot to take medications and 37% had run out of their medications within a year. These sobering data necessitate immediate policy and systems solutions to support patients in adherence. Medication adherence for cardiovascular diseases (CVD) has the potential to change outcomes, such as blood pressure control and subsequent events. The American Heart Association (AHA)/American Stroke Association (ASA) has a goal of improving medication adherence in CVD and stroke prevention and treatment. This paper will explore medication adherence with all its inherent issues and suggest policy and structural changes that must happen in order to transform medication adherence levels in the U.S. and achieve the AHA/ASA's health impact goals.

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**Abbreviations:** AA, African-Americans; ACE, angiotensin converting enzyme; AHA, American Heart Association; ASA, American Stroke Association; CDC, Centers for Disease Control and Prevention; CMS, Centers for Medicare and Medicaid Services; CVD, cardiovascular disease(s); DM, diabetes mellitus; EHR, electronic health record; EMERGE, ESPACOMP Medication Adherence Reporting Guideline; ESPACOMP, European Society for Patient Adherence, Compliance and Persistence; HF, heart failure; HTN, hypertension; MI, myocardial infarction; MTM, medication therapy management; PGY, postgraduate year; SES, socioeconomic status; SPRINT, Systolic Blood Pressure Intervention Trial; U.S., United States of America; VBP, value-based purchasing; WHO, World Health Organization.

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## Introduction

Medications do not work in patients who do not take them. Non-adherence is one of the largest challenges faced by providers in their management of chronic illness. Unfortunately, providers often do not directly address medication adherence with their patients primarily due to time constraints.<sup>1</sup> There is an additional myriad of issues that impact patients' ability to adhere to drug regimens, including other elements of the patient-provider relationship, as well as individual, societal, and systems-wide factors. In a cross-sectional survey of unintentional nonadherence in over 24,000 adults with chronic illness including hypertension (HTN), diabetes mellitus (DM) and hyperlipidemia, 62% forgot to take medications and 37% had run out of their medications within a year.<sup>2</sup> These sobering data necessitate immediate policy and systems solutions to support patients in adherence.

The American Heart Association (AHA)/American Stroke Association (ASA) has a goal of improving medication adherence in cardiovascular disease (CVD) and stroke prevention and treatment.<sup>3</sup> Among the elements to achieve this goal is identifying key questions that, if answered, could lead to significant impact. The reduction in cardiovascular deaths cannot be achieved with current levels of medication adherence.<sup>4</sup> This paper will explore medication adherence with all its inherent issues and suggest policy and structural changes that must happen in order to transform medication adherence levels in the U.S. and achieve the AHA/ASA's health impact goals.

## Definitions of adherence

Adherence is synonymous with dedication, support, observance, commitment and in its most simple form means the act or quality of "sticking-to" a plan. In the context of healthcare, adherence is commonly described as the "active, voluntary and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result".<sup>5</sup> It is ultimately the choice of the patient to actively and consistently follow the course recommended in order to achieve the desired outcomes whether diet, exercise, medications or follow-up. That choice may be influenced by a mix of factors including cost, health literacy, social support, and depression, among others.

## Classification of nonadherence

Medication nonadherence can be primary or secondary.<sup>6</sup> Primary nonadherence (also known as initiation) occurs when a provider prescribes a new medication and the order is never dispensed by the pharmacy or picked up by the patient. Secondary nonadherence occurs longitudinally and develops over time as a patient misses doses, prematurely discontinues therapy or takes inadequate amounts of doses required for the desired therapeutic effects. This type of nonadherence, which usually starts in the first few months after starting a medication, can be categorized as *nonpersistence*, whereby the patient stops taking the medication after starting it without consulting the prescriber, or *nonconforming*, which encompasses a variety of ways in which medications are not taken as intended by the prescriber.<sup>7</sup> Nonadherence can be intentional or unintentional and associated characteristics are depicted in Table 1.<sup>8</sup>

## Measures of adherence

Direct measures of adherence are the most accurate and provide proof that the drug has been taken through detection of the drug or metabolite in blood or urine, or detection of a biologic marker.<sup>9</sup> There are 4 general categories of indirect measurements: (1) self-reporting; (2) medication measurement (e.g., pill count); (3) electronic monitoring devices; and (4) prescription record review.<sup>10</sup> The Morisky scale (Table 2) is a structured, validated and frequently used 8-item self-reported adherence measure that can be easily incorporated into a follow-up visit and has demonstrated to be predictive of adherence.<sup>11,12</sup> Self-reported measures may overestimate adherence by the provider as there may be incorrect patient recall or a deliberate misrepresentation by the patient to placate the provider and avoid an anticipated "scolding". Prescription record reviews can be derived from insurance claims data, particularly refill record or from pharmacy-filling records.<sup>13</sup> Prescribing data from the electronic health record (EHR) can be helpful but only if timely and accurate.

## Prevalence of nonadherence

In 2003, the World Health Organization (WHO) reported the adherence rate to long-term therapies in developed countries was 50%.<sup>14</sup> Once-daily dosing schedules have significantly higher adherence rates compared to thrice daily or more frequent dosing.<sup>15–17</sup> Primary nonadherence occurs in more than 20% of individuals who are prescribed a medication from both inpatient and outpatient settings.<sup>18</sup> These rates have been consistently observed across a wide range of disease categories<sup>19</sup> and do not appear to be reliably predicted by whether the conditions are symptomatic or their clinical consequences. In contrast, some patient subgroups appear to be at particularly high-risk of nonadherence. In a systematic review of 53 studies evaluating adherence to statins, women had 10% lower odds of adherence than men and non-white individuals had a 53% higher odds of nonadherence than individuals of white race/ethnicity.<sup>14</sup> Income and socioeconomic status can also be key predictors of nonadherence.<sup>20–22</sup> Additionally, health disparities have been linked to non-adherence with factors affecting both, such as provider-patient communication and socioeconomic factors including poverty, illiteracy and lack of social support among others.<sup>23</sup>

## Consequences of nonadherence

As the WHO has cited, "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any new improvement in specific medical treatments".<sup>24</sup>

**Table 1**  
Characteristics of Intentional and Unintentional Nonadherence.

Intentional (active)	Unintentional (passive)
Side effects	Forgetfulness
Experience	Lack of understanding
Fear	Cost
Stigma	Underlying disease
Denial	Health literacy
Health belief system	Miscommunication

**Table 2**

The Morisky 8-item medication adherence scale.

1. Do you sometimes forget to take your high blood pressure pills?
2. Over the past 2 weeks, were there any days when you did not take your high blood pressure medicine?
3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?
4. When you travel or leave home, do you sometimes forget to bring along your medications?
5. Did you take your high blood pressure medicine yesterday?
6. When you feel like your blood pressure is under control, do you sometimes stop taking your medicine?
7. Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your blood pressure treatment plan?
8. How often do you have difficulty remembering to take all your blood pressure medication?

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Poor medication adherence portends poorer health outcomes and can adversely impact patient morbidity and mortality, clinical trials, cost-effectiveness of medical care and clinical decision making by providers. Nonadherence also has significant public health costs. A report from the Centers for Disease Control and Prevention (CDC) calculated that medication nonadherence in chronic diseases results in up to \$300 billion of avoidable healthcare costs in the U.S. annually accounting for 10% of total healthcare costs.<sup>25</sup> Among patients with cardiac disease, average healthcare spending for patients who are nonadherent is substantially higher than for individuals who are adherent. For example, compared to adherent individuals, annual average medical spending is \$8881 higher for nonadherent individuals with heart failure.<sup>22</sup>

### CVD and nonadherence

Medication nonadherence has been documented to occur in >60% of patients with CVD.<sup>26</sup> The asymptomatic nature of certain CVD, such as HTN and hypercholesterolemia, may contribute to high nonadherence rates in this population as patients may not immediately perceive a benefit from routinely taking antihypertensives or lipid-lowering agents. However, non-adherence to both antihypertensive agents and lipid lowering drugs have been linked to a higher number of deaths and CVD events. Each of these observations have had a “threshold” of adherence, although measured in different ways.<sup>27</sup> In a large, retrospective cohort study of patients with coronary artery disease, nonadherence to angiotensin converting enzyme (ACE) inhibitors, beta-blockers and statins increased risk for all-cause mortality, CVD mortality, coronary revascularization procedures and hospitalization for acute myocardial infarction (MI) or heart failure (HF) over a median follow-up of 4.1 years.<sup>28</sup> A population-based registry study of 73,527 hypertensive patients revealed that nonadherent patients had 3.81 and 3.01 times higher odds of stroke death when compared with adherent patients at 2- and 10-year follow-up after the start of continuous antihypertensive medication.<sup>29</sup> Among patients treated with secondary preventive drugs after a stroke, antihypertensive persistence rates decreased from 95.5% during the first 4 months after discharge to 74.2% at 2 years.<sup>30</sup> Persistence rates for warfarin showed even further decline from 89.1% to 45.0%. All of these can have limitations of methodology which compare outcome rates, i.e., unmeasured confounding.

Pharmacy claims data have shown that patients with high adherence (medication possession ratio of 80–100%) to antihypertensive medications were 45% more likely to achieve blood pressure control compared to those with medium or low adherence.<sup>31</sup> Similarly, a ~3.8 mg/dL reduction in low-density lipoprotein cholesterol was noted with each incremental 25% increase in proportion of days covered for statin medications.<sup>5</sup> Furthermore, a review of over 150,000 patients recently diagnosed with HTN, reported a significant reduction in CVD

events in the group that had ≥80% adherence to antihypertensive medications.<sup>32</sup> The reduction of HF events parallels the results of SPRINT with a > 40% incidence of HF<sup>33</sup>. Fig. 1 illustrates real-world scenarios and illuminates the complexities of CVD nonadherence as well as its consequences.

In 2015, the AHA recognized the role of social determinants of risk and outcomes for CVD with specific recommendations for better research and solutions.<sup>34</sup> Socioeconomic status (SES) cuts across racial/ethnic groups in a complex manner and can include social inequality, isolation, and acculturation. The relationship between racial and social disparities and medication adherence is perhaps best studied in HTN. Although African Americans (AA) have a higher prevalence of HTN, starting at younger age groups, and more CVD complications, they also have the lowest rate of control when compared to non-Hispanic Whites (49.5% vs 53.9%).<sup>35</sup> In fact, the CDC and Centers for Medicare and Medicaid Services (CMS) have identified nonadherence to medical therapy to be the number one factor in HTN control in the Medicare Part D era where accessibility to drugs rose. Overall 26.3% of beneficiaries in Part D were nonadherent with 35.7% observed in AA and by geography in the South.<sup>36</sup>

### Challenges to adherence

The challenges to medication adherence can be sorted into several overlapping categories which will require targeted policy interventions to address. Below is a discussion of these challenges, along with recommended policy solutions (Table 3).

#### Patient-level

Much research has tried to identify patient-level causes of nonadherence. The search for characteristics of the “nonadherent” patient has yielded inconclusive and, at times, contradictory findings. Demographic factors, such as younger age,<sup>37</sup> are associated with poorer adherence, but there are few psychosocial factors that are clearly associated with adherence. The relationship between personality characteristics and adherence is moderate and inconsistent.<sup>38</sup> Similarly, the relationship between patient healthcare beliefs or attitudes and patient adherence is mixed.<sup>39,40</sup> The American College of Preventive Medicine has divided patient level factors into the patient-related dimension and the psychological/behavioral factors as well as factors related to the condition itself and its therapies. Many of these factors intersect. (see Fig. 2).

Regardless of whether particular human characteristics lead to nonadherence, maintaining persistence and adherence to medications requires the individual to remember to consistently administer the medications, sometimes multiple times a day, as well as understand and differentiate the different medications that he/she is taking. To support these processes, the Community Preventive Services Task Force recommends that text messaging be used to improve medication adherence.<sup>41</sup> A meta-analysis of randomized clinical trials using text messaging for reminders of medications in patients with chronic disease found a 17.8% improvement in adherence over the 50% at baseline.<sup>42</sup> For patients having difficulty remembering several medications, fixed combination drugs may be helpful<sup>43</sup> and can simplify drug regimen, and reduce pill burden as well as co-pays.

Though nearly 90% of all medications now prescribed in the U.S. are generic and less expensive,<sup>44</sup> generic prescription drugs made by different manufacturers vary both in color and shape and are not required to have a similar appearance to brand-name drugs. Furthermore, U.S. trademark laws may require generics to vary physically from the original brand drug.<sup>45</sup> Though therapeutically interchangeable, this variation in appearance has been shown to lower patients' adherence<sup>46</sup> as patients may lose confidence in the safety or potency of the generic medication. As noted in a cohort and nested case-control study funded by the Agency of Health Research and Quality using health insurance claims of patients who had suffered an MI and were prescribed the

*Case #1:*

A 67-year-old woman presents to the emergency department from oncology clinic where she experienced symptoms of lightheadedness and dizziness accompanied by a blood pressure of 86/55 during triage. She was recently hospitalized for acute decompensated heart failure attributed to loop diuretic nonadherence which she self-discontinued due to excessive urination. From the emergency department, she is readmitted for a syncope work-up. During the history and physical examination, she reveals she received a new prescription at discharge for torsemide 20mg daily but also resumed her previous diuretic regimen of furosemide 40mg daily.

*Case #2:*

After a recent hospitalization for chest pain and subsequent percutaneous coronary intervention with placement of 2 drug-eluting stents, a 54-year-old man is admitted to the coronary care unit for worsening shortness of breath and chest pain. He is diagnosed with a ST-segment elevated myocardial infarction and is sent for emergent cardiac catheterization where he is found to have an in-stent clot and is subsequently revascularized. During discharge medication reconciliation, he states that he could not fill his initial prescription for ticagrelor due to the high co-payment and financial restraints.

*Case #3:*

During a primary care office visit, the blood pressure of a 79-year-old man is elevated to 166/98 and 162/100 repeated. He is normally controlled on lisinopril 20mg daily (“the pink pill”) and hydrochlorothiazide 25mg daily (“the white pill”) and reports adherence to his regimen. His provider increases his lisinopril to 40mg daily which he immediately starts taking. However a few days later he falls and fractures his hip. His fall is attributed to orthostatic hypotension. At his next office visit he brings his pill bottles and on review his lisinopril was dispensed with a different manufacturer that was yellow in color. He does not recognize this as antihypertensive which caused unintentional nonadherence resulting in dose escalation.

**Fig. 1.** Illustrative cases of nonadherence.



**Table 3**  
Policy recommendations for challenges to medication adherence.

Patient-Level Barriers	Medication Therapy Management (MTM) programs should be standardized and promoted by CMS. Insurers, payers and PBMs should support the use of special dosage and delivery products and innovative packaging methods (e.g., blister packs) to facilitate patients' understanding of and adherence to their drug regimen. Effort should be made to explore ways to increase time for patient/provider communication and trust development. Policies that facilitate efficient, bidirectional and proactive data sharing between the various points of care should be identified and implemented. Improved adherence should be promoted as an outcome metric in payment models. Health plans, providers, and other stakeholders across the care spectrum should have increased latitude to develop and test adherence programs that are cost-effective and tailored to the needs of the populations they serve. A new safe harbor under the Anti-Kickback Statute (AKS) that both explicitly protects adherence programs and incorporates safeguards to prevent fraudulent practices should be implemented.
Cost Barriers	Value-based Insurance Design models that support lowering or eliminating out of pocket costs for consumers for medications that are demonstrated to be "high-value" should be encouraged. FDA should implement mechanisms that encourage the development and use of generics when appropriate and result in lower costs for patients. Further examination of the pharmaceutical distribution chain is required to improve patients' understanding of where costs are being added to the overall cost of their medications. Actionable information regarding out of pocket costs for different medications should be readily available to patients at the point of sale. Gag clauses between pharmacies and pharmacy benefit managers should be prohibited.
System Barriers	States should be encouraged to allow prescriptions to expire 15 months after the date of the original prescription so that any time lag in a patient's scheduling of a follow-up visit does not risk impacting adherence to medication in the interim. Medication synchronization that aligns patient refills to occur on the same day so that the patient only needs to visit the pharmacy once per refill period, should be used to encourage adherence. Patients who intentionally stagger their refill schedules due to financial limitations, should be allowed to opt-out of these programs.
EHR Barriers	Wasteful or duplicative EHR metrics should be removed. Efficient electronic means of communicating the discontinuation of a drug from the EHR to the pharmacy and between providers should be implemented. Current medications should be verified and discontinued medications should be clearly deleted from patients' medication list.

standard group of medications, such as beta- blocker, statin and ACE inhibitor, a total of 29% of patients had changes in pill color, or shape with statins having the greatest number of changes.<sup>47</sup> Changes in the color appearance of the drugs increased non-persistence of therapy by 34% and changes in pill shape by 66%. Providers should warn patients about the change in appearance of generic drugs assuring them that the effects are the same as the brand.

Caregivers are often on the front lines of ensuring and improving medication adherence in the individual(s) they care for, as they play an active role in assessing risk of nonadherence and delivering interventions to optimize adherence.<sup>24</sup> In a qualitative study to discover caregiver and elder perceptions of barriers to medication management, among other factors, caregivers cited large and complex medication regimens and inadequate communication and coordination among healthcare providers, as barriers to adherence.<sup>48</sup>

*Provider-health system level*

There is a growing literature supporting the importance of the interaction between patient characteristics and provider, treatment, and

system level variables in predicting adherence. Patients who prefer an active role in healthcare, such as self-management and engagement in treatment decision-making, show significantly better adherence when matched with providers who promote patient self-management versus when matched with more doctor-centered providers.<sup>49</sup> Patients actively involved in healthcare show better adherence when given control over treatment (e.g., home dialysis vs. center dialysis), whereas patients who prefer a more passive role in healthcare show poorer adherence when given control over treatment.<sup>50</sup>

One area that has received significant attention is the doctor-patient relationship that traditionally has been paternalistic or doctor-centered, rather than patient-centered. For example, higher rates of patient-centered communication, defined as "an approach [to healthcare] that consciously adopts the patient's perspective"<sup>51</sup> by the physician were associated with increased adherence. A meta-analysis of 106 studies indicated that the odds of patient adherence were 2.16 times higher if a physician communicates effectively.<sup>52</sup>

New care models that have attempted to adjust the relationship in hopes of addressing nonadherence and other outcomes have had mixed results. Contrary to findings regarding medication adherence, studies have found no significant association between increased patient-centered care and other health behaviors such as glycemic control among patients with diabetes, increased exercise, or smoking cessation.<sup>53</sup> Interventions aimed at increasing patient-centered care on the part of the provider have failed to produce significant increases in patient adherence.<sup>54</sup>

Handoffs between providers or transitions of care, such as at hospital discharge, can impact medication adherence.<sup>55</sup> Restricted hospital formularies may necessitate changes in medication regimen during hospitalization, which are often not reversed upon discharge. In addition, hospital discharge is often a challenging and confusing experience for patients and the review of medications is often rushed leading to inadequate understanding of medication changes.<sup>56</sup> Clinicians may inadequately review the medications at discharge, or not at all, nor determine if the patient's insurance will cover the recommended drugs and if the patient can obtain the drugs. It is the responsibility of the discharging health care team to assure the appropriate medication list, dosing and availability. Errors at discharge can lead to readmissions<sup>57</sup> and/or worsening disease for patients with chronic diseases, such as HF, who have complex drug regimens.

Discharge summaries, are available less than a third of the time at the first post discharge visit and often omit an accurate list of discharge medications.<sup>58</sup> The reliability of discharge summaries varies by the years of training (PGY) level of author, particularly in academic settings.<sup>59,60</sup> Electronic records available within a system accessible to providers for both inpatient and outpatient summaries can be helpful but should not be relied on exclusively, particularly when the environment of care changes. Tools such as a "living" medication list can be useful in facilitating information sharing across care transitions. Strategies such as engaging the health care team with medication reconciliation and sending the discharge summary directly to the patient's primary care provider have been associated with lower 30-day readmission rates.<sup>61</sup>

In a rapidly changing health care environment, the time spent with patients has been cut short so that discussions about chronic disease and medications are often unacceptably curtailed.<sup>62</sup> Physicians are overtaxed and have insufficient staff support to uncover, assess, and build trusting relationships and improve adherence. Current documentation and regulatory requirements along with overly burdensome EHR design, supplants quality time with a patient. Engaging patients may help close the gap between what the provider assumes the patient is taking and reality.<sup>63</sup> Improved medication adherence in the U.S. largely depends on how well adherence interventions can be integrated into routine care in the daily practice of medicine and facilitated for the provider. Stimulating the needed infrastructures necessary to achieve this can be driven by payment reform.

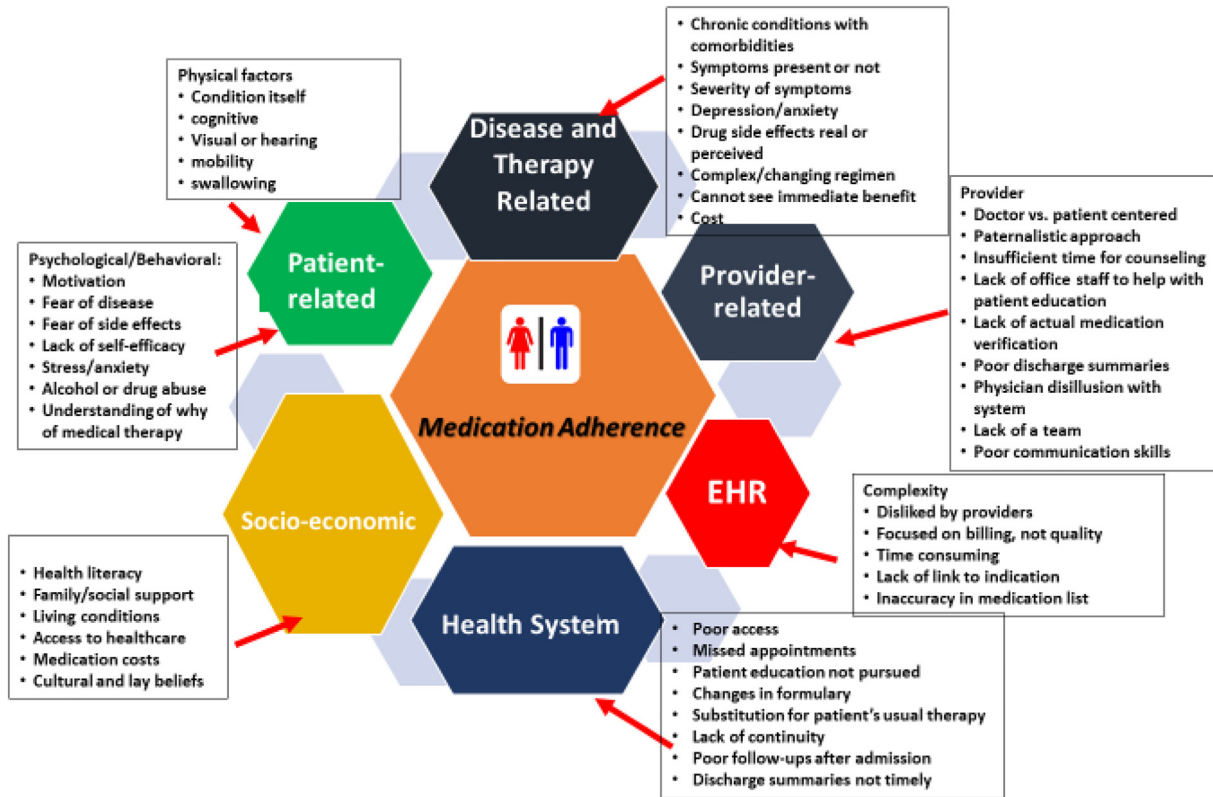


Fig. 2. Central Illustration. The overlapping factors that influence non-adherence. The boxes contain challenges found in each major factor that contribute to non-adherence including the consequences of not addressing the issues clearly and directly.

Early successes are being seen in new payment incentives emanating from CMS that tie reimbursement of Medicare fee-for-service patients to value-based purchasing (VBP) linking performance on quality metrics such as medication adherence to monies received for care. CMS has stated that by 2018, 90% of traditional Medicare payments will be tied to value based purchasing.<sup>64</sup> Early success of CMS VBP model has stimulated the private insurance sector to develop value-based purchasing models as well. Twenty major health systems, payers and employers have pledged to convert 75% of their business to value-based purchasing by 2020 with more predicted to follow suit. Among these are large provider groups such as Partners Healthcare and Atrius Health as well as insurers such as Aetna.<sup>65</sup>

Heavily weighting adherence measures in VBP models can be the impetus for systems and providers to develop the infrastructures needed to achieve better adherence in their specific patient populations. The Medicare program has already recognized this in its Medicare Advantage Star Program where medication adherence metrics represent either directly or indirectly almost half (22/48) of the quality metrics.<sup>66</sup> Medicare has gone one step further and requires the availability of medication therapy management (MTM) programs in Medicare Part D Programs. At least one study has shown substantial improvements in medication adherence and the quality of prescribing for patients with two or more chronic conditions in Medicare Part D programs.<sup>67</sup>

There is growing evidence that medication management services-including MTM, information sharing using EHR tools, and even health coaching programs targeting chronically ill patients can support adherence, achieve cost-savings, improve health outcomes, and facilitate the shift toward value-based arrangements.<sup>68,69</sup> However, given the increased emphasis on adherence in value-based arrangements, employment of these programs across CMS has not been particularly robust. This is due in part to concerns of violating the Anti-Kickback Statute which prohibits a healthcare provider from offering or receiving anything of value in return for referring a patient for goods or services

reimbursable by a federal healthcare program.<sup>70</sup> Several safe harbors, or anti-kickback exceptions, currently exist to protect other beneficial purchasing arrangements from criminal penalties, however no such provision exists explicitly protecting adherence programs.<sup>68</sup>

#### The challenge of cost

A report from the CDC detailed strategies used by patients to lower medication costs, such as skipping doses, buying medications in another country or using alternate therapy. Specifically, approximately 8% of adults did not take their medicines as written, particularly in the ages of 18–64 and those with incomes below the federal poverty level.<sup>71</sup>

Medication costs or co-payments are inversely associated with adherence though surprisingly less than the impact of patient and provider predictors.<sup>72</sup> When medications are free or co-payments are lowered, evidence demonstrates small improvements in adherence.<sup>73,74</sup> However, the vast majority of physicians do not have knowledge of the financial burden of medications on their patients,<sup>75</sup> and as such, often prescribe more expensive brand-name products<sup>76</sup> despite the availability of well-proven, equally effective and less costly generic drugs. Failure to prescribe generic medications when available has also been inconsistently associated with adherence. In a study of over 300,000 privately-insured adults aged 18 or older, the use of generic drug therapy was variably associated with improved adherence, with small effects.<sup>77</sup> A copayment of \$0 was the strongest and most consistent predictor of adherence. Providers may be convinced that the benefits of a newly approved branded drug outstrip the generic, or perhaps order a newer drug based at the patient's request after reading about the latest therapy in public information and advertising.<sup>78</sup>

The impact of cost on adherence also seems to interact with other patient factors. Even in systems with universal access to health care including medications, social disparities still affect medication adherence.<sup>79</sup> Among a sample of older adults with diabetes,

nonadherence was significantly associated with out-of-pocket costs, but this association was moderated by age and gender.<sup>80</sup> Specifically, the impact of cost on nonadherence was highest among younger patients and female patients. Similarly, in those who reported lower levels of trust in their provider, medication costs significantly predicted poorer treatment adherence. However, among patients who reported greater trust in their provider, the relationship between costs and adherence was nonsignificant.<sup>81</sup>

Recognizing that the treatments and drugs differ in clinical benefit, and the clinical benefit of a treatment or medication is largely dependent on patient-level factors, momentum for value-based insurance designs that align patients' out-of-pocket costs with value is growing among public and private payers.<sup>82</sup> An increasing body of evidence demonstrates that clinically nuanced copayment reductions may not only improve adherence but potentially achieve long-term cost-savings for health systems.<sup>83–85</sup>

### System barriers

Current healthcare systems may impede a patient's ability to adhere to their drug regimen. Synchronizing medication refills by renewing all medications at the same pharmacy at the same time has been shown to improve adherence<sup>86</sup> while infrequent refill consolidation is associated with poorer medication adherence.<sup>87</sup> It should be recognized, however, that some patients may be unable to afford the copay of multiple drugs at once and may need to have all the meds on cycles<sup>88</sup> or pursue alternative methods of payment, such as payment schedules. Medication synchronization programs can provide better insight into challenges, such as costs of multiple drugs, that patients face when managing their treatments, facilitating opportunities for pharmacists to cost compare, and possibly substitute for more affordable treatment options, when appropriate.<sup>89</sup>

Similarly, prescription renewal is used to encourage patients to come into the office for a provider visit rather than using prescription renewal.<sup>90</sup> Instead, an extended 15-month prescription interval allows flexibility for the patient and physician as the practicality of seeing the patient on the exact same date 365 days later is unlikely.<sup>91</sup> In the era of increasing telehealth approaches, renewal to encourage office appointments will need a serious re-examination.

### Electronic health record

Though e-prescribing has simplified initiating and refilling medicines, the process of communicating the discontinuation of a medicine or dose of a medicine to the pharmacist is not always seamless and can lead to medication errors and patient safety concerns. In a study of the most commonly prescribed medications in the outpatient setting, pharmacists continued to dispense discontinued medication for 1.5% of patients.<sup>92</sup> Many providers, who clearly and appropriately take action to discontinue a medicine in the EHR, may incorrectly assume that the pharmacy is notified of their orders automatically. Further adding to patient confusions, EHR systems may automatically add instructions that are not appropriate to the particular medication or situation.

As diagnosis precedes prescribing, systematically presenting best therapeutic choices via EHR systems would ease clinician burden and streamline the process. Implementing indication based prescribing will potentially improve safety, assist physicians in prescribing and enhance team communication.<sup>93</sup> Incorporating indications into the prescription order improves patient education which supports adherence. Although intuitive and simple, it will require communication among the care team. In addition, providing the patient with educational materials about their disease and treatments can support the patient's understanding of therapies.

### Digital health and device methods to improve adherence

As medicine moves more toward remote monitoring and reporting, several modalities of telemedicine have been explored in the adherence field. Modalities can include text-messaging, apps, wearable and implanted devices. However, some of these modalities are driven by the market and may not have the approval of the Food and Drug Administration for reliability and actionable alerts to change outcomes. A review of these options by Khan and colleagues from John Hopkins found some bright spots<sup>94</sup> but early success does not equal sustainability and in general, there are limited data to adopt existing modalities. Some include smart phone applications that can be linked to another health goal, e.g. blood pressure control. Morawski and colleagues randomized 411 patients with difficult to control blood pressure to either a smartphone app or control. Although those that were randomized to the app had a small improvement in self-reported adherence, there was no change in blood pressure levels when compared to controls.<sup>95</sup> In the era of extensive use of smartphones, it should compel the community of researchers to explore and produce well-constructed trials. A pilot study of an app using video-chatting as a social motivator to encourage adherence was tested on a small group of patients in a lipid clinic.<sup>96</sup> With a web-based physician calendar to view patient adherence, the web was well-accepted by both patients and providers. The AHA has encouraged expansion of media health and well-done studies in its scientific statement on the current science of mobile health in 2015<sup>97</sup> and more recently in funding a number of focused research networks on digital health technologies and trials. Only with a well described, scientifically sound structure, statistical analysis, results and implementation, will the field truly move forward. Below are suggestions for standardizing studies on adherence using set definitions and approaches that will allow interpretation of interventions.

### Research gaps and future research needs

Much of the confusion and uncertainty of interventions to improve adherence have arisen from lack of uniform definitions, types of interventions and how to assess results. In 2011, the Network for Excellence in Health Innovation, a health policy organization focused on enabling innovation, created a *Patient Medication Adherence Roadmap*, defining the multiple touchpoints and associated processes that will need to be addressed to achieve a comprehensive and cohesive medication adherence strategy in healthcare delivery settings.

#### Recommendations:

- a) Health information technologies including electronic medical records, e-prescribing, health information exchange, reminder technologies;
- b) Care coordination models including provider, hospital and pharmacy practice models that actively manage drug therapy identifying, preventing and resolving medication-related problems;
- c) Manufacturer sponsored payment innovation initiatives;
- d) Quality improvement standards and measures of medication use and management for provider, hospital and pharmacy practices;
- e) Patient engagement tools and interventions including incentives offered through benefit design as well as services focused on patient education, activation and motivation;
- f) Medication product innovations by manufacturers; and
- g) Research to identify best practices especially practices that can be scaled up within an increasingly complex health care practices and delivery systems.<sup>98</sup>

In 2018, the European Society for Patient Adherence, Compliance and Persistence<sup>99</sup> (ESPACOMP) developed the EMERGE medication adherence guideline in an attempt to standardize research related to medication adherence. EMERGE was derived from experts in multiple countries reaching consensus, thus, using 4 criteria to be specified for



**Table 4**  
Research recommendations.

1. Which adherence measure or which combination of measures has the broadest impact across patient groups, health conditions?
2. What is the direct impact of improved medication and adherence in specific patient populations or healthcare conditions on actual healthcare outcomes and costs they experience?
3. Does adherence to medications for multiple medical conditions differ from adherence if only one medical condition is present? If yes what additional tools, resources needed?
4. Are there patient subgroups for whom spending on adherence interventions yields more benefit in terms of reducing future healthcare costs than other patient subgroups?
5. What provider-patient communication strategies most impact medication adherence in a positive direction?
6. To what degree does payment reform and incentives impact medication adherence rates?
7. Which adherence measure or which combination of measures has the broadest impact across patient groups, health conditions?
8. What is the direct impact of improved medication and adherence in specific patient populations or healthcare conditions on actual healthcare outcomes and costs they experience?

each phase of medication adherence, (initiation, implementation and persistence):

1. precise definition of each examined phase;
2. methods used for measurement of each phase;
3. measure performance; and.
4. the results of the analysis pertinent to each phase.

Understanding the appropriate infrastructures and interventions will be paramount to success in achieving improved medication adherence by patients yet significant gaps currently exist in medication adherence research database making evidence-based selection of programs and interventions difficult.

The creation of an internationally accepted operational definition for medication adherence research, such as EMERGE that allows for comparative analysis of different interventions is a critical area that needs to be addressed. The heterogeneity of definitions and adherence measures that currently exists has severely limited comparison of studies and their adherence rates to date.<sup>100</sup> A taxonomy guiding medication adherence research would significantly overcome this flaw, improving the overall quality of this type of research.

Additional concerns voiced by reviewers are that study designs have been relatively small, of short duration even though adherence in chronic conditions may be lifelong limiting ability to evaluate true effectiveness for a population of patients over time. Little information has been forthcoming as to how study designs were operationalized, severely limiting their ability to be replicated in other settings and with other populations. A large number of studies used a multi-component interventional design compared to a usual care arm,<sup>101</sup> yet only a limited number actually went on to examine the actual contribution each intervention had on the outcome achieved. Isolating the contribution of each component in future study designs will be important. Critical areas for future researchers studying medication adherence to address are shown in Table 4.<sup>102</sup>

## Conclusion

Adherence to medical therapy is complex and involves multiple and overlapping parameters and levels of interaction. Each patient may have a complex set of health beliefs, socio-economic difficulties, memory loss, and depression. In parallel, providers are as complex as the patients they care for and only by first recognizing the presence of nonadherence in a nonjudgmental way, will patients and providers together discover specific solutions supported by appropriate policy and systems change.

## Declaration of competing interest

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