

Non-adherence in type 2 diabetes: practical considerations for interpreting the literature

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Abstract: The rising prevalence of type 2 diabetes poses a serious threat to human health and the viability of many health care systems around the world. Although several prescription medications can play a vital role in controlling symptoms and preventing complications, non-adherence to these therapies is highly prevalent and has been linked to increases in morbidity, mortality, and health care costs. Although a vast array of significant adherence predictors has been identified, the ability to explain or predict non-adherence with known risk-factors remains poor. Further, the definitions, outcomes, and various measures used in the non-adherence literature can be misleading for the unfamiliar reviewer. In this narrative review, a practical overview of important considerations for interpreting adherence endpoints and measures is discussed. Also, an organizational framework is proposed to consider published adherence interventions. This framework may allow for a unique appreciation into areas of limited knowledge and thus highlights targets for future research.

Keywords: medication adherence, compliance, type 2 diabetes, adherence interventions

Introduction

Type 2 diabetes mellitus is a metabolic disorder associated with elevations in blood glucose as well as other important risk factors such as blood pressure, cholesterol, and coagulation.¹ The prevalence of this condition is high and it continues to climb, as a result of an aging population and rising obesity rates across the world.² In fact, it is predicted that the global prevalence of diabetes will increase by 65% over the next 20 years.²

Rising prevalence rates are a major concern for governments and health-insurance providers because patients with type 2 diabetes suffer from multiple comorbid conditions in far greater numbers than those without. Fortunately, outpatient management with several readily available medications such as glucose-lowering, cholesterol-lowering, and blood-pressure-lowering medications can significantly lower the risks for macrovascular and/or microvascular complications.¹ As a result, these medications are recommended for concurrent use by typical patients, especially those with increasing age or multiple risk factors.¹

Unfortunately, the requirement for multiple chronic medications is almost inextricably linked to problems with medication adherence. Indeed, among people with type 2 diabetes, the prevalence of non-adherence is high³⁻⁵ and appears to be an important cause of increased morbidity and mortality.⁶⁻¹¹ Moreover, when all non-adherence related hospitalizations were identified in four US hospitals, diabetes was the second leading cause behind mental health conditions.¹² Considering the

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consequences of non-adherence have been estimated at \$100 billion per year in the United States alone,¹³ it would appear that non-adherence in diabetes is an extremely costly problem. It has been estimated that increases in medication adherence of only 20% could reduce total health care spending by \$1074 for every person with diabetes.¹¹ Unfortunately, it remains unclear whether adherence interventions can consistently improve adherence rates by this magnitude. Thus, the cost-effectiveness of adherence-enhancing interventions remains unknown.¹⁴

Definition of non-adherence

Over the years, several alternative terms have been proposed to describe medication non-adherence such as concordance, compliance, obedience, observance, conformity, acceptance, and persistence.^{15–17} The World Health Organization (WHO) defined adherence as “the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.”¹⁸ However, we believe medication adherence should be described simply as the extent to which individuals take medications that have known health benefits. This proposed definition avoids any reference to the origins of non-adherence and specifically represents the public health epidemic resulting from an underuse of potentially life-saving medications. In contrast, the WHO definition specifies a particular problem relating to an agreement between patient and provider when most studies are not able to determine whether such an agreement has ever occurred.³ As such, non-adherence needs to be identified and addressed in its entirety, without prior assumptions relating to cause or culprit.

Non-adherence rates require careful interpretation

The first year after starting a chronic medication poses the highest-risk for medication non-adherence for all types of chronic diseases. On average, 50% of new medication users will fail to consume at least 80% of prescribed doses during their first year of therapy.^{13,18,19} Rates of non-adherence to anti-diabetic therapies appear to follow this general observation quite closely. However, research papers often cite wide-ranging estimates. A systematic review of anti-diabetic therapies found adherence rates between 36% to 93%.³

Several factors contribute to the wide variability in adherence rates observed in published studies. First, studies restricted to individuals starting new medications will almost always find lower adherence rates compared to studies

where “experienced” users are included. This observation results from a consistently high rate of attrition observed in the first few months after starting any new medication.^{20,21} Second, adherence rates expressed as percentages can vary substantially depending on whether they are categorical percentages (ie, percent of a population achieving $\geq 80\%$ adherence) or are mean percentages (mean percent adherence achieved in a population). When both measures are calculated on the same set of adherence data, categorical percentages will always be lower than mean percentages. For example, suppose a mean adherence rate of 70% is measured among a sample of medication users. It can be reasoned that approximately half of these individuals will have achieved an adherence level of 70% or higher (assuming the data is near-normally distributed). If only half of the subjects achieved 70% adherence, even fewer will have achieved 80% adherence (which is the conventional definition of categorical adherence).^{6,22} Thus, in our hypothetical cohort, adherence could be reported as a mean of 70% or a categorical percentage of $<50\%$ (eg, 45%), where both percentages accurately represent the exact same adherence level. Unfortunately, the specific type of adherence measure is not always clearly identified; thus, readers should be careful to avoid using these rates interchangeably.

Another important source of variability in reported adherence rates results from the many different methods of assessment. Quantitative measures are often derived from electronic refill records, electronic pill bottle monitors, self-reported visual analog scales, or manual pill counts. Alternatively, a number of different qualitative measures are also available. For example, non-adherence was defined as at least one positive response to any of the four item Morisky questions in a recent study by Lewis et al: (1) “Have you ever forgotten to take your blood pressure (BP) medicine?” (2) “Are you sometimes careless in regards to your medicine?” (3) “Do you skip your medicine when you are feeling well?” (4) “When you feel badly due to the medicine, do you skip it?”^{23,24} In another study investigating the validity of items in an adherence questionnaire, non-adherence was defined simply as self-reporting a missed dose in the previous week.²⁵

Reconciling the different measures and reported rates can be difficult because self-reported and quantitative adherence measures are not highly correlated²⁶ and no single gold-standard approach is available. Self-reported measures are more easily implemented in clinical settings (ie, doctors’ offices),²⁷ but validity may be affected by social desirability bias in some individuals.²⁸ In contrast, electronic

refill records allow for efficient assessments of large study populations; however, the act of taking medications is not directly assessed by medication refills. Clearly, the type of adherence measure as well as the specific summary statistic used (mean versus categorical) can substantially contribute to variability in published adherence rates. Therefore, readers must take special care to evaluate these issues, especially in cases where adherence findings are unexpectedly high or low in any specific study.

Patterns of non-adherence

Non-adherence in the first year appears to be consistently driven by three unique patterns of medication use: (a) primary non-adherence, (b) non-persistence, and (c) noncompliance or poor execution.^{21,29} Primary non-adherence refers to patients who receive a prescription but never actually obtain the medication. Rates of primary non-adherence for anti-diabetic therapies have been reported between 4% and 31%, even though troublesome symptoms would be expected for individuals who do not receive glucose-lowering medications.^{4,5,30}

Non-persistence and poor execution are patterns of non-adherence that are demonstrated by patients who actually begin taking their medications. Those exhibiting non-persistence stop taking their medication altogether, whereas poor executors continue taking prescribed medications but fail to consume the recommended quantity on a regular basis.³¹ Recent studies suggest that “early non-persistence,” where individuals discontinue a medication soon after obtaining the first prescription, contributes disproportionately to overall non-adherence in the first year of therapy.^{5,21,32} For example, individuals who discontinue antihypertensive or statin medications within the first 3 months of therapy make up between 30% and 50% of all cases of non-adherence in the first year.^{21,32} Moreover, many of these individuals appear to quit after receiving the very first dispensation as evidenced by no further fills during a full year of follow up.^{21,32} These are important observations because both antihypertensives and statins have clear benefits in reducing major cardiovascular events in patients with type 2 diabetes.¹

Understanding the various patterns of non-adherence is also important because widely acknowledged non-adherence factors such as forgetfulness or complexity may not be applicable to a high proportion of non-adherent patients who discontinue soon after the very first dispensation or for those who neglect to start taking a medication altogether.^{4,33,34} Correspondingly, certain adherence support strategies such as reminders³⁵ or dosing organizers³⁶ may be irrelevant for

these patients. Interestingly, a significant body of research has been directed towards the barriers associated with initiation of insulin therapy in type 2 diabetics.^{37,38} Considering the high rates of primary non-adherence and early non-persistence observed with all glucose-lowering medications, perhaps greater preparation is required for patients starting any type of anti-diabetic therapy, not just insulin.

Predictors of non-adherence

Well recognized paradigms are available to help understand the vast array of possible barriers to achieving good adherence (Table 1).^{13,18,39,40} Meichenbaum and Turk⁴⁰ organized determinants of non-adherence into the following categories: (a) characteristics of the patient; (b) characteristics of the treatment regimen; (c) features of the disease; (d) prescriber-level factors (including patient-physician relationship); and (e) the clinical setting. All evidence suggests the determinants of non-adherence in type-2 diabetics are consistent with other chronic conditions, although some may argue that insulin use is associated with unique barriers because of its requirement for subcutaneous injection.^{37,38} Paradigms such as the one outlined above highlight the importance of external factors that shape a patient’s interpretation of the appropriateness of any medication. In addition, the contribution of unwitting non-adherence cannot be overlooked as an important cause of non-adherence.⁴¹ Although unwitting non-adherence is often attributed to forgetfulness, it is highly likely that a substantial portion of non-persistent individuals simply do not understand their medications are supposed to be taken long-term.

Non-adherence is not considered to be a result of baseline personality type.⁴⁰ Rather, models of health behavior¹⁸ and adherence behavior⁴⁰ support the notion that non-adherence is often a result of external influences rather than baseline preferences.^{40,42} Although compelling anecdotes and personal experiences with “disobedient patients” are powerful influences to practicing health care professionals, these types of patients probably contribute only a small part to the overall problem of medication non-adherence.⁴⁰ As a result, individual patient factors are known to contribute minimally (if at all) to the overall occurrence of non-adherence observed in population-based studies.^{42,43}

The fact that currently known adherence predictors are only weakly associated with the development of non-adherence might be surprising considering the vast number of research articles published in this area. One possible explanation for the lack of clarity around adherence predictors arises from conventional approaches used to report their associations.

Table 1 Theoretical frameworks of non-adherence

World Health Organization ¹⁸	Osterberg and Blaschke ¹³	Balkrishnan ³⁹	Meichenbaum and Turk ⁴⁰
Patient factors	Patient factors	Demographic variables	Patient factors
Social/economic factors		Patient's health-related knowledge and beliefs	
		Economic variables	
Condition related factors		Medical variables	Disease factors
Therapy related factors		Medication related variables	Treatment factors
Provider behaviors	Provider factors	Physician-patient interaction	Relationship to providers
Health care system factors	Health care system factors		Clinic organization

Specifically, many studies use odds ratios to represent the “risk” associated with adherence predictors; however, this measure can be misleading if it is considered equivalent to a relative-risk. To illustrate the difference, consider a retrospective study of subjects with heart failure where older age (ie, ≥ 65 years) was a significant negative predictor of optimal adherence to beta-blockers.⁴⁴ The percentage of older patients achieving optimal adherence was 66% (764/1165) while the corresponding percentage among those < 65 years was 71% (177/249). Using a relative-risk calculation, the effect of old age can be expressed as 0.93 (66%/71%), corresponding to a 7% reduction in the occurrence of optimal adherence. In contrast, the same unadjusted effect expressed as an odds ratio equals 0.78 (1.90/2.46), or a 22% reduction in the “odds” of optimal adherence. This example highlights a well-known limitation of odds ratios, namely they are a poor reflection of the relative risk when highly prevalent outcomes are examined.⁴⁵ It should be recognized that non-adherence is a highly prevalent outcome in the vast majority of published studies (often between 40% to 60%). As a result, the effect of any adherence predictor will almost always be overestimated if the odds ratio is interpreted as a relative-risk.

Not only are individual factors weakly predictive on their own, multivariable models do not predict or explain more than a fraction of the massive burden of non-adherence observed in population studies.^{42,43} For example, Wong et al could explain less than 4% of all cases of non-adherence (measured from prescription refill databases) using available patient-level and clinic-level factors from administrative data sources among 444,418 patients with diabetes registered in the National Veterans Affairs database in the US.⁴³ However, one of the major limitations to these population-based studies is the inability to capture patient-specific factors such as attitudes, beliefs, and knowledge. In addition, it is possible that more eloquent representation of prescriber factors may help contribute to our understanding of the non-adherence phenomenon.

Factors relating to the prescriber cannot be overlooked as important determinants of non-adherence.^{33,42,46–51} Prescribers may influence adherence through simplifying dosing regimens or consolidating refills to keep patients organized.⁵² Also, certain prescribers might provide greater education and preparation prior to prescribing a new chronic medication.⁵¹ However, the specific nature of the association between prescriber and non-adherence has yet to be fully elucidated. Also, the extent to which these factors can be harnessed to optimize adherence remains unknown. Although prescriber-relation might substantially influence adherence, we believe that front-line physicians are largely unaware of their potential influence in this area.⁵³

Published adherence interventions

The literature describes numerous strategies for addressing non-adherence in patients with type 2 diabetes as well as many other chronic conditions. However, no single or combined strategy has resulted in more than small to modest benefits in rigorous trials.^{14,54–60} Additionally, for every published successful intervention, it is often possible to identify one failed approach where very similar strategies were employed. This observation is very important to recognize because the literature is full of recommendations from well-respected organizations suggesting multifactorial,^{13,61} multidisciplinary,⁶² and patient-focused strategies.^{18,63} Although these recommendations have been developed by recognized experts making logical interpretations of available data, many of the published interventions are of poor quality and none have followed diabetic patients prospectively to determine if health outcomes are ultimately improved.^{14,64} In reality, much more research is needed before reliable adherence strategies can be recommended with a high level of certainty and generalizability.

It may be useful to organize adherence interventions by the source of the intervention (allied health care professional,

prescriber, peer, institution/health system, or message-based), the target of the intervention (allied health care professional, prescriber, patient, or institution/health system), or by the nature of the strategy (motivational/behavioral, cost, reminders, etc) (Figure 1). Using this framework, two important observations can be made about published adherence interventions in diabetes. First, allied health care professionals deliver the vast majority of published adherence interventions whereas prescriber-delivered interventions are infrequently attempted.^{14,60} For example, in a systematic review of adherence interventions targeting type 2 diabetics, none of the 21 eligible studies was delivered by prescribers.¹⁴ Second, adherence interventions overwhelmingly target patients directly,^{14,60,63,65} whereas few interventions focus on prescribers⁶⁶ despite a significant body of research suggesting they play an important role.^{33,42,46–51}

The strategies used to support medication adherence vary widely from reminder-based systems like text messaging to complex behavioral and chronic disease management approaches. Reminder type strategies such as text messaging have not consistently improved adherence or clinical markers such as hemoglobin A_{1c}.^{54,55,67} Similarly, complex, multifactorial interventions have not been consistently positive either.^{56,68} Among studies that have been successful, only modest benefits are typically observed and adherence improvements are frequently lost following completion of the study intervention.^{14,58}

Interestingly, non-adherence cannot be prevented even if patient drug costs are completely eliminated. Choudhry et al examined the influence of eliminating drug costs for individuals discharged from the hospital.⁶⁹ Although the study was not aimed at type 2 diabetics per se, the study population was made up of post-myocardial infarction patients where 35% (2023/5855) had diabetes at baseline. Surprisingly, full-coverage for statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers resulted in very little improvement

to average adherence (38.9% to 43.9%) over a median of 394 days. However, the occurrence of vascular events was significantly reduced by this intervention (hazard ratio for total major vascular events or revascularization = 0.89; 95% confidence interval 0.90–0.99; $P = 0.03$). These findings reinforce two major lessons regarding adherence interventions. First, medication adherence has many possible determinants⁴⁰ so eliminating a single barrier, even something as important as cost,⁷⁰ will not solve the problem. Second, small improvements to multiple medications may have substantial reductions in morbidity associated with chronic diseases.

Where do we go from here?

It has been clearly shown that none of our current strategies are very effective at reducing the occurrence of medication non-adherence. However, the intervention framework proposed herein outlines many areas for future research that have not been explored. For instance, it is not known if the success of a specific adherence intervention will vary depending on the person who delivers it. We could find only one prospectively designed intervention delivered directly by physicians.⁶⁶ In this case, adherence was extremely high in both intervention and control groups, making it difficult to assess the performance of this strategy. In virtually all other studies, follow-up visits to improve adherence are carried out by allied health care professionals, often with little coordination to the actual prescribing physician. In addition, prescribers could be targets of adherence interventions whereby aggregate statistics of adherence could be regularly fed back to physicians for the purposes of monitoring overall success and following trends over time.

While we await future discoveries in this area of research, currently proposed recommendations by key organizations represent our best knowledge^{13,18,62,63} and attempts should be made to raise awareness about medication non-adherence in all health care settings and empathize with the struggles of

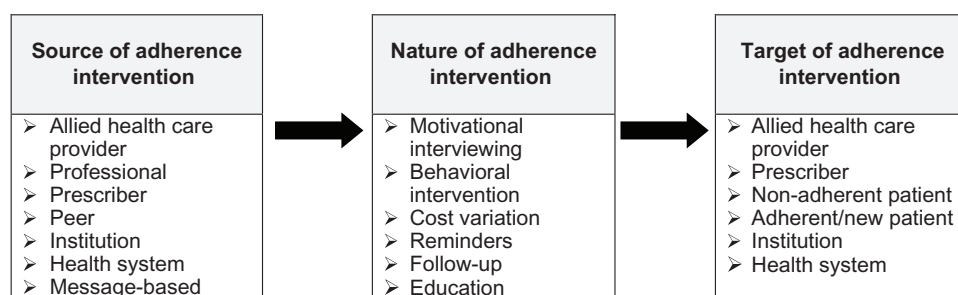


Figure 1 Proposed framework to classify adherence interventions.

diabetic patients to embrace prescription medications as part of their daily lives.

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