Chapter 14
Medication Adherence in Primary Care

Andrew M. Peterson

14.1 Introduction

Medication adherence is "the extent to which patients take medications as prescribed by their health care providers" (Osterberg & Blaschke, 2005). There continues to be a high concern over patients' ability to comply with a prescribed medication regimen. It is well documented that 20–30% of prescriptions are never filled and of those that are filled, only about 50% of medications used for chronic conditions are taken as prescribed (Peterson et al., 2003; Osterberg & Blaschke, 2005; Viswanathan et al., 2012). Further, this lack of adherence spans age, gender, and ethnic demographics and constitutes a health problem in and of itself. Therefore, it is imperative that practitioners working with patients understand and support the factors which contribute to good medication adherence and strive to overcome barriers which prevent it (Choudhry et al., 2008; Osterberg & Blaschke, 2005).

14.2 Definition/Diagnostic Criteria

There are two terms used to describe the phenomenon of people not taking their medication as prescribed: medication compliance and medication adherence. Various organizations and professions have put forth different yet similar definitions of these terms. The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) defines medication compliance as "the extent to which a patient

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acts in accordance with the prescribed interval and dose of and dosing regime" (Cramer et al., 2008, p. 46). The World Health Organization (WHO) defines adherence as "the extent to which a person's behavior – taking medications, following diets, or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (Sabaté, 2003, p. 17). While the two terms – medication adherence and medication compliance – are similar and often used interchangeably, currently the use of adherence is more commonly employed because it implies a mutual agreement between the healthcare practitioner and the patient versus the superior/subordinate relationship implied by the term compliance.

Several factors contribute to the phenomenon of medication nonadherence including patient-related, treatment-related, and relationship-related factors. The patient-related factors include medication and disease knowledge, the patient's socioeconomic status, demographics, and their living situation. Those factors related to treatment include the medication effects, dosage form/route of administration, and dosage frequency. Lastly, the relationship factors include the patient-provider relations, the provider's communication style, and the information exchanged between the patient and the provider (Table 14.1).

Like the multitude of factors affecting adherence, there are several types of medication adherence. Vrijens and colleagues describe three major phases of medication adherence – initiation, implementation, and discontinuation (Fig. 14.1). These phases of adherence begin when the patient takes the first dose of medication and ends when the patient stops taking the medication. Prior to initiation is another phase of adherence – initial medication adherence or primary adherence. This is related to a patient's willingness and ability to obtain the medication in the first place.

Medication adherence can be seen as a fault in one of the three processes: initiation, implementation, and discontinuation (Vrijens et al., 2012). Individuals can be nonadherent in the (1) failure to present an initial prescription for filling or taking it once retrieved (initial nonadherence), (2) failure to take first dose of medication (initiation), (3) failure to follow medication instructions (implementation), and (4) failure to refill medications used for chronic conditions (discontinuation). Patients who do not initially fill their medication do so because of various factors, including

Table 14.1 General factors affecting medication adherence

Category	Factors
Patient-related	Knowledge of the medication Knowledge of the disease state Socioeconomic status Patient abilities/patient support system Patient demographics
Treatment-related	Disease characteristics Medication effects Medication dosing frequency/medication route administration/dosage form
Relationship-related	Provider-patient communication Educational support

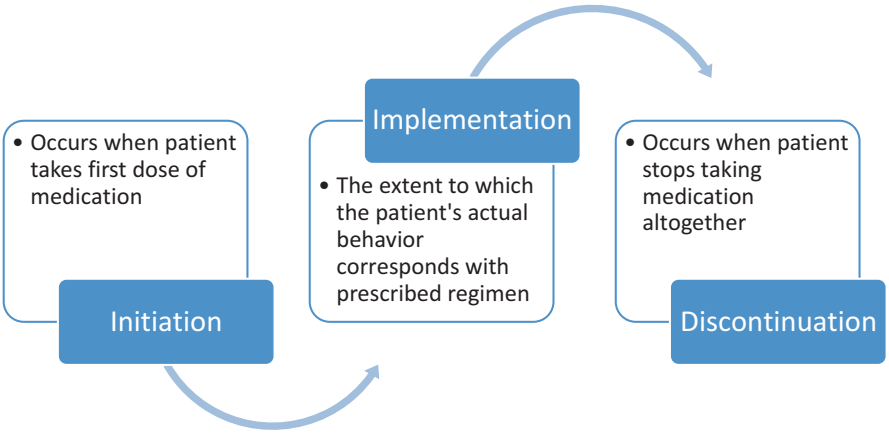

Fig. 14.1 Phases of medication adherence

due to their perception of the efficacy, safety, and cost of the medication and possibly their inability to access a pharmacy (Lehman et al., 2014; Pednekar & Peterson, 2018). For all the types of nonadherence, multiple theories exist to explain the cause and the complexity of this phenomenon.

14.2.1 Initial Medication Adherence

The first step in medication adherence is obtaining the medication in the first place. Initial adherence must occur before the three other phases of adherence occur (Hutchings et al., 2015). This includes taking the prescription to the pharmacy and retrieving the filled prescription. When patients fail to obtain a medication in an acceptable period of time, it is deemed initial nonadherence or primary medication nonadherence (PMN) (Adams & Stolpe, 2016).

Patients who fail to present the prescription for the initial fill do so either intentionally or unintentionally. The intentional failure to present may be due to health beliefs regarding the medication, fear of the side effects, or even perception of cost or lack of insurance.

Unintentional failure is usually forgetfulness or, at times, loss of the paper prescription. In either case, current technology known as electronic prescribing minimizes the failure to present as the prescription is sent directly to the patient's pharmacy electronically from the prescriber's office (Gleason et al., 2009). This leads to the second component of initial medication adherence – abandonment. Abandonment is when a prescription is filled by a pharmacist, but the patient does not pick it up, and it must be returned to stock. The primary reason for patients abandoning their prescription at the pharmacy is because it cost more than they expected and they are either unwilling or unable to pay for it. (Shrank et al., 2010)

14.2.2 Initiation

According to Vrijens, "(i)nitiation occurs when the patient takes the first dose of a prescribed medication" (Vrijens et al., 2012). There are a multitude of patient, provider, and system variables which influence the initiation of treatment.

Patients' perceptions of the efficacy, safety, and value of the drug are primary drivers of patient treatment initiation. Evidence has shown that patients who have a good understanding of the reason for the medication in their treatment and believe that the medication will work have a higher likelihood of initiating the medication therapy (Fischer et al., 2014).

The providers – those involved in the prescribing, dispensing, and administration of medications to patients – play a key role in aiding the patient's ability and willingness to take a medication. These providers can offer education and counseling on the need for the medication and how it will impact their care. Further, these providers can offer insight into what side effects to expect and how to manage them and answer questions regarding drug-drug interactions or just address patients' concerns in general. This type of communication aids in improving a patient's belief about the value of their medication in treating their disease as well as providing the level of support that making a decision to start the medication is the right one. So, good communication between the provider and the patient at the time of prescribing, along with patient counseling by the pharmacist, improves the likelihood that patients will take the medication the first time (Fischer et al., 2014).

System factors that influence the initiation, and ultimately the implementation of medication treatment, range anywhere from insurance coverage and medication cost to ease of use of the product. Patients with poor or no insurance coverage are likely not to even obtain the medication to begin with, or if there are significant hurdles to overcome (prior-authorization approvals, step therapy), the patient may feel discouraged and wonder about the value of the medication (Gleason et al., 2009).

14.2.3 Implementation

As noted earlier, with a typical PMN rate of 20–30%, that leaves 70–80% of medications in the possession of patients to be taken as prescribed. When patients have filled a prescription but do not take a medication as scheduled, Vrijens considers this a failure of implementation. This implementation failure could be due to forgetfulness, intentional dose-skipping, or delays in refilling prescriptions. The clinical consequences of implementation failure are a function of the both the disease and the drug. For example, patients taking highly active antiretroviral therapy (HAART) for HIV disease had 63% virologic failure when 80–90% compliant and only 21% failure when >95% compliant (Paterson et al., 2000). In contrast, some drugs such as aspirin are more forgiving. Due to its irreversible binding to platelet when used to prevent clotting, lack of compliance with aspirin is less troublesome because the drug activity in the body outlasts the dosing interval (Albassam & Hughes, 2021).

Patients in the implementation phase who continue to take their medication, whether as prescribed or not, are considered to be "persistent." The ISPOR defines persistence as "the accumulation of time from initiation to discontinuation of therapy. Measured by time metric" (Cramer et al., 2008).

14.2.4 Discontinuation

When patients stop taking their medication altogether, that is, they are no longer persistent, Vrijens considers them entering the discontinuation phase. Adverse effects were the most commonly cited reason for discontinuation, and others include lack of efficacy, lack of symptoms, and high cost (Gajria et al., 2014; Roborel de Climens et al., 2020).

14.3 Prevalence

Medication nonadherence knows no boundaries. Patients of any age, socioeconomic status, gender, or ethnicity are likely to be nonadherent to medications. As noted earlier, about 20–30% of prescriptions are never obtained by the patient, and in patients taking medications for chronic conditions, only about 50% adhere to long-term therapy. This lack of adherence results in about 33% to nearly 70% of all medication-related hospital admissions.

14.4 Risk Factors

A myriad of risk factors exist which can help identify patients who are at risk for not adhering to a medication regimen. This ranges from socioeconomic factors specific to a patient, the provider/patient relationship, or disease states and specific therapies which can affect a person's willingness and ability to adhere to a medication regimen.

14.4.1 Patient-Related Factors

14.4.1.1 Knowledge of the Medication and Disease State

Self-efficacy, defined as "a patient's belief in his/her ability to succeed in adhering to prescription medications" (Lee et al., 2013, p. 35), has a positive impact on medication adherence. Lee et al., (2013) used a 13-question, 3-point scale (Self-Efficacy

for Appropriate Medication Use Scale – SEAMS) to measure self-efficacy as part of a broader model for predicting medication adherence. Their results showed that with each unit increase in self-efficacy score, medication adherence increased by 27% in elderly patients (Lee et al., 2013).

Rhee studied adolescents (12–20 years old) with asthma, examining medication adherence and three measures of cognitive awareness: self-efficacy, barrier perception, and outcome perception. Their results show that self-efficacy predicted better asthma medication adherence, in contrast to barrier perceptions which predicted poorer adherence and poorer asthma control. They also found that outcome expectations did not have a relationship to medication adherence or asthma outcome, but self-efficacy independently predicted fewer missed doses (Rhee et al., 2018). It is then reasoned that lack of knowledge about the disease and the reasons medication is needed are important factors but that the concept of self-efficacy is a mediator to medication adherence.

14.4.1.2 Socioeconomic Status

Patients with a good social and family support network willing and able to assist in their healthcare regimens tend to be more adherent (Barcenas et al., 2012). Patients living in an unstable living environment or with limited access to healthcare tend to have worse medication adherence. Further, these situations may be worsened if there is a lack of health insurance or complicated work schedules which prevent people from accessing medications or making time to take medications. Lastly, and not to be overlooked, is the rising cost of medications. Cost of treatment is a major factor. Co-payments decrease medication adherence in an inverse fashion – the higher the co-payment, the lower the adherence (Gast & Mathes, 2019; Gellad, 2007).

14.4.1.3 Patient Demographics

Some research shows that medication adherence decreases with increasing age (Raji et al., 2004) and others do not demonstrate the relationship (Krueger et al., 2015). Age-related nonadherence may be more directly related to factors associated with aging: impaired physical and cognitive functions or the patient's understanding of the effects of nonadherence (Barat et al., 2001). Further, males are less likely to be adherent as compared to females among elderly patients (Jin et al., 2016). Individuals belonging to different races and ethnicities can have different beliefs and attitudes toward health and medications. Studies have shown that Black and Hispanic seniors are less likely to be adherent as compared to White seniors, though this may also be a socioeconomic issue (Gellad et al., 2007).

14.4.1.4 Patient Abilities and Support Systems

While intuitive to most individuals, physical impairment by patients is one of the most overlooked reasons for medication nonadherence. Patients with conditions such as arthritis (Pasma et al., 2013) or fibromyalgia may have difficulty opening medication bottles or manipulating inhalers or syringes. Similarly, visually or cognitively impaired individuals may be unable to read or follow directions on a bottle or even a medication pamphlet. Lack of knowledge about a disease state and the reasoning for a medication also impair a person's willingness to adhere to a treatment regimen.

Physical impairments and cognitive limitations may increase the risk for nonadherence in patients. These impairments may be true limitations or barriers to a patient's adherence, and recognition of them, coupled with specific strategies for overcoming them, can improve adherence. For example, elderly patients with compromised physical dexterity such as decreased muscle strength or deformities associated with conditions such as rheumatoid arthritis can affect their ability to open medication bottles or use an inhaler. Fialová and Onder (2009) found that restrictions in mobility, fine motor skills, and upper body functioning were significant factors associated with difficulty in patients taking medications.

Further, individuals who are blind or visually impaired (due to glaucoma, loss of vision, or poor vision) may have compromised ability to read prescription labels or instructions, determine the color and markings characterizing medications, or see scales on medical devices. Such individuals may rely on their memory or caregiver to take medications or may not take medications at all. Patients with visual impairment were less likely to have good adherence compared to those with no impairment (18.42% vs 53.26%) (Shruthi et al., 2016). Similarly, patients experiencing difficulty in swallowing or dysphagia may discourage patients to take medications, and hence it may negatively impact medication adherence (Kelly et al., 2010).

14.4.2 Treatment Related

14.4.2.1 Disease State

Grenard et al. (2011) conducted a meta-analysis demonstrating that the odds of a patient with depression being nonadherent is 1.76 greater than a person without depression. This effect was seen across patients with various chronic diseases including diabetes and cardiovascular diseases and did not vary significantly across these disease states. This clearly demonstrates that practitioners need to be aware of the increased risk of nonadherence in patients who develop depression while taking other chronic medications (Grenard et al., 2011).

A meta-analysis found that for less serious diseases (e.g., hypertension, arthritis), patients with higher severity of disease are more likely to be adherent than the patients in better health. In contrast, in patients with cancer and HIV, adherence was lower in patients with a higher disease severity versus those in better health (DiMatteo et al., 2007). Similarly, Elsous et al. (2017) showed that patients suffering from the disease for longer time are more likely to be adherent than those patients with shorter duration of disease. The authors postulated that newly diagnosed patients do not understand their disease well enough and that as they learn more about it, their attitude toward the disease and treatment evolves and the interaction between their provider improves (Elsous et al., 2017).

It is often thought that patients with symptomatic diseases (e.g., hypothyroidism, pain) would be more adherent to their medication regimen than patients with asymptomatic diseases. The concept is that the absence of symptoms does not reinforce the notion that the patient has a disease; thus, there is no perceived need to take a medication. Conversely, in those diseases in which symptoms are controlled when taking a medication, adherence is more likely due to the association of symptom resolution when adherent. There are mitigating factors to this, however. Carney et al. (1998) conducted a study demonstrating that patients with symptomatic angina were *less adherent* to twice-daily aspirin than their asymptomatic counterparts. Intuitively, one could see that the patient might consider the aspirin ineffective, thus choosing not to take it.

14.4.2.2 Medication Effects

In a semi-structured interview study of community pharmacy patients, Rathbone et al. (2021) showed patients perceived that if a medication did not have a physical effect (i.e., a side effect or a therapeutic effect), the medication was considered "weak," and the patient was therefore "not motivated to take (it)." Further, the researchers noted that medication adherence had a social component. The participants voiced the notion that it was necessary to take medications as prescribed to avoid social consequences (e.g., from the healthcare providers, peers, family) of nonadherence.

14.4.2.3 Medication Route/Administration/Dosage

Patients suffering from multiple chronic disease conditions are often prescribed multiple medications which make their dosage regimen complex. Both the higher number of medications and the greater complexity of the diseases are significantly associated with lower medication adherence among older adults (Rolnick et al., 2013).

In 2013, Srivastava and colleagues published a meta-analysis demonstrating that medication adherence improves when dosing is reduced to once daily. The overall results indicated that once-daily dosing was associated with patients being three

times more likely to be adherent than more than once-daily regimens. This held across all disease states studied (hypertension, diabetes, depression, HIV/AIDS). Interestingly, this also held true for once-daily vs twice-daily dosing. In general, this study confirmed that adherence rates declined as dosing frequency increased.

14.4.3 Relationship-Related

14.4.3.1 Provider-Patient Communication and Educational Support

The provider-patient relationship has tremendous impact on medication adherence. Relationships that have a higher level of trust (Schoenthaler et al., 2014) provide reinforcement and encouragement and have a more positive impact on adherence (Gu et al., 2017). Similarly, poor communication, particularly as it relates to medication purpose, side effects, and the importance of taking the medication, is associated with lower adherence. Poor or lack of communication concerning the benefits, instructions for use, and side effects of medications can also contribute to nonadherence, especially in older adults with memory problems (Gellad et al., 2011). It is evident that older patients with low levels of education are more likely to be nonadherent to the medications (Jin et al., 2016). It could be possible that more educated people may have more knowledge about the benefits of medication adherence, disease condition, and healthier habits. Further, since Velligan and colleagues' systematic review indicated that negative attitudes toward medications are directly associated with intentional nonadherence (Velligan et al., 2017), perhaps educating the patient on the importance of the medication would improve adherence.

14.5 Effective Screening

There are a number of means by which practitioners can successfully screen patients for medication nonadherence. Commonly used assessment tools include the Rapid Estimate of Adult Literacy in Medicine – Revised (REALM-R) and the Morisky Medication Adherence Scale (MMAS) (Miller, 2016). Together, these tools can be helpful to assess a patient's initial ability to adhere to a medication regimen (*initiation)* then an ongoing screening for their continued adherence (*implementation*).

The REALM-R, a tool that measures health literacy, is an eight-word recognition/pronunciation tool assessing a patient's ability to read medical words (e.g., flu, allergic, jaundice, constipation). Raehl and colleagues (2006) found a positive relationship between seniors' intention to be adherent to their regimen and better scores on the REALM-R when taking into consideration the patient's socioeconomic status, age, and over-the-counter drug use. Patients who score low on this assessment may need additional support to initiate their medication regimen.

Once the patient has initiated their regimen, there are a series of tools that can be used to assess a patient's continued adherence. Two versions of the MMAS exist – a four- and an eight-question validated assessment survey. Both the four- and eight-item scales are equally valid, and both take little time, so either may work. Either of these tools can be used to determine if nonadherence exists and are often used as screening tools in this manner. However, they are not good for identifying the reason for the nonadherence and therefore cannot provide guidance to the clinician how best to proceed (Tan et al., 2014).

14.6 Preventing Medication Nonadherence

Preventing medication nonadherence is a multifactorial process. Providers must first prevent PMN (lack of initial medication adherence) so that the patient can start medication therapy as prescribed. Aside from e-prescribing, there appears to be little that helps to improve PMN – including automated and live phone call reminders (Zeber et al., 2013; Fischer et al., 2014). The strongest association with lack of initial adherence appears to be financial, with out-of-pocket expenses (copays, coinsurances, etc.) showing a negative linear effect (Zeber et al., 2013). That is, as out-of-pocket expenses increase, initial adherence decreases.

Many of the factors affecting initial medication adherence are similar to those affecting implementation. Once the patient initiates medication, it is incumbent on the practitioner to aid in the continuation of the medication regiment. Behavioral interventions – those designed to influence or change a specific behavior – have shown promise (Peterson et al., 2003; Zeber et al., 2013). Specifically, medication pillboxes or blister packs designed to organize medications and make them more readily available have been proven to be effective (Peterson et al., 2003; Ruppar et al., 2015).

Technology has had a positive impact on medication adherence in the initial and implementation phases. For example, electronic prescribing (e-prescribing) has a positive impact on initial medication adherence. A paper by Lanham and colleagues (Lanham et al., 2016) reviewed some of the literature and found a 10% improvement in PMN using e-prescribing versus paper prescriptions. Further, using electronic reminder tools designed to record if a patient took a medication has also shown improved adherence (Checchi et al., 2014).

A study by Choudhry and colleagues (2010) demonstrated that lowering copayments to nearly zero for patients taking statin drugs or clopidogrel had a 2.8% and 3.8% increase in monthly adherence, respectively. While the size of this effect may not appear large, from a population perspective, it may have a large impact on reducing overall healthcare costs.

Educational interventions, aimed at the patient, show promise as well, with one meta-analysis indicating nearly an 11% improvement (Peterson et al., 2003). However, team-based care, where pharmacists reconciled and tailored medication regimens in coordination with primary care providers, coupled with medication

refill reminders showed a 15% higher rate of adherence compared to those not receiving these services. This is consistent with other literature suggesting that no single intervention – behavioral or educational – is more effective but that, combined, there is an overall improvement (Peterson et al., 2003).

Overall, it appears that identifying the patient-specific reason for the medication nonadherence and then tailoring an intervention aligned with that reason are the best approaches to preventing nonadherence. Practitioners must consider that the reasons for nonadherence may change over time. For example, a patient's financial situation may change, thus creating a reason for nonadherence when one did not exist before. Further, identifying populations at risk – the elderly, patients with low literacy or with a lower socioeconomic status – and tailoring interventions specific to their situation are key to improving adherence.

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