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OVERVIEW OF MEDICATION NON-ADHERENCE

"Drugs don't work for patients who don't take them"[1]

- **Medication adherence can be defined as "the process by which patients take their medication as prescribed"**
- **Medication non-adherence has been associated with adverse health outcomes, such as worsening disease, increased mortality and increased healthcare costs**
- **Causes of medication non-adherence are complex and often due to a combination of intertwined factors**
- **Interventions to improve adherence should be individualised to the patient and targeted to the causes of non-adherence in that patient**

INTRODUCTION

Medication adherence can be defined as "the process by which patients take their medication as prescribed".[2] The term "adherence" is preferred to the term "compliance", which has been associated with negative connotations; other terms used in the literature include persistence and concordance.[3] Medication adherence has three components: 1) initiation (when the patient takes the first dose of a medicine); 2) implementation (the patient's actual dosing compared to the prescribed dosing regimen); 3) discontinuation (the end of therapy); patients may be non-adherent during any of these stages.[2,3] Persistence represents the time (e.g. days, months, years) over which the patient continues the treatment, and immediately precedes discontinuation.[2,4] Note that the terms poor adherence and non-adherence are used interchangeably in this document.

The medication adherence rate in patients with chronic medical conditions is considered to be on average approximately 50%.[1,5-10] It is estimated that between 15 to 25% of these patients with chronic conditions do not initiate their prescribed medicines, and that 20 to 40% of patients who do start have suboptimal implementation of their medicines.[11] A European study (2018) of older populations (n=39,186) (≥65 years) reported suboptimal implementation and premature discontinuation rates of 52% and 56% for anti-hyperlipidaemics, 61% and 60% for osteoporotic therapies and 30% and 47% for oral antidiabetics respectively.[12] An Irish observational study (2018) of community-dwelling older patients with multimorbidity (n=855) reported that 20% to 40% of patients were non-adherent to their medication (higher adherence was noted in conditions such as hypothyroidism, type 2 diabetes and heart disease).[13]

Poor adherence has been associated with adverse health outcomes, such as worsening disease, increased mortality and increased healthcare costs.[1,8,11,14-18] An Irish longitudinal study of multimorbid older adults (aged ≥70 years) (n=1050) reported that suboptimal medication adherence was associated with increased healthcare utilisation (e.g. GP visits).[16]

Poor medication adherence is a growing public health concern, and is considered by the World Health Organisation (WHO) as one of the largest unsolved gaps in healthcare.[5,6,14] The WHO advises that increasing the effectiveness of adherence interventions may have a greater impact on a population's health than any improvement in specific medical treatments.[5] Non-adherence to medicines is a complex and multidimensional healthcare problem and requires a patient-centred approach.[3]

This bulletin will outline the causes of non-adherence and interventions to improve adherence.

CAUSES OF NON-ADHERENCE

While poor adherence to medicines is often perceived to be the fault of patients, **the causes of non-adherence are complex and often due to a combination of intertwined factors** that include: 1) socioeconomic factors; 2) healthcare system factors; 3) patient-related factors; 4) treatment-related factors and 5) disease-related factors (see table 1).[3,9,14,19-21]

Table 1: Factors impacting on adherence to medicines[1,3,6,14,22]

Category	Examples
Socioeconomic factors	Family and social support, employment status, lack of transportation, cost of medicines
Healthcare system factors	Access to healthcare professionals (HCP) (e.g. prescriber, pharmacist), insufficient communication with the patient regarding the medicine, poor HCP-patient relationship, prescribing complex drug regimens
Patient-related factors	Intentional non-adherence (e.g. patient may not believe that the treatment is necessary, concern about adverse effects) Unintentional non-adherence (e.g. forgetfulness)
Treatment-related factors	Complex treatment plans, duration of therapy, past failures, therapeutic changes, and adverse events
Disease-related factors	Asymptomatic condition, severity of the disease

Socioeconomic factors that may impact on adherence are listed above in table 1.

Healthcare system factors can impact on adherence in a number of ways. Fragmented healthcare systems contribute to poor medication adherence by impacting on the coordination and access to care for patients.[22] **Good communication with the patient and between the various healthcare professionals (HCPs) (e.g. general practitioners, hospital doctors, pharmacists, nurses)**

involved in a patient's care is positively associated with patient adherence.[3,6,7,22,23] HCPs may contribute to poor adherence in various ways such as 1) not recognising poor adherence and/or failing to stress the importance of medication adherence, 2) a lack of shared decision making with the patient regarding their treatment, 3) failing to explain the benefits and adverse effects of a medicine effectively, 4) a lack of explanation about the medicine regimen, 5) not considering the financial burden to the patient and 6) having multiple prescribers (which may in part be due to guidelines focusing on individual diseases rather than multimorbidity).[1,11,22] A lack of HCP time to engage the patient in a discussion on the importance of medication adherence and/or a poor relationship with the patient may also contribute to poor adherence.[3,9,22]

Patient-related factors are especially important to consider and can be categorised as **intentional non-adherence (where the patient actively decides not to use the medicine or adhere to the recommended regimen) or unintentional non-adherence (where the patient cannot follow the recommendations e.g. due to cognitive impairment).**[3,7,20] There are inconsistent reports from studies on differences in adherence between males and females.[24-27] In some studies, middle-aged participants (50 to 69 years) have been reported to be more adherent to their medication than both younger (<50 years) and older cohorts (≥70 years).[24,28] Another patient factor that may impact on adherence is multimorbidity,[25] especially co-morbid mental health problems (e.g. depression).[3]

Intentional non-adherence usually reflects a patient's beliefs on their need for treatment.[3] Factors that may contribute to a patient's decision not to be adherent to medicines include 1) lack of involvement in the treatment decision-making process, 2) a lack of understanding of the need for treatment of the condition, 3) concern about adverse effects and/or the emergence of adverse effects during treatment, 4) concern about taking too many medicines, 5) lack of understanding of the efficacy of long-term medicines for asymptomatic conditions, 6) previous negative experiences with medicines, 7) cost of medicines and 8) interference with day to day activities or social events.[1,3,7,11,14,20,22] These factors may contribute to a lack of motivation to use the necessary medicines and/or to prematurely discontinue the medicine(s).[3,11,22]

Unintentional non-adherence is unplanned behaviour and occurs due to factors that are outside the patient's control; they include forgetfulness, poor recall, difficulties understanding the instructions to use a medicine, visual impairment, difficulty using the medicine (e.g. medical devices such as inhalers) and sub-optimal medical literacy.[1,7,15,28] **Forgetfulness on the part of the patient is the most frequent cause of poor medication adherence.**[6]

Treatment-related factors: Polypharmacy (frequently defined as the use of ≥5 medicines daily)[29] is associated with an increased risk of complex dosing regimens and consequently with poor adherence.[3] The need to manage complex drug-drug interactions may also result in complex dosing regimens and have an impact on adherence (e.g. the need to take bisphosphonates separately from calcium).[3]

Disease-related factors: Certain conditions are associated with better adherence than others. Some literature reports that adherence rates are higher among patients with acute conditions (70 to 80%)[6,30,31], than in patients with chronic conditions (50%).[1,5-7] Adherence is highest in patients with human immunodeficiency virus infection, arthritis, gastrointestinal disorders, or cancer, and lowest in patients with pulmonary disease, diabetes mellitus and asymptomatic disease (e.g. hypertension).[3,22,30] Adherence in conditions such as cardiovascular disease (CVD) and psychiatric conditions is especially challenging.

Cardiovascular disease: Improved medication adherence in patients with CVD is associated with improved CV outcomes (including mortality), while non-adherence is associated with adverse outcomes.[32,33] However, medication non-adherence is a significant issue among patients with CVD.[33] For example, studies reported that 27% to 34% of patients with a diagnosis of acute coronary syndrome (ACS) were non-adherent to their medication up to 1 month following hospital discharge, and 55% to 60% were non-adherent up to 2 years following ACS (with further reductions seen over 10 years).[33] Similarly, studies have found that medication adherence declines even after significant events such as stroke,[22,34] therefore it is not surprising that adherence is even more challenging in asymptomatic conditions such as hypertension,[22,35] where many patients focus on medication adverse effects and do not see the benefits of taking antihypertensive agents because of the asymptomatic and chronic nature of the disease.[22,35,36] Factors associated with poor adherence to CV medication include older age, lack of belief in the effectiveness of the medication, concern about adverse effects, lower socioeconomic status and low social support (in the older person).[31,33-35]

Psychiatric conditions: Medication adherence is also related to improved clinical outcomes in psychiatric conditions, while poor adherence is a major risk factor for poorer outcomes including relapse in patients with schizophrenia, bipolar disorder and depression.[37] A major contributor to poorer outcomes in individuals who are not adherent to their medications is the abrupt cessation of psychotropic medicines.[37] Medicine discontinuation rates of 25% to 50% within one year of discharge from hospital have been reported in patients with schizophrenia.[38,39] **It is recommended that adherence should be assessed in patients with psychiatric conditions.**[37]

IDENTIFYING POOR ADHERENCE

It is important for HCPs to consider that non-adherence is common and that most patients are non-adherent some of the time.[7] Medication adherence is considered one of the most sensitive health behaviours for HCPs to address with patients; HCPs may not wish to embarrass or upset the patient, while patients fear disapproval and judgement from the HCP.[11] Table 2 lists some of the major predictors of poor adherence to medication.[1]

Table 2: Major predictors of poor adherence to medication[1]

- Socioeconomic factors e.g. cost of medication
- Healthcare related factors e.g. presence of barriers to healthcare or medications, poor healthcare professional-patient relationship, inadequate follow-up or discharge planning
- Patient-related factors e.g. presence of cognitive impairment, patient's lack of insight into the illness, patient's lack of belief in the benefit of treatment, presence of psychological problems, particularly depression, missed appointments
- Treatment-related factors e.g. complexity of treatment, adverse effects of medications
- Disease-related factors e.g. treatment of asymptomatic disease

INTERVENTIONS TO IMPROVE MEDICATION ADHERENCE

The serious consequences of poor medication adherence may be prevented by improved management of adherence.[3,14,37] It is important to identify a non-adherent patient and the causes for their non-adherence, which may be multifactorial and inter-related.[1,3,6,14,40] **Interventions to improve adherence should be individualised to the patient, as a single approach will not be effective for all patients.[1,3,7,40]** Due to differing methodologies, studies have shown mixed findings on the effects of interventions to improve adherence and more research is required;[3,10,40] some evidence suggests that strategies combining multiple interventions (educational and behavioural) may improve the proportion of people who are adherent to their medications.[33,41] A Cochrane systematic review (2014) on interventions to improve medication adherence advised that many complex interventions require frequent interactions with patients; such interventions are costly and there is uncertainty regarding their effectiveness.[10]

Health systems: Increased usage of electronic medical records and electronic prescribing could identify some patients at risk of non-adherence and assist in targeting them for intervention.[22] Communication about medication between HCPs from the patient's different healthcare settings is important (e.g. admission to nursing homes, following hospital discharge and outpatient appointments).[7,10,42]

Patients interact with several HCPs (e.g. doctors, pharmacists and nurses) and there are many opportunities where HCPs can support patients to improve their medication adherence.[1,11,22,33] Medication reviews may help to optimise medicines use and to improve adherence. Good communication between the HCP and the patient is a key aspect to improve patient adherence.[1,3,7,23] **The more empowered patients feel, the more likely they are to be motivated to manage their disease and adhere to their medications.[22]** The choice of therapy should include consideration of the patient's cognitive function, the patient's understanding of their condition, the potential adverse events associated with the medicine and potential financial implications for the patient.[6,7,22] Adherence may be improved by providing the patient with relevant information about the medicine (see table 3 and the Health Service Executive "Know Check Ask" initiative).

Table 3: Relevant medicine information to provide to the patient[7,22]

- The name of the medicine
- The indication for the medicine and the rationale for choosing it
- The frequency of dosing of the medicine and when it should be taken
- How long the medicine should be taken for
- The potential side effects

The prescribing of numerous new medicines at one visit should be avoided if possible.[22] For patients where the cost of a medicine is a problem, it may help adherence to consider ways to reduce the costs (e.g. prescribing generic medicines when possible).[7] **Addressing medication concerns before the treatment commences, rather than later in the treatment process, may be more beneficial to the patient and lead to better adherence.[21]**

Patient interventions may be targeted to the causes of non-adherence for the individual patient.[7,11] **Patients who miss appointments are often those who need the most help to improve their ability to adhere to a medication regimen.[42]** Positive feedback to patients on their efforts can improve adherence.[11,22] Interventions that focus on increasing knowledge about the disease and its treatment and addressing patient concerns or fears about potential medication side effects may provide solutions for intentional non-adherence.[3] Interventions for unintentional non-adherence include simplification of dosing regimens, reminders and blister packs.[3,40]

Educational interventions are frequently used to improve medication adherence,[1,28,43] even though they may not always result in improved adherence.[33] Educational interventions include telephone counselling, face to face interventions and educational programmes.[28] **It is estimated that patients recall as little as 50% of what is discussed during a typical medical consultation,[44] therefore effective patient education should be multifactorial and include support from all HCPs.[67,22]** The involvement of different HCP team members may be especially useful for non-adherent patients who are resistant to change.[11] The format and content of the information provided should meet the needs of individual patients.[7] Inadequate health literacy may be a cause of non-adherence; possible solutions to this include providing the patient with pictorial and audiovisual educational material instead of written instructions.[22]

Behavioural interventions should be considered for patients where motivation is a barrier to medication adherence.[33] Behavioural interventions include medication self-monitoring, symptom or side effect self-monitoring, reminders or other stimuli or cues to take medication, adherence or symptom feedback, and associating medication-taking with other daily activities.[7,43]

Interactive health technology is an emerging area of medication adherence intervention.[43] The use of mobile phone calls (e.g. with reminders), text messages and applications have been shown to improve adherence,[3,33,45] although without demonstrable clinical outcome improvement.[10,33] These technologies should be tailored to those patients who have difficulty remembering to take medications and who can use the technology.[33] Real time medication monitoring involves an electronic medicine box which registers the date and time that the box was opened, and where a text is sent to the patient who doesn't open the box within a certain time.[3,46]

Treatment-related interventions: Adherence may be improved by simplifying treatments, for example by prescribing fixed-dose combination pills, once daily dosing of medicines (rather than multiple daily dosing) and avoiding complex treatment regimens if possible.[1,6,10,22,33] It is challenging to manage complex drug regimens in patients with complex multimorbidity, and there may not be an option to simplify drug regimens due to the patient's morbidity burden.[22] If complex treatment regimens cannot be avoided, acknowledgement of this by the prescriber may improve adherence.[22] In psychiatry, the prescribing and administration of long-acting antipsychotics, e.g. depot injections may prevent the abrupt discontinuation of medicines with their associated consequences and provide certainty about the level of adherence.[37]

Medication-taking systems: The use of daily pill boxes or multi-compartment aids (e.g. boxes or trays) may be helpful to improve adherence in patients with unintentional non-adherence.[1,7,28,37] Some medicines are unsuitable for inclusion in a compliance aid (e.g. oro-dispersible formulations) and it is worth considering that

compliance aids are labour intensive to fill, can make it difficult to change prescriptions at short notice and the process of filling the devices is error prone.[37] Adherence can also be improved by using specific forms of drug packaging (e.g. single-dose blister and calendar packaging).[3,28,37,47]

ASSESSMENT OF ADHERENCE

The purpose of assessing adherence is not to monitor patients but to determine if patients need more information and/or support them to take their medicines.[7] Assessing adherence can be challenging and a combination of measures may be required; there is no gold standard method.[4,20,22] **Adherence should be assessed whenever medicines are prescribed, dispensed and at medication review.[1,7,37]** Table 4 includes some questions that may be useful when assessing adherence. **Medication adherence may improve in the 5 days before and after an appointment with a HCP (also known as "white-coat adherence").[1,22]** Patient repeat prescription records, pharmacy medication records and return of unused medicines may also be used to assess adherence.[7]

Table 4: Questions a healthcare professional can ask to assess a patient's medication adherence[21,22]

- I know it must be difficult to take all your medications regularly. How often do you miss taking them?
- Of the medicines prescribed to you, which ones are you taking?
- Of the medicines you have listed, which ones are you taking?
- Have you had to stop any of your medicines for any reason?
- How often do you not take medication X?
- When was the last time you took medication X?
- Have you noticed any adverse effects from your medication(s)?
- Have you any questions/concerns about your medication?

Other methods (direct and indirect) are also used to measure medication adherence (see table 5), however each method has advantages and disadvantages, and some may not be practical to use in a clinical setting.[1,20] It is important to be aware that **patient self-reporting of adherence may be overestimated;[11,36]** in some circumstances a combination of patient self-reporting of non-adherence and the use of non-invasive objective evidence (e.g. mass spectrometry urinalysis, blood concentration of the medicine) may be useful especially in tertiary referral centres (although cost needs to be considered).[36] For example, an Irish study (2022) found that in patients (n=73) referred to a tertiary hypertension clinic, self-reported adherence to antihypertensive medication was 73%, while mass spectrometry urinalysis indicated 27% adherence.[36] Patient self-reported questionnaires to measure adherence include the Medication Adherence Report Scales (MARS)[48] and Voils' self-reported medication non-adherence measurement.[49]

Table 5: Methods of measuring medication adherence[1]

TEST	ADVANTAGES	DISADVANTAGES
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measure of the level of medicine or metabolite in the blood	Objective; may be useful for some medicines such as antiepileptics	Variations in metabolism and "white-coat adherence" can give a false impression of adherence; expensive
Measurement of the biologic marker in the blood	Objective; in clinical trials can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patients
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g. pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive
Measurement of physiologic markers (e.g. heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g. increased metabolism, poor absorption, lack of response)
Patient diaries	Helps in circumstances of poor recall	Easily altered by the patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

SUMMARY

Poor adherence to medication is common, and it contributes to worsening of disease, mortality and increased healthcare costs.[1] The causes of non-adherence are multifactorial and often intertwined. To improve adherence HCPs can identify the causes of non-adherence in the individual patient, and work with the patient to identify strategies to improve adherence, such as those outlined in table 6.

Table 6: Strategies for improving adherence to a medication regimen[1]

- Identify poor adherence
  - Look for markers of poor adherence: missed appointments, lack of response to medication, missed refills
  - Enquire about adherence without being judgemental
- Emphasise the value of the medicine regimen and the effect of adherence
- Elicit the patient's feelings about his/her ability to follow the regimen, and if necessary, suggest supports to promote adherence
- Provide simple, clear instructions and simplify the regimen as much as possible
- Encourage the use of a compliance aid if appropriate
- Listen to the patient, and customise the regimen in accordance with their wishes
- Obtain the help of family members, friends and community services when needed
- Reinforce desirable behaviour and results when appropriate
- Consider more "forgiving" medications when adherence appears suboptimal (e.g. medications with long half-lives and extended-release formulations)

List of references available on ePublication on www.nmic.ie.
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