https://doi.org/10.31925/farmacia.2023.2.2 **REVIEW**

ADHERENCE TO TREATMENT – REVIEWING METHODS OF ASSESSMENT AND IMPROVEMENT

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Abstract

According to the World Health Organization (WHO), adherence is considered "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendations from a health care provider". Adherence rates average 50% in countries such as the United States, exerting important pressure on health systems. Factors which influence medication adherence can be related to the patient, the clinical conditions, therapy, socioeconomic factors and the healthcare system. Methods of adherence assessment are direct and indirect. While direct methods measure a certain drug or metabolite in body fluids of patients, indirect methods refer to self-report measures, pill count, electronic monitoring devices, electronic databases. The continuous growth of worldwide mobile phone use makes mHealth an important tool for both evaluating as well as improving adherence.

Rezumat

Conform Organizației Mondiale a Sănătății (OMS), aderența este măsura în care comportamentul unei persoane cu privire la administrarea medicamentelor, respectarea unei diete și/sau realizarea modificărilor stilului de viață, corespunde recomandărilor făcute de furnizorul de servicii de sănătate. Nivelurile de aderență sunt de 50% în țări precum Statele Unite, exercitând presiune importantă asupra sistemelor de sănătate. Factorii care influențează aderența la tratament pot fi legați de pacient, de condițiile clinice, de terapie, de factori socioeconomici și de sistemul de sănătate. Metodele de evaluare ale aderenței sunt directe și indirecte. În timp ce metodele directe măsoară un anumit medicament sau metabolit în lichidele biologice ale pacientului, metodele indirecte fac referire la cele de auto-raportare, la numărarea comprimatelor, la dispozitivele electronice de monitorizare precum și la bazele de date electronice. Creșterea continuă la nivel global a utilizării telefoanelor mobile face ca mHealth să fie o metodă importantă atât pentru evaluarea cât și îmbunătățirea aderenței.

Keywords: adherence, self-report, electronic monitoring devices, mHealth, apps

Introduction

While the nature of the doctor-patient relationship is constantly evolving, it is, rightfully so, considered to be the foundation of medicine [20, 42]. For a better understanding of the dynamics of this relationship, the roles for each participant should be highlighted and understood, since the general perception is one of patients' rights and professionals' duties and responsibilities.

It is expected of healthcare providers to secure the medical welfare of patients either through proper medication prescribing or specific recommendations regarding lifestyle changes, while also taking into consideration aspects such as the patient's patho-physiological state, lifestyle, beliefs as well as preferences [36].

Since medical treatments affect their health status, patients have the right to expect quality care, to have a choice in the decision-making process regarding their medical state, as well as to have privacy regarding their personal information. What is not as often talked about is that rights come with duties of equal importance [30].

In a study which aimed to highlight patients' responsibilities in the context of publicly funded healthcare, Evans pointed out that patients have at least 10 such duties. Several of these suggest that the patient should take into consideration the recommendations made by his healthcare provider, be them related to treatment or to lifestyle. In other words, patients should adhere to professionals' recommendations [13].

Adherence, compliance, concordance, persistence

A simple, general definition of adherence could consider it the act of "sticking-to" a plan, since the word could be synonymous with attachment, support, commitment, dedication. In the context of healthcare, it is considered the "active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behaviour to produce a therapeutic result" [21].

The definition given by the WHO (World Health Organization) to adherence to long-term therapy is "the extent to which a person's behaviour – taking medication, following a diet, and/or executing life-style changes corresponds with agreed recommendations from a health care provider". This suggests certain nuances which would help in differentiating adherence from other terms used in drug-taking behaviour studies, such as compliance [51]. Although the two terms are sometimes used interchangeably, differences exist [9] and should be noted.

Compliance comes from the Latin word "*complire*", which refers to completing an action or process and fulfilling a promise. It is one of the oldest terms used in regard to treatment administration by the patients. The difficulties regarding this specific term are related to the fact that this paternalistic approach portrays the patient as lacking autonomy in the care process, thus describing a hampered therapeutic relationship. Paternalism was defined as going against a patient's expressed wishes, with the aim of an overall benefit for the patient [22]. This one-sided interaction highlights the fact that patients must comply to the clinician's decisions about the specific treatment, without taking into consideration its suitability. In short, it means to do as you are asked to or to obey your instructions.

Adherence, a term which is considered non-judgmental has steadily replaced the term of compliance. It comes from the Latin word "*adhaerere*", which means to keep close or to remain constant [6] thus highlighting a new type of patient-provider relationship, one in which the appropriate treatment is decided after discussion between the two. It has been conceptualized as a set of behaviours ranging from complete refusal to take drugs, to following medication regimens partly or to precise and regular intake of medications [11].

Other terms used in medication-taking behaviour studies are concordance and persistence. Concordance refers to the process in which doctors and patients make decisions together regarding the treatment, in a consultative and consensual manner, while persistence is the ability of the patient to continuously follow the medical advice given, either for a few days or even for the rest of his life [33].

Factors influencing adherence

Non-adherence has been described by the WHO as a "worldwide problem of striking magnitude", with adherence rates averaging 50% in countries such as the United States. It can be seen in numerous conditions such as diabetes, hypertension, kidney transplant, epilepsy, Parkinson's disease, HIV. Besides negative health-outcomes, non-adherence also puts pressure on the economic system due to its associated costs. Research has shown that medication non-adherence determines almost 200,000 deaths annually as well as €125 billion in costs, in Europe [48].

It is obvious that by tackling non-adherence, improvements regarding health status of patients as well as health-expenditure can be made. Thus, emphasis should be put on discovering factors that can determine non-adherence. The WHO suggests a number of factors that interact and enhance each other's influence in a determined multidimensional framework: the patient-related factors, condition-related factors, treatment-related factors, social and economic factors, health-care team and system-related factors [51]. Figure 1 shows the most common factors that influence treatment adherence. According to the National Institutes of Clinical Excellence (NICE) adherence guidelines, these factors could be barriers or enablers to adherence and are generally categorized as either practical or perceptual [24, 37].

Perceptual factors refer to those which derive mainly from cognitive processes, such as emotions, motivation or subject perceptions and beliefs regarding the disease and therapy, while practical factors relate primarily to external environment associated to society, treatment or individual which may affect behaviour [23]. Moreover, these factors may lead to intentional or unintentional non-adherence. While there is little consensus on the ideal classification of factors influencing adherence, their broad organization into intentional and unintentional is also widely used to explain the behaviours and actions of drug administration by the patients [7, 26, 27, 32, 52]. The patient's knowledge, beliefs or motivation about the disease or treatment underlie intentional non-adherence. Unintentional non-adherence is associated with demographic factors, age, gender, socio-economic status, language barriers, ethnicity, misunderstanding the regimen, access to medications, patient routines or memory [15, 31].

Knowing these factors can aid professionals in selecting the right intervention for ensuring optimal adherence. For example, unintentional non-adherence could be tackled by simplification of dosing regimens, by using various reminders as well as by improving communication with the physician. Intentional non-adherence might be approached by improving patients' health literacy and education and addressing their concerns and fears related to the disease and treatment [25].

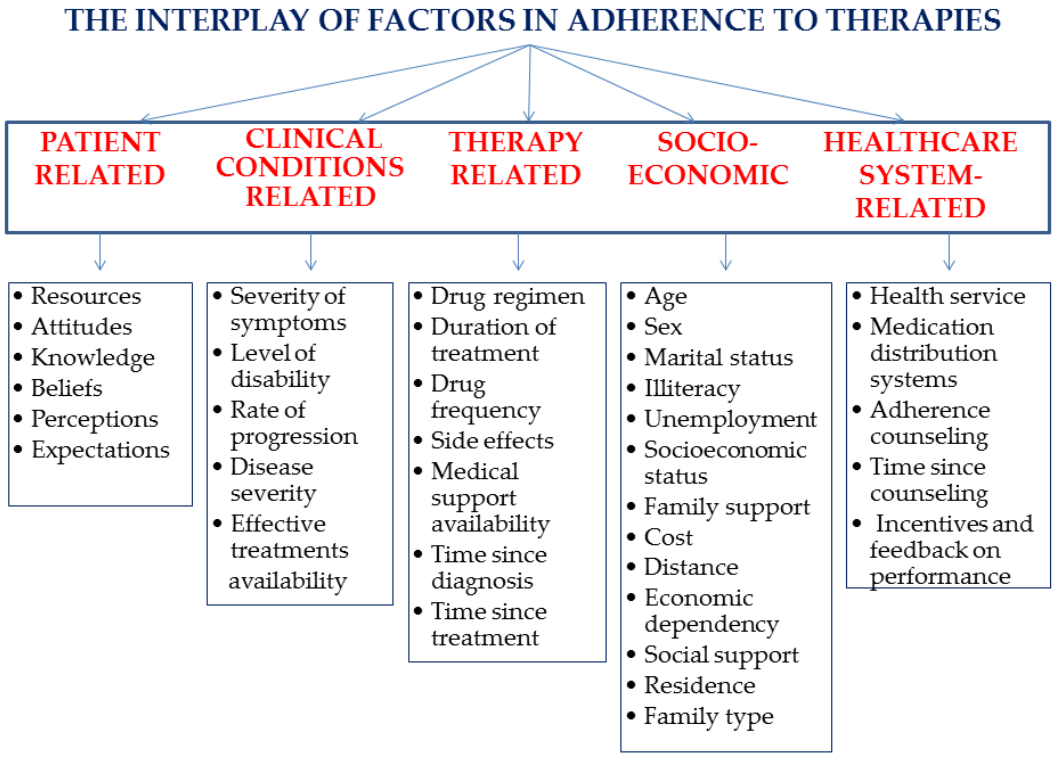

Figure 1.
The Interplay of Factors in Adherence to Therapies

To determine the degree in which the above-mentioned factors influence adherence rates, levels of adherence in patients should be measured. Anghel *et al.* have shown one of the most common classifications of adherence assessment methods considers these methods either subjective or objective. Subjective methods are inclined to a certain level of bias, since they involve patient's own assessment of their medication taking behaviour (*e.g.*, by using a certain scale or a questionnaire), while objective methods are considered better for measuring adherence (*e.g.*, following clinical outcomes, dose counts, electronic monitoring of drug administration, pharmacy records). Further classification also refers to direct and indirect methods of assessment.

Adherence assessment methods

Direct methods refer to more invasive type interventions and aim at measuring the drug or a metabolite in the body fluids of the patient, such as blood or urine. While useful in certain situations, some limiting-aspects should be taken into consideration. For example, individual variation in drug pharmacokinetics, as well as interactions with other drugs or with food might decrease the method's accuracy. This method is appropriate for monitoring the adherence to one drug therapy regimen and it does not offer information regarding possible causes for non-adherence. Another potential bias would be patients that take their drugs before measurements. Indirect measures are often the preferred options, due to their ease of use. Such methods are patient self-reports and questionnaires, electronic health records, pill counts, rates of prescription refills, patient diaries, measuring physiologic markers [5].

Although methods for assessing treatment adherence can be grouped according to the treated diseases, it is considered that the most used methods are prescription record reviews, constant observation of the patients, interviews, questionnaires, diaries, electronic monitoring devices and medication weight. Results can vary, in accordance with the specific type of method used [45]. Medical records measure the amount of medication which is prescribed. Dispensing records measure the amount of drug which was dispensed, medication event monitoring systems (MEMS) measure how often the container was opened, pill counts measure the amount of medication removed from the container, while self-report measures what patients recall regarding their medication use.

Specific methods could be used in various settings. For example, in order to quantify adherence to topical treatment, medication weight is considered and a mathematical formula is used:

$$W_a = (W_u/W_{ex}) \times 100,$$

where W_a is the medication weight adherence (%), while W_u is the medication weight used (weight dispensed – weight returned) and W_{ex} is the medication weight expected. In this specific situation, the possibility of deliberate discharge of the medicine or dissimulations of use should be considered [45].

It is important to note that there is not one single method which is considered suitable for all adherence research as well as that indirect measures do not necessarily reflect what the patient has taken, or if he did so, being variables indicative of adherence and not measures of medication use [17].

Indirect methods for adherence assessment

Self-report measures

As we have mentioned above, there is no current "gold standard" regarding measuring adherence to medication and the choice will depend on the specific situation. One of the most appropriate and widely used methods are self-report methods. They usually rely on a scale or a questionnaire, which evaluates adherence based on patients' subjective responses to questions. Despite their known-disadvantages (*e.g.*, patients tend to overestimate their level of adherence), self-report measures are the most pragmatic methods which can be used in clinical practice and research, ideally coupled with other methods of measuring adherence [17].

Before selecting the appropriate tool, researchers must be informed regarding their relevant psychometric properties and predictive validity, since several self-report measures have been developed and validated for different medical conditions and patient demographics. The tools which are to be used should have good psychometric properties and should be chosen according to the patient population for which it was developed and validated. Other aspects which should be taken into consideration are the reliability and internal consistency, which show if the tool measures the intended behaviour or if it has the ability to predict clinically relevant outcomes. Such a tool should offer information regarding both intentional as well as un-intentional non-adherence and should also be applicable in different patient groups and disease conditions.

Examples of self-reported questionnaires are the Medication Adherence Rating Scale (MARS), with 10 and 5 items, the Adherence to Refills and Medications Scale (ARMS), the Simplified Medication Adherence Questionnaire (SMAQ), the Hill-Bone Scale, the Morisky scale, the ProMAS questionnaire [46]. While some of these tools address the issue of general adherence, others also contain items which offer information regarding pathology-specific aspects (*e.g.*, the Hill-Bone Compliance to High Blood Pressure Therapy Scale could offer information regarding adherence as well as salt-intake and fast-food consumption [28].

Pill count is an indirect objective measure that counts the number of dosage units that have been administered between two scheduled appointments, which is then compared to the total number of units received by the patient. Thus, the adherence ratio can be calculated. This is a low cost and simple method, but it has a number of limitations. Removing the correct dosage units from the container does not mean the drug has been administered. This method does not generate a medication-taking pattern, nor does it contribute to the identification of the cause of non-adherence [29].

A more objective method of measuring adherence is the use of electronic adherence monitoring devices (*EMD*): electronic pill bottles, pill boxes, or inhaler attachments which contain a computer chip that records dates and times of device use. Due to their increasing affordability and accuracy, as a result of technological advances, these devices are becoming more and more utilized. It seems that electronic adherence monitoring devices are extremely useful for the assessment of implementation adherence, which is "the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen" and which compares medication taking behaviour over time to the prescribed medication regimen over time [35]. The use of EMDs reduces adherence overestimation, which is often seen in patients using self-reported measures and also identifies intentional pill dumping before clinic appointments. Studies which evaluate the use of EMDs show that they are useful tools for different categories of patients. In a study done on African American hypertensive patients which used EMDs, it was shown that the method can be utilized for monitoring adherence in low-income minority populations, the majority of patients (93%) stating that the device was easy to use [40].

A review done by Aldeer *et al*. [4] highlighted that the main electronic devices or systems used for measuring adherence could be grouped in sensor-based systems, proximity sensing, vision-based systems as well as fusion-based systems. Sensor-based systems include smart pill containers, which refer to pillboxes and pill bottles equipped with sensors that detect cap removal, while other devices are also equipped with an accelerometer, which monitors pill pickup. These sensors contribute to the monitorization of drug-taking activity. Although unable to confirm if drugs are actually taken, the systems do not require attaching sensors to the human body, ensuring user comfort as well as accuracy, due to the accelerometer sensor [4].

Wearable sensors are divided into two main categories: neck-worn and wrist-worn. Neck-worn sensors are pendant-style necklace devices which include a piezo-electric sensor, a Radio Frequency board and a battery. The piezoelectric sensor senses skin motion during pill swallowing and generates a voltage as a response. Another option would be the use of acoustic sensors, which focus on collecting data *via* a microphone placed by the throat. Although this approach requires further research, it could be a good method of monitoring [4].

Wrist-worn sensors usually refer to personal sensors, a class of wearables such as smartwatches which can use Inertial Measurements Units (IMU). Thus, these devices can detect the intensity, direction and angle of movements regarding medication intake, in a 3D

coordinate system. Although a good way of collecting data regarding medication taking behaviour, these methods require validation before widespread clinical use [4].

Challenges regarding these approaches refer to user comfort and social acceptance, since the necklaces need to be placed and fixed in contact with the skin, so it can observe the act of swallowing. The wearables also need to be recharged frequently, since they are usually powered by small batteries, which could be an obstacle, especially for elderly patients [4].

Ingestible devices/sensors are to be swallowed and travel the gastrointestinal tract and digestive system, collecting data about specific parameters and then sending the information to a body-worn or nearby device, for processing. This method has been tested by researchers and the results were favourable, the detection accuracy of medication ingestion being more than 99%. An obstacle in implementing such systems refers to wearing a banded device throughout the day or even for years, for data processing [4].

Proximity sensing refers to the monitoring of objects use in our daily lives, by sensing proximity to other things. The most commonly used technologies in this regard are radio frequency identification (RFID) and near field communication (NFC). The advantages of these methods are non-invasiveness as well as the possibility of retrieving information such as dosage instructions (quantity, frequency and timing). Its main disadvantage refers to the fact that the pill container must be in the vicinity of the system's reader.

Vision-based systems usually refer to systems that use a camera installed in the medication area and which aim to track user medication-taking. The main disadvantages refer to their limitation in use and accuracy as well as their cost.

Fusion-based systems have been developed to combine different methods in order to obtain better adherence-assessment results. Such techniques refer to proximity-sensor systems, proximity-visual systems, visual-sensor systems as well as sensor-app systems [4].

The main issues regarding the above-mentioned methods are the accuracy and fidelity of the data obtained, the systems' lifetime and energy consumption as well as user's comfort and acceptability [4]. Other challenges which must be taken into account refer to active non-compliance of patients which deceive the system – behaviour which could be observed when the patient does not agree with the selected treatment, but does not challenge the healthcare provider's judgment.

Another indirect measure uses electronic databases in which information regarding the patient's treatment, diagnosis and medical history is recorded (*e.g.*, pharmacy and insurance claim databases, registries). This method requires the existence of an electronic system which connects dispensers and prescribers. Prescription refill data can roughly estimate adherence, since it does not demonstrate the actual intake of drugs, but rather the possession of medication. While the advantage of this method is that it can offer information regarding non-adherence in a large population over an extensive period of time, its downside is that it cannot offer information about potential barriers to adherence [5].

Improving adherence

By improving conceptualization and monitoring of adherence, better interventions for improving and sustaining adherence can be developed. It is important to note that adherence interventions could be categorized according to the specific level of the intervention into regimen-, provider-, system- and patient-level interventions. Regimen interventions usually refer to the approaches that involve the drug regimen. For example, complex treatments should be simplified, when possible. Combining multiple drugs into a single once-daily administered drug is a good example of adherence-improving regimen interventions.

Provider-level interventions refer to improving provider communication skills as well as attention to shared decision-making with patients. Professionals should be able to respond to the health problems of their patients in a non-judgmental and constructive manner, earning their trust and helping them overcome challenges. System level interventions involve medication refill date synchronization, extended prescription length and health care coverage and delivery. Patient-level interventions refer to aspects such as reminders, direct counselling, behavioural support, education regarding the disease and its management, which have been shown to determine optimal levels of adherence [43, 50].

Research on patient-directed interventions is increasing, especially studies that use different technologies for improving adherence. This could be due to the advancement of information technology as well as to the presence of mobile technology, especially mobile devices.

mHealth / telemedicine

The ubiquity of mobile phones offers numerous opportunities for patients to improve health outcomes, allowing for scalable tailored interventions with prompt feedback [41], since it is one of the most important sources of information and communication. It is estimated that approximately 6.5 billion people use such devices worldwide [12]. In many low- or middle-income countries, it is more likely that people have access to a mobile phone rather than a bank account, electricity or clean water [14].

According to the WHO, mobile health, termed mHealth is defined as a medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants and other wireless devices [16]. Telehealth and tele-

medicine are other frequently used interchangeable terms related to mobile devices. Telemedicine is considered to be "the remote diagnosis and treatment of patients by means of telecommunication technology" and is not a specific clinical service, but includes a wide collection of applications [1].

Mobility, instantaneous access as well as direct communication, all of which characterize mobile technology supports public health and medical practices. Thus, mHealth could positively contribute to the delivery of health services at a global level, especially in low- and middle-income countries. mHealth is being used for patient monitoring, communication and education, for improving access to healthcare services, diagnosis and adherence to treatment as well as for the management of chronic diseases [34]. According to the European Patient Forum, healthcare should be available, adequate, accessible, appropriate and affordable. Scarcity of health resources is an impediment for what is stated above, but mHealth has the potential to overcome some barriers [19].

One of the most important features of modern mobile telephones is the use of applications. In 2020, more than 100,000 health mobile applications were available in mobile stores for Android and iOS. Mobile applications integrate sensors and other technologies that are useful for collecting data regarding physical activity, human body images as well as other aspects related to health-care, which could lead to a better monitoring of health status. There are two broad categories of mHealth apps, depending on who the intended users are: either patients or healthcare providers. Apps for healthcare professionals refer to scientific literature, monitoring and diagnosis of patients, psychological health applications, education applications and personal care applications, while apps for patients refer to individual care applications (*e.g.*, fitness, auto diagnosis), applications for checking personal health records, apps for contacting their health-care provider, as well as educational apps [38].

Another classification of mHealth apps used in the UK was established by the National Health Service (NHS). According to their functionality, the apps aimed to: Support clinical diagnosis and/or decision making; Improve clinical outcomes from treatments through behaviour change and patient adherence; Act as standalone digital therapeutics; Deliver disease related education [39].

In a review done by Ahmed *et al*. in which the authors analysed available medication adherence apps for patients, three categories were identified: educational apps, reminder apps and behavioural apps. The educational category aimed to inform the user regarding treatment adherence and its importance, by providing structured and easily accessible treatment- and disease-related education. The reminder apps informed users regarding the moment in which they should take their medication, while behavioural apps aimed at implementing strategies which could lead to behaviour changes and ultimately to increase adherence. Out of the apps they tested, it seemed that most of them (59.5%) used only one of the methods mentioned above, while 35.5% combined two of the methods. Only 5.2% of those apps used all three methods for adherence improvement [3].

Further analysis allowed authors to subdivide these categories into subcategories, according to the principle of action. For example, the reminder category was subdivided in alarms, push notifications as well as short messaging services (SMS). The alarm consisted of an audio alert which was present at specific moments. Push notifications refers to internal messages which appeared on the mobile device at a set time which reminded patients to take their medication. The last subcategory refers to short messaging service (SMS), which also delivered a text message with a reminder to take the medication [3].

Behavioural strategies were subdivided in external monitoring, personal tracking and gamification. While external monitoring enabled users to send information regarding their adherence to others such as friends, family or their healthcare providers, personal tracking referred to the capacity of an app to allow users to monitor their medication taking, while also creating records of it [3]. Gamification is based on the idea that people are driven to have a sense of achievement [2] and uses elements from video games in activities which are not regularly associated with games. Such elements are colourful aesthetics, avatars, a certain storyline with specific quests, social competitions, as well as point systems [47].

The use of mHealth apps can lead to higher levels of adherence among patients, especially if the app also provides a positive user experience. Patients' satisfaction regarding the app's features on managing their health condition will make them more involved in the process of care [49].

While mHealth methods have grown exponentially and the use of mHealth apps has increased, it must be said that for obtaining the best results in the interest of patients, a series of barriers should be addressed. Zkerabasali *et al*. have categorized barriers to mHealth adoption into three main groups: individual, healthcare system and technical. Individual barriers refer to lack of support from a physician, difficulty in understanding, human appeal, knowledge and limited literacy as well as resistance to change, while healthcare system barriers refer to legal barriers, economic and financial factors, lack of standards and health system policies as well as reimbursement and accountable care organizations [53]. Technical barriers refer to aspects such as lack of user-friendliness, connectivity speed, interoperability with other technologies, compatibility with the work-flow, lack of existing technology, lack of regulation and efficacy of apps as well as security and privacy concerns [53].

Indeed, regulation of these technologies is often limited and their assessment is unstandardized. This could be

addressed by health authorities in such a manner that patients' safety is ensured and continuous technological advancement is not hampered [8].

Another important barrier is the privacy of users' data. In a study done by Tangari *et al*. it was highlighted that for approximately 20,000 medical, health and fitness apps, most of them collected and potentially shared data with third parties, with only about half of them being compliant with their privacy policies [44]. Other aspects which would need regulation refer to healthcare providers and their ability to recommend the use of certain mHealth apps, thus acting as a filter for patients, there is limited guidance for the professionals in this sense. Most often, healthcare providers are on their own when it comes to navigating this area [10]. Another expanding field related to digital healthcare refers to the use of artificial intelligence (A.I.), which has great potential. In 2018, the Food and Drug Administration (FDA) approved the first AI system that is used to detect diabetic retinopathy without supervision from a specialist. Thus, it is a useful tool in the diagnostic sector, especially for detecting and classifying diseases [18].

Conclusions

Improving medication adherence requires the involvement of several professionals (*e.g.*, physician, pharmacist, nurses, etc.) and the combined use of tools for assessment and improvement, according to the specific context of the patient.

Obtaining high levels of adherence should be a priority for healthcare professionals due to the positive impact it could have on public health.

Conflict of interest

The authors declare no conflict of interest.

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