OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article **Clinical Pharmacy**

Use and Effectiveness of Digital Adherence Tools

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DOI: 10.36348/sjmps.2023.v09i03.003 | **Received:** 25.01.2023 | **Accepted:** 04.03.2023 | **Published:** 09.03.2023

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Abstract

Adherence to (or compliance with) a medication schedule refers to the extent to which individuals take drugs as advised by their medical professionals. Many medical practitioners prefer the term "adherence" over "compliance," as the latter suggests that the patient is merely following orders from their doctor passively and that the treatment regimen is not founded on a therapeutic alliance or partnership between the patient and the provider. Particularly for chronic illnesses, maintaining commitment to a therapy regimen is challenging, which frequently hinders patients from reaping the full advantages of therapies. Negative health effects include treatment failure, more frequent hospital admissions, drug resistance in some circumstances (for example, in HIV or antibiotic regimens), and higher use of healthcare resources as a result of poor adherence. Effective chronic disease self-management and successful health outcomes depend on medication adherence. HIV patients, asthmatic patients, and hypertensive patients can enhance their adherence with the use of DATs. Further analysis of both short- and long-term effectiveness if the costs of these systems will be covered by better results, fewer ER visits, and fewer inpatient stays.

Keywords: Digital Adherence, Effectiveness, Digital Adherence Tools.

BACKGROUND

The degree to which patients take medications as recommended by their health care providers is adherence to (or compliance with) a medications schedule [1]. Many health care professionals prefer the word "adherence" because "compliance" implies that the patient is passively following the instructions of the physician and that the treatment plan is not based on a therapeutic partnership or arrangement between the providers and the patients [2]. Achieving adherence to a therapeutic regimen specifically in chronic conditions is difficult, which often prevents the patient's from realizing the full benefits of treatments. Poor adherence leads to negative health outcomes, such as treatment failure, increased frequency of hospital admissions, drug resistance in some cases (for instance (human immunodeficiency virus or antibiotic regimens), and increased consumption of healthcare resources [2]. The total cost of nonadherence is estimated to be between the US $100 and the US $300 billion moreover, responsible for more than 125,000 deaths per year in the United States alone [3].

In Saudi Arabia, a study was carried out in 2019 by AlQarni and colleagues, which measured the adherence of diabetic patients with their medications in Khobar city, Saudi Arabia. It included 212 subjects and a third of the subjects were found to be highly adherent to anti-diabetic medications 76 (35.8%) [4]. Another study measured adherence to hypertension medication. It included 198 subjects. The result was 51 (25.76%) subjects were classified as being poor adherents, 132 (66.67%) categorized as moderately adherent to their medication, and 15 (7.58%) patients were considered as a good adherent to anti-hypertensive medications [5].

The approaches available for measuring adherence can be divided into direct and indirect methods of measurement. The Table 1 describe advantages and disadvantages for each of them, and no method is considered the gold standard [6, 7].

Table 1: Method of Measuring the Adherence

Direct methods	**Advantages**	**Disadvantages**
Observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in the blood.	Objective	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 questionnaire and patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to the error with increases in time between visits; results are easily distorted by the patient.
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (for example; pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence
Electronic medication monitors,	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials.
Measurement of physiologic markers (for example., heart rate in patients taking beta-blockers),	Often easy to perform	The marker may be absent for other reasons (for example., increased metabolism, poor absorption, lack of response)
Patient diaries When the patient is a child, a questionnaire for caregiver or teacher	Help to correct for poor recall Simple; objective	Easily altered by the patient Susceptible to distortion

There are two types of non-adherence and they are known as unintentional non-adherence and intentional non-adherence. Unintentional non-adherence depends on potentially modifiable factors, such as poor understanding of the treatment, low health patient literacy/numeracy, forgetfulness, or simply irrationality. Digital health tools in unintentional nonadherence can be helpful in encouraging a patient into adherence. Intentional nonadherence, patients weigh the pros and cons of their medical conditions and the benefit of adherence to their treatments and rationally decide to not adhere to their treatment. Here the tools might not be helpful to increase adherence, whereas a good physician-patient relationship can be more useful. Therefore, the use of digital health tools are recommended to change behavior and increase adherence for patients who display unintentional non-adherence [8].

The review was prepared with an objective to discuss articles that looked at medication adherence with the DATs (SMS, ERD, ingestible sensors and, serious games) and included conditions where this technology has been studied.

Data source

Literature searches were conducted in the PubMed database and Google Scholar. The English language was just included and with no limit of time. The keywords used were "Digital adherence technologies" "medication adherence" "miHealth intervention "electronic reminder "SMS reminder" "ingestible pill".

The use of digital adherence technologies (DATs) is an alternative approach to improve adherence. DATs use cellular communication and other telecommunication to perform a variety of functions, including reminding patients to take medications, digitally observing doses taken, and compiling dosing histories that can be used by healthcare providers [9]. The following are examples of DATs.

- Cellphone short messaging service (SMS) texts.
- Electronic reminder device (ERD)
- Ingestible sensors.
- Serious games.

The Adherence Support coalition to End Tuberculosis (ASCENT) project, whose activity cover Ethiopia, South Africa, Tanzania, Philippines, Ukraine. They introduce and evaluate three different types of DATs that will be available in the participating health care facilities at no extra costs to the patient [10]. The technology used includes medication sleeve, smart Pill Box, and video Supported Treatment and more details are available as follows:

- Medication Sleeve: In a customized envelope the patient receives their tuberculosis (TB) medication sleeved. A hidden number is revealed when the patient pushes out their pills from the blister pack, by which they are instructed to make a toll-free call (or text) to that number is automatically record their daily dose [10].
- Smart Pill Box: The patient is provided with a specially-designed box to store their TB medications. The embedded system sends a signal every time the patient opens the box, which notifies the health care worker automatically [10].
- Video Supported Treatment: During medication intake, the patient records a video message using a customized app on their mobile phone. After completion, the video is sent to the health care worker for review [10].

The Institute for Healthcare Informatics identified the US $500 billion in savings across 186 countries with the responsible use of medication and noted that about 8% of the global total health expenditure could be avoided by improving adherence to medication [11].

Digital Adherence Technologies

- **Short Message Service texts.**

In 2014 a systematic review conducted to look at the effect of miHealth (a new model of remote health delivery via mobile phone) on medication adherence. It included 20 articles; were categorized depending on the target population into three different groups:

- HIV-infected patients: five studies were included out of twenty.
- Patients with other chronic diseases (asthma, coronary heart disease, diabetes mellitus, hypertension, infectious diseases, transplant recipients, and psoriasis): eleven studies were included out of twenty.
- Healthy individuals: four studies were included out of twenty.

In HIV-infected patients, five studies, involving 1399 patients, were reported. The length of the trials ranged between three months and one year. The intervention consisted of sending SMS in two studies, in one trial an interactive voice response "the participant required to respond to the question "have you taken all your medicines yesterday?" with a "1" if they had not missed any doses in the previous 24 hours and "2" if they had", and one study the intervention was limited to medication reminders. Half of the studies used motivational and reinforcement content for the remainder of the message, and three studies used two-way communications to allow respondents to ask questions using their mobile phones. The frequency of delivery of messages ranged from daily in one study to once a week in three studies, while or both frequencies were included in one study. Four studies reported increased adherence rates and in one study the increase was sustained during the 6 months after the removal of the intervention. Higher adherence rates were recorded, when SMS was sent on a weekly basis (12).

Eleven studies were identified that focused on adherence in chronic diseases. The chronic diseases were examined asthma, coronary heart disease, diabetes mellitus, hypertension, infectious diseases, and psoriasis. Patients with multiple chronic diseases who underwent liver transplants were also, examined. A total of 1333 patients were examined, with an age range of 1–78 years. The duration of studies ranged from 1 to 13 months. All studies documented using SMS, the content of which included medication reminders in five studies, medication and healthy lifestyle reminders in four studies, disease perceptions and medication beliefs in one study, and in one study patients were randomized to receive medication reminders and health education messages, only health education messages, or no messages. The frequency of message delivery ranged from daily to twice weekly. The adherence improved in all the studies except three studies. A study by Marquez Contreras and colleagues found different findings that sending SMS did not improve adherence to antihypertensive care compared with the control group, in the first, third, and sixth months of the study (13). This type of intervention has also not enhanced the adherence rate in patients undergoing antibiotic therapy after their discharge from the emergency department or in patients receiving treatment for tuberculosis. (12).

In healthy individuals, four studies were included, each of which sent SMS as a reminder to increase vaccination rates, malaria chemoprophylaxis, vitamin C intake, and use of oral contraceptives among soldiers returning from malaria-endemic areas. Medication reminders were sent daily, while a few days before the appointment, vaccine reminders were sent. In particular, for the third dose of hepatitis A + hepatitis B, the vaccination rate increased. In the remaining situations, however, adherence was not improved using this type of intervention. In the study on oral contraceptives, no pregnancies were reported [12].

The Vanderbilt-Meharry Center of Excellence of Sickle Cell Disease conducted a randomized control trial using a two-way SMS reminder on sickle cell disease and asthma in children and adults. SMS medication reminders were sent over a 60-day period using Research Electronic Data Capture (REDCap) software.The SMS reminders included the following text: "Did you take your [hydroxyurea] [asthma] medication [this morning] [this evening] [today]?" . Study participants receiving SMS medication reminders were prompted to reply '(1) yes' or '(0) no' as to whether they took their medication. Those how responded with '(0) no' received an additional SMS reminder two hours later reminding them to take their

medication. The response rate to a daily message is different. However, patients in the intervention group showed a statistically significant improvement in medication adherence scores (p =0.001), whereas the control group did not. Sub-analysis demonstrated a greater increase in adherence in the intervention group compared to the control group in those with asthma medications alone, and of children alone, but the differences were not statistically significant (asthma medications alone: p=0.182; children: p=0.156) [14].

- **Electronic Reminder Device**

In 2016, Inoue and colleagues looked at hydroxyurea adherence in the sickle cell patients as one of the adherence tools using the container-monitor-reminder device called GlowCap^{TM}. Actually, the system acts as a medication container as well as a signal transmitter. Each time the cap is opened, an electronic signal is sent to the central receiving office of the manufacturer, where the date and time are registered. The device that is plugged into a household electrical outlet has a separate reminder device on it. When the device is programmed, it transmits a reminder first by flashing lights, then by sounding chimes if the patient opens the cap late. When two hours pass without the patient opening the cap, there is a telephone call alert. The results of the study hydroxyurea adherence rates were (n=12) 85% as measured either by the GlowCap electronic pill bottle or the possession ratio of medication; laboratory hydroxyurea adherence markers varied; a few technical challenges were also reported [15].

Laster and colleagues looked at adherence to pilocarpine eye drop using TimeCap^{MT} reminder. Thirteen patients were invited to participate in the study. For each patient, the study was divided into 2 30-day phases, one with the medication alarm device and the other without. Thus, each subject served as his or her own control. The response rate was (n=12) 95.8% for patients with glaucoma using an electronic medication alarm device [16]. In 2004 Rosen and colleagues, showed an increase in adherence of 15% (n=17) for patients with diabetes using an electronic monitoring cap, which records the date and time the bottle was opened in a trial of 3.5 months [17]. Chan and colleagues study demonstrates the effectiveness of digital interventions in improving clinical outcomes, including asthma control, adherence, and symptom-free days [18] in agreement with asthma, children aged 12 years and older reported high satisfaction and perceived value electronic sensors and a digital health platform [19].

- **Ingestible sensor**

The FDA-approved the first ingestible sensor with aripiprazole in psychiatric patients. The ingestible sensor is a device that enables patients, families, and clinicians to measure in real-time drug intake and adherence patterns, correlate pharmaceutical compliance with important physiological metrics, and take appropriate action in response to the adherence pattern and relevant health metrics of a patient [20].

No adverse events were associated with device use and no discontinuations were seen in an open-label pilot study performed over a four-week period with 20 healthy volunteers. There was a high level of reported adherence, although other variables, including the Hawthorne effect, study visits, and frequent text message reminders, may have prompted the authors to theorize adherence [21].

In a four-week retrospective study of 16 subjects with schizophrenia and 12 subjects with bipolar disorder stable on their current medication (mood-stabilizer or antipsychotic), Kane and colleagues performed a feasibility and safety study of ingestible sensor technology. Subjects with greater severity of depression, psychosis, or mania were excluded. The adherence rate ranged from 74% [27] to 96% (28) of subjects completing the study. There were no serious adverse events due to the ingestible sensor [22]. Holender and colleagues performed a qualitative study using focus groups with elderly patients to assess the attitudes and practicality of the use of various technology modalities to improve elderly drug adherence to cardiovascular drugs. Due to improved control of adherence by providers and caregivers, ingestible sensors have been seen as "helpful" for community-dwelling elderly patients with a cognitive disability [23].

- **Serious games**

Another technology that could be used is serious games, an ideal approach to portray medication information [24]. It’s an innovative way of providing interactive health behavior education by skill-building activities is technology-based serious games [25]. Serious games are digital tools that provide interaction activities through a responsive narrative to educate participants through role-play and practicing skills. Indeed, it works to convey meaningful information through interactive environments similar to real-life situations which are unlike traditional video games [26, 27]. Over the past decade, the use of serious games on computer and cell phone platforms to encourage awareness of health conditions has grown in popularity. In one study, children picking up prescriptions in the pharmacy were reported to have asked for interactive games to learn about their medications [28]. A recent systematic review concluded that serious games have the ability to reduce the knowledge gaps of patients and resolve misconceptions, which can also, lead to increased adherence to medication and minimized errors [29].

The following are examples of eight games that assessed patients' understanding of medications for managing chronic and acute health conditions.

- Games for antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) adherence: Viral Combat, Adherence Warrior, Epic Allies, and Battle Viro were developed to promote adherence to ART and PrEP (24).
- Game for cancer treatment medication adherence: Re-Mission (30).
- Game for diabetes medication education and adherence: L'Affaire Birmann [31].
- Game for asthma medication education: Wee Willie Wheezie [32].
- Games for microbiology and antibiotic education: Microbe Quest and e-Bug Junior and Senior [33, 34].
- Game for prescription drug abuse education: CSI Web Adventures [35].
- Game for over-the-counter (OTC) medication safety: Alchemy Knights [36].

DISCUSSION

Due to the wide access to mobile technologies SMS reminders have been shown to produce significant improvement in medication adherence in individuals with various illnesses [12, 14]. It is important to note that mobile apps develop much more rapidly than other interventions, and while apps can be validated over a particular period, more improvements may be added to the original version thus, make it difficult to evaluate the long-term effect of the baseline version. An ingestible sensor may help address a gap in care by providing real-time objective medication-taking adherence information to clinicians. However, it needs a better understanding and more studies to validate the uses. Regarding serious game the review mention that there has been an increased interest in the application of serious games to improve medication use outcomes, but there is an issue with the generalizability of results due to a small number in sample size [29].

There are circumstances that the digitals adherence tools are not effective like in intentional nonadherence its recommended to use non-digital tools like behavioral interventions, the aim of the behavioral intervention is to change individual behavior in those aspects related to everyday life; in case of adherence, they aim to modify patients' behavior toward treatment. Interventions are characterized by cognitive–behavioral techniques and therapies focused on dysfunctional emotions, behaviors, and cognitions with the aim to promote healthy lifestyles, and positive changes toward symptoms and treatment [37]. Medication management programs involving pharmacists, such as Memo and Delphi studies, provided interesting results in decreasing nonadherence and discontinuation in chronic therapy. As a secondary outcome, structured counseling sessions and continuous monitoring of drug use improved patient satisfaction and medication knowledge; furthermore, since the intervention was tailored to nonadherence and high-risk patients, cost-effectiveness was favorable. But not cost-effective and not easily implemented in everyday clinical practice [38, 39]. Another intervention is patient education, health care providers can educate patients to promote medication adherence by adequately explaining how to take a medicine, by raising and discussing with patients any reluctance to take medicines, and by discussing with patients their beliefs and knowledge about their health and associated treatments [37]. The last intervention is medication packaging, a study aimed at analyzing how medication packaging helps older patients. Two groups of elderly people who have high blood pressure were compared, one group was asked to use a daily dose blister packaging (Pill Calendar), and the other group used usual bottles of loose tablets. It turned out that patients with the Pill Calendar had a higher adherence, refilled their prescriptions more often, and it had a positive effect on their clinical outcomes [40].

Many systematic reviews indicated that, because of the significant clinical and methodological heterogeneity in the studies, they were unable to perform a meta-analysis [12, 41]. Many studies had a small sample size and thus make it difficult to generalizability of data. Currently, the application of innovative digital technologies to enhance medication adherence is still mainly limited to clinical trial settings, thereby not reaching the healthcare professionals and patients in real-life practice. In addition, awareness of healthcare professionals and evidence on the effectiveness, availability, and implementation of adherence enhancing technology is limited, the technology is usually not embedded in a broader understanding of the reasons for suboptimal adherence and there is a lack of collaboration between key stakeholders to jointly work towards shared implementation goals. most interventions that were associated with adherence improvement did not lead to improvements in health outcomes, such as quality of life, patient satisfaction, biomarkers, morbidity, mortality, health care utilization quality of care, and costs [42]. Most of the studies are mainly focused on short-term adherence, and no consistent results were presented for long-term evidence. It will be important in future research to evaluate the efficacy of intervention tools on long-term effects.

In Saudi Arabia, there are a variety of studies conducted about medication adherence with different diseases but couldn't generalize the result because of the small number of sample sizes. Therefore, it is recommended to do a systematic review or meta-analysis to gather the result of different studies for useful outcomes. Also, there is not enough data discuss the technologies that used to improve adherence.

CONCLUSION

Medication adherence is critical to effective chronic disease self-management and positive health

outcomes. The DATs used as tools to improve adherence to HIV patients, asthmatic patients, and hypertensive patients. Further evaluation of short- and long-term efficacy. Whether, improved outcomes, avoided emergency room visits, and fewer inpatient admissions will recoup the costs of these systems.

Conflicts of Interest: We have no conflicts of interest to disclose.

ACKNOWLEDGMENT

Many thanks to Dr. Jamilah Alsaidan (department of Clinical Pharmacy, College of Pharmacy, King Saud University) for her guidance and comments in manuscript.

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