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The rate of medication nonadherence and influencing factors: A systematic Review

Mohamad Aljofan [1], Ainash Oshibayeva [2], Ikilas Moldaliyev [2], Yerbolat Saruarov [2], Tilektes Maulenkul [2], Abduzhappar Gaipov [3*]

[1] Department of Biomedical Sciences, School of Medicine, Nazarbayev University, Astana, KAZAKHSTAN
[2] Department of Medicine, Khoja Akhmet Yassawi International Kazakh-Turkish University, Turkistan, KAZAKHSTAN
[3] Department of Medicine, School of Medicine, Nazarbayev University, Astana, KAZAKHSTAN
***Corresponding Author:** abduzhappar.gaipov@nu.edu.kz

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ABSTRACT

Lack of adherence to recommended therapy will reduce its effectiveness and can subsequently lead to disease progression, disabilities or even death. A vast number of research studies have emphasized the magnitude of medication nonadherence and its effect on treatment outcomes, patient's health, healthcare providers and the associated costs; medication nonadherence remains a major concern that is believed to be widely practiced amongst medication taking patients. The current systemic review aims to cohere the available evidence regarding medication nonadherence rate, practices, and potential affecting factors and predictors. A search through different databases was conducted, including PubMed, Medline, and CINHAL for recently published research articles, within five years. The terms used for the search include medication nonadherence, medication nonadherence, factors affecting medication nonadherence and predictors of medication nonadherence. The search was limited to human subjects, English language journal articles and exclusion of review articles, case studies, and data from clinical trials as patient adherence is closely observed.

The search resulted in 667 articles and only 65 articles were included and further screened. However, according to our exclusion criteria, 15 articles only were included in this review. The three most reported practices of medication nonadherence are prescription abandonment, nonconforming, and non-persistence. There are five reported factors that may lead to nonadherence practices such as socioeconomic-related factors, healthcare system-related factors, patient-related factors, disease-related factors, and therapy-related factors. In conclusion, medication nonadherence practice is a multi-dimensional phenomenon that requires a multi-targeted solution.

Keywords: medication, adherence, compliance, factors and predictors

INTRODUCTION

Medication adherence can be defined as the extent to which the patient follows and strictly adhere to medical instructions including medication timing, dosage, and frequency [1, 2]. Medication adherence can also include patient compliance with disease or medication related practices such as diet, exercise, or lifestyle changes [3]. Adherent patients are those who take prescribed agents at doses and times recommended by a healthcare provider and agreed to by the patient [3, 4].

Commonly, prescribed medical therapy is expected to be strictly followed by the patient to achieve their intended medical outcomes. From a disease management point of view, patient's failure to strictly adhere to the prescribed medication regimen will likely result in serious and detrimental effects.

Therapeutic nonadherence is still a common in healthcare and no significant change has occurred despite the various studies trying to address and highlight the issue [2, 3]. According to World Health Organization (WHO), approximately 50% of patients do not take their medications as prescribed [5]. This percentage can be far greater in the developing countries and is affected by numerous factors that range from patient literacy to the prescription of complicated regimens [5].

Medication adherence can be measured by a number of different methods including direct or indirect methods [4]. The direct method of assessing patient's adherence to prescribed medications is when the patient receives medication at healthcare institute, or when testing patient's blood or urine samples [6]. The direct method of testing blood or urine drug and metabolite concentrations, or observed therapy are generally used in research during the use of high risk medications, or when public health needs to value additional costs, and required resources for implementation [4].

However, there are two indirect medication adherence measuring methods, which are designed to measure adherence in research and administrative settings, or in patient care facility [7, 8]. The indirect method used in research and administrative settings utilizes mathematical equations that calculate medication possession ratio (MPR), which is calculated as the total number of days supplied, divided by the

Table 1. A description of articles of interest to be included in the review

Population	Patients with medication taking behavior
Medical subject headings (MeSH) and/or terms used	Patient noncompliance Medication nonadherence Determinants of medication nonadherence Predictors of medication nonadherence Patient dropouts Treatment refusal
Primary outcome measures	The primary measures of interest including: Rate of medication adherence Rate of medication adherence in general population Predictors of medication nonadherence Factors affecting medication adherence Patients attitude to prescribed medicines
Type of studies	Quantitative cross sectional studies, qualitative studies, or mixed methodology

number of days between the first and last refills; and the proportion of days covered (PDC), which is calculated as the total number of days supplied during an interval, divided by the total number of days during that interval [9].

The current manuscript represent a systematic review of the literature to investigate the rate of medication nonadherence, its influencing factors and predictors.

METHODS

The current review was performed according to the guidelines shown in *Johanna Briggs Institute database of systematic reviews and implementation reports* [10] and the *Cochrane handbook for systematic reviews of interventions* [11].

Search Strategy

The terms used to search through the available databases were patient noncompliance and medication nonadherence.

The PubMed search was performed through advanced search using the following terms: factors that affect medication nonadherence, determinants of medication nonadherence, and predictors of medication nonadherence.

The following terms were used to search through Medline database: treatment noncompliance and patient noncompliance. This search also yielded other synonymous terms that were later used in the search as well including: patient dropouts, and treatment refusal.

Inclusion criteria

The search was limited to human subjects, specifically adults, and English language journal articles only. Exclusion criteria included studies of pediatric populations only, review articles, case studies, and data from clinical trials as patient adherence is closely observed. **Table 1** shows the medical terms used in the search, the primary outcomes measures, and the type of studies that were included in the search.

Study Selection and Quality

Three team members and two independent research assistants performed the study search, selection, and quality assessment. Differences were solved by discussion.

The quality of the studies were assessed in accordance with the quality of the body of evidence the GRADE approach (see reference [12]).

Types of Selected Studies

Quantitative cross sectional studies, qualitative studies, or mixed methodology.

Types of Participants

Studies involving medication taking adults, males, and females, were included, regardless of country or disease.

Types of Interventions

Studies reported rate and/or prevalence of medication nonadherence were included. Also, studies that reported factors that may contribute to medication nonadherence and meet the selection criteria were included.

Types of Outcome

The primary measures of interest including rate of medication nonadherence in the adult population. Secondary outcomes factors influencing medication nonadherence.

Data Extraction

The extracted data included the name of the first author, publication year, methodology, and findings.

Publication Limitations and Bias

The aim of this review was to analyze the general reported nonadherence practices in the adult population only. Therefore, the study does not necessarily reflect all aspects of medication nonadherence related to other populations, for example pediatric populations. A large number of manuscripts were excluded due to subject duplication, language (other than English, and inaccessible articles. Another possible bias is that the review did not particularly study the types of interventions and, thus intervention studies were not included.

RESULTS

The search produced 667 articles of which six hundred and two were removed for duplication and relevancy. There was 65 remaining articles of which 50 were removed after reading the abstract including some that were irretrievable. Out of these articles, only 15 met the criteria of inclusion. **Figure 1** describes the steps of searched articles through the different phases. **Figure 1** illustrates the stages of search for this systematic review. The initial search resulted in a large number of manuscripts, but many were excluded after reviewing the abstract. However, 15 articles only were included in the review following subsequent screening.

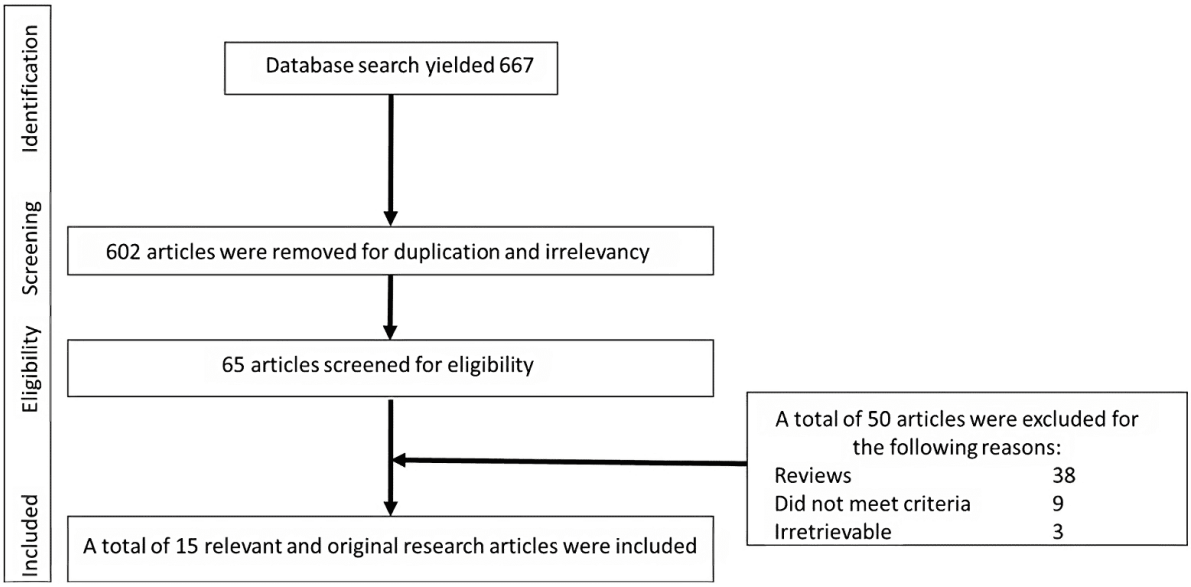

Figure 1. Flow of the information searched through the current systematic review (adapted from Liberati et al., 2009)

Table 2 shows the articles included in the review with a brief summary of the findings.

The study [13] aimed to assess patient adherence rate to hypertensive therapeutic regiment in Jordan. It is a cross sectional study with a total of 192 participants (mostly women) with the mean age of 52.8 years and range between 20-80 years. The mean time since disease diagnosis was 7.5 years with the mean time of treatment initiation was 7.2 years.

The study investigated different types of medication adherence factors such medication taking behavior, which was

Table 2. List of studies included in the review

No	R	Article name	Year	RM	SS	Country	Summary of the findings
1	[13]	Self-reported adherence to therapeutic regimens among patients with hypertension	2017	CS	192	Jordan	Rate of adherence: Nonadherence ranged from 50.48% to 57.28% Factors affecting adherence: Disease knowledge, frequent physician visits, & gender
2	[14]	Treatment and disease related factors affecting nonadherence among patients on long term therapy of antidepressants	2015	CS	103	India	Rate of adherence: 53% adherence rate Factors affecting adherence: Cost of medication & disease period
3	[15]	Factors affecting medication adherence: Patient perspectives from five veterans affairs facilities	2014	FG	45	the USA	Rate of adherence: 80% adherence rate Factors affecting adherence: System level barriers, lack of medication knowledge, medication cost, & physician communication
4	[16]	Factors influencing medication knowledge and beliefs on warfarin adherence among patients with arterial fibrillation in China	2016	CS	288	China	Rate of adherence: 67.7% adherence rate Factors affecting adherence: Medication knowledge & disease knowledge
5	[17]	Factors affecting medication adherence in elderly people	2016	CS	160	South Korea	Rate of adherence: 47.5% adherence rate Factors affecting adherence: Patient satisfaction with services, lack of medication counseling, medication knowledge, education level, disease related factors, & dosing frequency
6	[18]	Adherence to treatment in patient with open-angle glaucoma and its related factors	2016	CS	130	Iran	Rate of adherence: 34.6% adherence rate Factors affecting adherence: Patient-related factors (age, education, income, gender, marital status, & geographic location), & disease knowledge & duration
7	[19]	Factors affecting adherence to statins in hypercholesterolemic Kuwaiti patients: Across-sectional study	2017	CS	200	Kuwait	Rate of adherence: 41.5% adherence rate Factors affecting adherence: Patient's age & co morbidities
8	[20]	Level of adherence to ocular hypotensive agents and its determinant factors among glaucoma patients in Menelik II Referral Hospital, Ethiopia	2016	CS	359	Ethiopia	Rate of adherence: 42.6 % adherence rate Factors affecting adherence: Patient related factors (marital status, educational, & income), medication related factors (polypharmacy, dosing frequency, side effects, & cost), & physician-related factors
9	[21]	Medication adherence to oral iron therapy in patients with iron deficiency anemia	2016	CS	96	Turkey	Rate of adherence: 59.4% adherence rate Factors affecting adherence: Medication knowledge & treatment side effects
10	[22]	Factors associated with low compliance with lipid-lowering drugs in hyperlipidemic patients	2000	CS	193	France	Rate of adherence: 94% or more adherence rate Factors affecting adherence: Age & side effects

Table 2 (Continued). List of studies included in the review

No	R	Article name	Year	RM	SS	Country	Summary of the findings
11	[23]	Evaluation of factors affecting adherence to asthma controller therapy in chest clinics in a Sub-Saharan African setting: A cross-sectional study	2016	CS	201	Cameroon	Rate of adherence: 55.2% adherence rate Factors affecting adherence: Not visiting specialists & patient age
12	[24]	The epidemiology of prescriptions abandoned at the pharmacy	2010	CS	5,249,380	the USA	Rate of adherence: Low rate of prescription abandonment Factors affecting adherence: Medication cost & new users
13	[33]	Patient nonadherence to medication in inflammatory bowel disease	2003	CS	153	Canada	Rate of adherence: 58.8% adherence rate Factors affecting adherence: Therapy & patient related factors
14	[39]	Beliefs of chronically ill Japanese patients that lead to intentional non-adherence to medication	2004	CS	154	Japan	Rate of adherence: 66.8% adherence rate Factors affecting adherence: Patient's belief & relationship with healthcare provider
15	[57]	Suboptimal statin adherence and discontinuation in primary and secondary prevention populations	2004	RO	4,802	USA	Rate of adherence: 20.4% & 21.5% non-adherence rate Factors affecting adherence: Disease related & therapy related-cost

Note. R: Reference number; RM: Research method; SS: Sample size; CS: Cross-sectional; FG: Focus groups; & RO: Retrospective observational

estimated to be as high as 89.8%, keeping medical appointment has a rate of 85%, and reduction of sodium intake was reported as 80.5%, which brings the overall adherence rate to approximately 85%. The study has also investigated sociodemographic factors and stated that gender, frequency of visiting treating physician, and educational background were the most likely factors that can influence patient adherence.

Another study [14] investigated potential factors affecting long term treatment, which performed a cross sectional study in Kapada, a state in India, to determine treatment and disease related factors that influence nonadherence among patients on antidepressants. The study has a total 103 participants and was performed over a period of six months. They included outpatients only, who are over the age of 18 years, suffering from depression only and excluding other psychiatry diseases. The study reported an overall adherence rate of 53% among the participants. They found that patients who have previously used antidepressants had a nonadherence rate of 57%, those with poly pharmacy reported a 52%, and patients with disease repercussion had a 50% nonadherence rate. Other factors that can influence medication nonadherence were medication affordability, accessibility to physician, family support, disease duration and patient satisfaction with the treating physician.

The study [15] is a focus groups study that investigated potential factors that could influence patient adherence to hypoglycemic medications among 12 focus groups in five different veteran affairs facilities in the USA. The study has 45, predominantly male patient participants, with the mean age of 69 years that ranges between 50-89 year olds. While all patients have reported various comorbidities and poly pharmacy, they study claimed that seven of the 12 groups have reported a high adherence rate, and the remaining five have showed variable rates. The study attributes the high level of adherence in some of the groups to good overall system level facilitators including pharmacy services such as ordering and delivering of medications through different specific mechanisms like automated phone refill services, and Web-based prescription system. However, the study lists lack of alignment among prescriptions, insufficient communication and education levels as major factors that can influence medication adherence.

The study [16] examined potential factors that can affect medication knowledge and disease amongst patients with atrial fibrillation to warfarin in China. The study is a cross sectional study that was conducted in Zhengzhou city on 288 patients who were diagnosed with atrial fibrillation and using warfarin for the last 6 months. The mean age of participants is 59.2 years that ranged between 32-84 years. There was no significant difference in gender, educational background, number of medications and comorbidities among the participants. The study reported an adherence rate to warfarin of 67.7%, who they described as those with good disease knowledge and strong belief in warfarin necessity. They described non-adherents as of younger age, likely to have combined medications, and those who believe that all medicines are harmful.

The study [17] is a cross sectional survey based that investigated potential factors, which can affect medication adherence in the elderly patients in Gyeonggi Province in South Korea. The study has 160 consented participants with the mean age of 67.9 years with an age range of 65-83 years, of whom 70% were females and 83.8% were taking at least one prescribed medication. The study reported a poor adherence rate of 52.5% amongst the participants, who were more likely male, not completed high school, health-related problems, fewer self-reported chronic diseases, negative expectancy of treatment, have low income, and were currently taking more than three prescription drugs. The study reported different patient related factors such as age, level of education and comorbidities; medication related for example medication related factors frequency; and healthcare team related factors including pharmacist-patient relationship and patient satisfaction.

The study [18] is a cross sectional prospective study that investigated adherence to open glaucoma treatment and its related adherence factors. The study has 130 participants with mean age of 55 years with the average of 94 months of glaucoma duration. Interestingly, 65% of the participants did not adhere to their prescribed medications. The authors reported that patient medication adherence was mostly affected by a number of patient related factors including age, education level, and income.

The study [19] is a cross sectional study that investigates factors affecting patient adherence to statins in hypercholesteremic patients in Kuwait. The study has 200 participants with an age range of 30-69 years of whom 43.5% and 42% reported diabetes and hypertension, respectively. The study has categorized adherence as low, medium and high adherence, with 58.5% reported low adherence, 41.5% medium, and 0% as high adherence. The study claimed that patient's age, comorbidities (diabetes and hypertension), and

duration of treatment are important factors that influence patient adherence.

The study [20] is a hospital based cross sectional study that was conducted at the glaucoma clinic in Menelik Province in Ethiopia to investigate the level of adherence to ocular hypotensive treatment and its determinant factors. The study has 359 participants with mean age of 60.9 years that ranges between 18-88 years of which 69% were males, 64% have low education level and 97.5% were using one or more medications. The study reported that 67.4% of the participants were non-adherents and that the main contributing factors were educational level, occupation, monthly family income, dose frequency, route of administration, and financial source to obtain the medications.

The cross sectional study [21] investigated potential factors affecting medication adherence in patients who used oral iron therapy due to iron deficiency anemia. The study has 96 participants who have received oral iron therapy within the recent three years due to iron deficiency anemia. The participants have a mean age of 30 years with a range between 18-53 years. The authors reported more than 40% of participants as non-adherents due to medication's side effects including gastrointestinal side effects and weight gain. The findings are in line with that of [22], which listed medication side effects as one of the possible contributors to medication nonadherence [12].

The study [23] is a cross sectional study that evaluated potential factors affecting adherence to asthma therapy in chest clinics in Sub-Sahara Africa. A total of 201 patients were included in the study with a mean age of 41 years that ranges between of 12-87 years of which 66% were females. The study categorized the rate of adherence as high, which was reported at 18.9%, medium adherence scored 36.3% and low adherence was shown to be 44.8%. While participants younger than 40 years and those with low education were likely to be non-adherents, the study claimed that the only significant factor that can affect adherence is absence of chest physician consultation during the last 12 months prior to the study.

Types of Medication Nonadherence

There are different forms and types of nonadherence to prescribed medicines with different contributing factors. These factors vary greatly and depend on the patient, their disease, and the prescribed medications, all of which will lead to nonadherence to prescribed therapy. Some of the reported types of nonadherence include the followings.

Prescription abandonment

This occurs when patients avoid filling their prescriptions for many and some unknown reasons. A recent study [24] reported that 3.3% of 110 million prescriptions filled by pharmacies were abandoned.

Nonconforming

This type of nonadherence occurs when the prescribed medications are not taken as prescribed; including skipping doses, taking medications at incorrect times, incorrect doses, or taking more than prescribed [25].

Non persistence

When a patient stops a medication after starting it, in the absence of a professionals' advice [25]. This type sometimes is called "intelligent nonadherence", which reflects a reasoned choice rather than necessarily a wise one, for example patients who feel better may decide that they no longer need to take prescribed medications [26].

Causes of Poor Medication Adherence

Poor adherence to medical treatment is a common phenomenon that often compromises patient outcome and increases patient mortality. The complexity of medication adherence is the result of an interchange of a number of factors including patient-related factors, physician-related factors, and health system/team building-related factors [5, 25, 27].

Figure 2 illustrates a summary of the most reported predictors in literature that can lead to medication nonadherence including factors related to patients, physician related factors, disease related factors or therapy related factors. However, medication nonadherence occurs as a result of numerous factors that have been classified by WHO into five

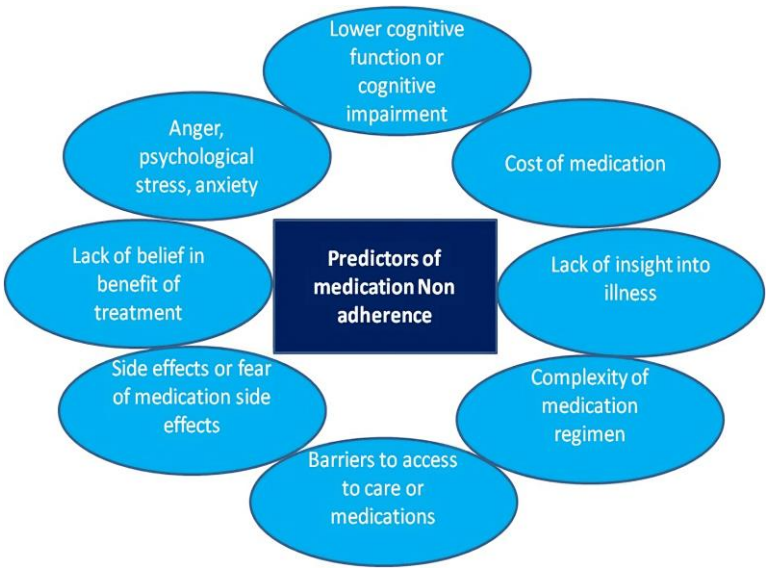

Figure 2. A schematic summary of reported behaviors that lead to nonadherence to prescribed medication (Source: Authors' own elaboration)

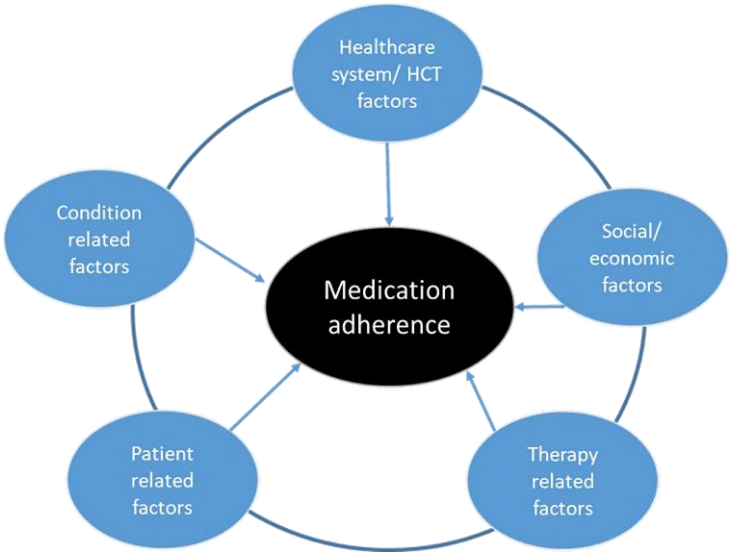

Figure 3. Five interacting dimensions that can affect medication adherence (Adapted from the WHO-Five Dimensions of Medication Adherence)

dimensions (**Figure 3**) [3], including socioeconomic factors, factors associated with the healthcare team and system in place, disease-related factors, therapy-related factors, and patient-related factors [1].

Socioeconomic-related factors

It is a commonly reported factor that contributed to patient nonadherence. The study [18], which investigated patient adherence to open-angle glaucoma and its related factors, reported more than 65% of the studied patients were non-adherent. The study attributed the low adherence rate to patient's socioeconomic status such their educational levels, lifestyle, and their average monthly income [18]. This claim was also supported by findings from [17], which studied potential factors affecting medication adherence in elderly people. The study claimed that participants with lower adherence rate have reported that medication's cost as one of the common causes for being non-adherent [17].

The study [28] investigating the effect of socioeconomic and environmental factors on asthma and patient adherence to asthma therapy, reported that poverty status, big family size, smaller size of home, maternal cigarette smoking low-birth-weight, and maternal age <20 years at the child's birth were significantly associated with increased rates of childhood asthma. The study suggested that low income can affect adherence through the inconsistent primary healthcare, inability to pay for medications, lack of transport, family dysfunction and substance abuse [28].

Similarly, a finding in [29] claimed that socioeconomic status such as income, education and occupation can positively affect patient adherence to antiretroviral treatment. Furthermore, patient's culture and lay beliefs about illness and treatment can also influence the acceptance of their therapies. Beliefs such as fear of the healthcare system or distrust of prescribed therapies such as repurposed medicines can affect patient adherence [1, 30]. This claim was also supported by [16], which suggested that patient belief as one of the important predictors of medication adherence.

Healthcare team-related factors

The physician-patient relationship is complex as it involves two individuals who have been brought together by illness, and each individual may hold different health beliefs [31]. Reduced patient satisfaction with their treating physician is considered a major cause of physician-related medication nonadherence factor [32].

The study [15], investigating factors affecting medication adherence for diabetic patients, reported several healthcare team related problems including poor overall pharmacy services, communication breakdowns between departments (e.g. providers and pharmacy), which affects medication logistics. Also, lack of alignment in prescription refilling times, where patients had to order medications at different times leading to frequent refilling orders. Another reported barrier was the lack of education about medications as well as difficulties in managing complex medication regimens [15]. Likewise, the study [13], which investigated patient adherence to therapeutic regimens among hypertensive patients, claimed that frequent physician visits were among the most likely factors that can improve medication adherence [13]. This finding was similar to that reported by [23], which reported that visiting specialist chest clinics was a determinant factor for medication adherence among asthma sufferers in Sub-Saharan Africans.

The prospective study [33], investigating patient adherence with inflammatory bowel disease medication, has reported that patient-physician discordance directly correlated with patient nonadherence. A more recent meta-analysis reported that a 19% higher risk of nonadherence was reported with patients whose physicians communicates poorly than those patients whose physicians communicate well [34].

Furthermore, it was reported that over 60% of patients interviewed immediately after visiting their doctors misunderstood the directions regarding prescribed medications [35]. Another study reported that 40-60% of patients were not able to correctly recall what their physicians expected of them approximately 10-80 minutes, following physician visit [36].

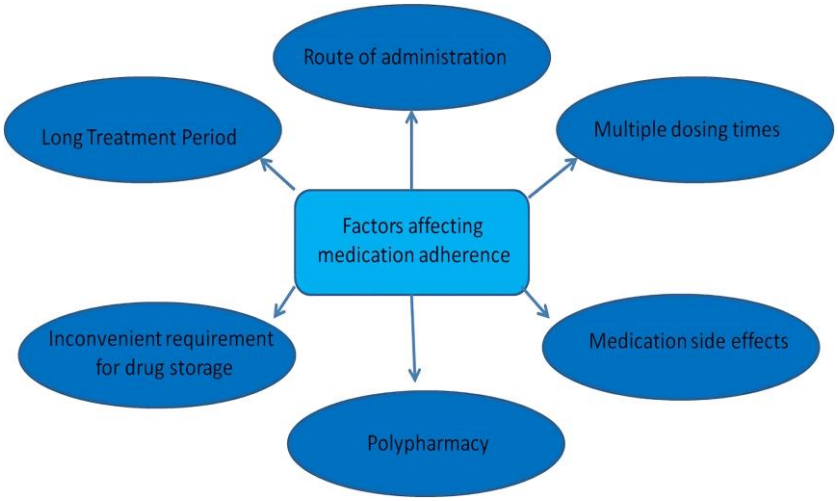

Figure 4. A schematic summary of the most reported therapy-related factors that can lead to medication nonadherence (Source: Authors' own elaboration)

Disease-related factors

The severity of disease symptoms, such as the level of disability (physical, psychological, social, and vocational), rate of progression and severity of the disease and the availability of effective treatments are considered to be strong disease related determinants of medication adherence [1].

Strong evidence shows that many patients with chronic illnesses have difficulty adhering to their recommended medication regimen [5]. Furthermore, a significant drop of about 50% in adherence rate for medications that were designed to be taken over an extended period [25].

A recent study [14] suggested that disease duration represent an important factor that can influence medication adherence. They claimed that the nonadherence rate was 53% for patients with more than one year period of illness, and 1% for those who had disease duration of less than one month [14].

An essential factor that thought to affect medication adherence for chronic diseases, like hypertension, is when patients do not have unpleasant symptoms during the nonadherence period [25]. Moreover, it was reported that patients with concomitant diseases were more likely to be non-adherents to statin therapy than those with hypercholesterolemia only [19]. This claim was further supported by [17], which reported that elderly patients with comorbidities have low adherence rate.

Therapy-related factors

Medication taking manners is an intricate one that involves different practices and beliefs. Patients may be reluctant to take expensive therapies, or those with known side effects. Often, patients unintentionally fall in the nonadherence category due to their misunderstanding of treatment, particularly when given complex regimens. Therapy nonadherence may also occur because of complex medication regimen, such as improper timing of drug administration, or administration of numerous medications at frequent or unusual times during the day [25]. **Figure 4** shows the most likely medication related factors that may lead to nonadherence.

The rate of adherence was found to be proportionally affected by the number of daily doses [3, 37-40]. It was reported that nonadherence increase proportionally with the frequency of prescribed dosing: 20% for once daily, 30% for twice daily, 60% for three times a day, and 70% for four times daily [22, 38, 41]. One of the many barriers to medication adherence reported by [17] was the frequent dosing of the medications. However, the purpose of therapy was found to be an important determinant of medication adherence, with one study reported more than 77% of patients demonstrated high degrees of adherence for medications used to cure a disease and only 63% of patients complied preventative therapy [5, 41, 42]. Medication's adverse effect was reported as one of the most commonly cause of nonadherence. A drug's adverse effect was reported to be the second most common reason for nonadherence with antihypertensive therapy in Germany [43].

The study [21], which investigated medication adherence to oral iron therapy in iron deficient patients, reported a significant relationship between medication nonadherence and treatments' gastrointestinal and weight gain side effect. Likewise, it was reported that medication's side effects and route of administration were most reported barriers amongst non-adherent patients [20].

Therefore, patients should be provided with all necessary and important information, including the name of the medication; its purpose; the rationale for choosing it; the frequency of dosing; when it should be taken; how long it should be taken; and any potential adverse effects, their likelihood of occurring, whether they will resolve without intervention, and how the treatment plan may change if they do not resolve [5, 41, 44].

Patient-related factors

Patient nonadherence varies between and within individuals, as well as across time, recommended behaviors and diseases [45]. The patient adherence with their medication is significantly different amongst different age groups, for instance the rate of adherence in the elderly population was estimated to be 45% [46], which is less than that of the general population. This may in part be due to other comorbidities commonly seen in this patient group such as Alzheimer's disease that impairs their cognitive ability.

The most commonly reported patient-related factor is missing of medication doses due to forgetfulness, changing schedules or busy lifestyles [1, 3]. Patient's lack of understanding of their disease is another commonly observed

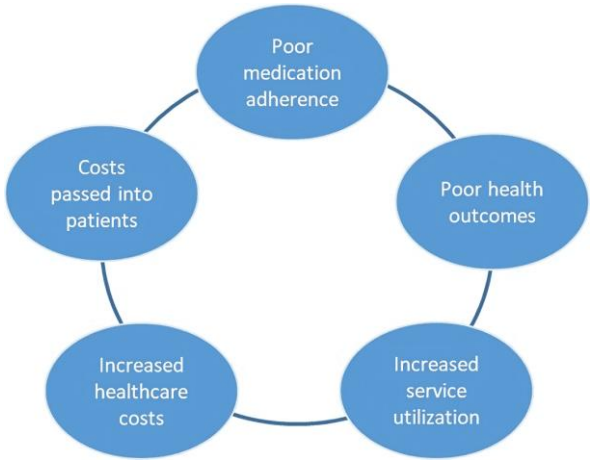

Figure 5. Mechanisms that may contribute to maintenance of medication nonadherence problem in healthcare system [6]

factor [47]. Patients frequently forget instructions given to them by a physician during a clinic visit [48].

Other reported patient-related factors that lead to intentional and unintentional poor adherence with prescribed therapy include anxieties about possible adverse effects [1], lack of involvement in the treatment decision making process [49], low treatment expectations [1], and poor medical literacy [50]. In a study to determine potential factors that influence medication knowledge and beliefs on warfarin adherence among patient with atrial fibrillation in China [16] stated that patient's age and belief of the effect of the medication were the two most important factors that can determine medication adherence. Both [19, 23] reported that patient's age as an important determining factor for medication adherence.

Patients with low literacy may have difficulty understanding instructions; this would result in reduced adherence and poor medication management [41]. Gender, personality, and cultural factors may also influence adherence rates [25]. In fact, the studies [13, 17, 20, 23] have all listed patient's education about their disease and therapy was a crucial factor in determining their adherence with their prescribed medication.

The Effect of Medication Nonadherence on Healthcare

Medication nonadherence is a widespread and recognised public health consideration, which affects both health outcomes and overall healthcare costs. Medication nonadherence leads to poor outcomes, which will increase health care service utilization and overall health care costs [6]. Evidence suggests that patients suffering from chronic diseases such as asthma, hypertension, diabetes and HIV/AIDS, have poor adherence rate to their recommended regimens, which results in suboptimal management and control of their illnesses; thus, reducing potential clinical benefits [1, 51].

In 2013 the costs of healthcare in the USA exceeded $2.5 trillion and accounted for 17.1% of the gross domestic product of which 20-30% of dollars spent in the US health care system have been identified as wasteful [52-54]. **Figure 5** displays the mechanisms of medication nonadherence that may contribute to the overall cost of healthcare system.

Furthermore, it was suggested that 10% of hospitalizations in older adults may be caused by medication nonadherence [55]. Consequently, implementation of programs that improve medication adherence after discharge will significantly lead to lower healthcare costs [56].

DISCUSSION

The current manuscript is a systemic review of the literature that aims to define common nonadherence practices by adult patients, and to determine reported rate of medication nonadherence practices. The study determines and lists the most reported and likely predictors of medication nonadherence as well as potential influencing factors. Determining the rate of nonadherence and its potential influencing factors will increase the knowledge of healthcare professionals about patient's medication taking behaviour, which will encourage them to participate in improving patient medication adherence.

Despite the growing number of studies that highlight the problem with patient nonadherence with recommended medications, the issue remains as a main concern in improving healthcare outcomes. Medication adherence is the primary determinant of treatment outcome. The success of pharmacological treatments depends on the medication efficacy and patient adherence to the prescribed regimen [5]. Strong evidence suggest that poor adherence results in suboptimum clinical benefit and that good adherence improves the effectiveness of interventions [1].

Patient medication adherence represent a complex phenomenon that can occur during any of the medication taking procedure includes physician visit, medication taking processes, and lifestyle modification such exercise and diet. The current review included 15 different studies from different parts of the world including developed, developing and underdeveloped countries. The articles discussed different factors that can affect medication adherence including socioeconomic related factors, healthcare team related factors, disease related factors, therapy related factors, and patient related factors.

Each article discussed different factors that influence medication nonadherence; some articles have listed more than one factor, as some of these factors can interrelate to each other, such as patient related factors and socioeconomic factors. However, some of these factors can somehow be labelled as country specific such access to healthcare or lack of transport, which in some of the underdeveloped countries with less developed healthcare and transport systems represent important predictors of adherence.

These factors were reported in [20, 23], which were reported in two different underdeveloped African nations. Furthermore, an advanced healthcare system can result in improved medication adherence, as shown in [15] that was conducted in the USA, which reported a high adherence rate. This indicates that the status of the healthcare system where the population reside can significantly affect patient adherence.

The studies [14, 18] were carried out in two different developing countries, namely Iran and India, respectively in which they both stated that medication's cost, patient's educational levels and income can affect patient's medication adherence rate. This factor was also reported in developed countries such South Korea [17], which suggested that high cost of medications can result in a reduced adherence rate amongst patients. Healthcare systems represent one of the

many reported factors that may contribute to medication nonadherence. These may include medication high costs or co-payments to which many patients may refrain from adhering to the prescribed therapy [3]. Also, lack of health information technology may prevent physicians from easily accessing information from different healthcare venues that may lead to reduced patient care, timely medication refills, and patient-physician communication [5].

Likewise, socioeconomic background of the patient represents another important factor that can affect patient's adherence [28]. In fact, socioeconomic background was reported as a significant factor that led to reduced adherence rate in developing countries. Socioeconomic factor is one of the very complicated ones, which not only depends on the patient's income, but on the healthcare system of the country in which they live in. While the socioeconomic factor may not be of a great concern for short term treatments, it is considered a crucial factor especially for patients with chronic disease as the treatment period could be life-long [57].

A number of studies reported that patients with no insurance or those with low income were more likely to be non-adherent to therapeutic regimens than others [58]. Nevertheless, health expenses could still be a problem even for those with health insurance. It has been claimed that more than one in ten seniors in the USA reported using less of their required medications because of cost [3].

The majority of the reviewed studies reported some patient-related factors including the patient's gender, age, their educational background, and comorbidities represent important factors that can significantly affect patient's medication adherence [13, 16, 19, 59].

While patient education is the key to improving adherence, use of adherence aids, proper motivation and support is shown to overcome the patient-related medication nonadherence factor [25]. Therefore, a multi-level targeting approach that can target more than one barrier has been shown to be the only effective mechanism that will improve patient adherence [1].

However, it was reported that the illness itself as an important factor that affected the rate of medication adherence [14, 17]. Furthermore, it was documented that patients suffering from chronic diseases have higher nonadherence rate than those with acute illnesses [18]. This factor may not be changed, but good physician communication and patient motivation can improve patient adherence [13, 53].

Another important factor that deters patients from their medications is the medication itself. These may include their side effects, dosing frequency and route of administration [17, 20, 21]. It was reported a 40% nonadherence rate amongst patient using oral therapy to treat iron deficiency, due to the medications side effects [21]. Also, it was suggested that medication's frequency is one of the many factors that contributed to the high rate of medication nonadherence in their studied populations [13, 17, 20]. Thus, counselling and involving patients with the choice of their treatments will likely improve patient adherence [5, 23, 44]. Therefore, the treating physicians should work closely with their patients and try to address their medication related concerns where possible [15].

CONCLUSION

The findings from this review demonstrated that medication adherence is a multi-dimensional and a complex matter that needs to be addressed at different levels. Healthcare providers and policy makers should focus more efforts on improving patient medication adherence. This can be achieved when healthcare providers, physicians, pharmacists and nurses interact more with patients through regular follow-up visits and appointments. Also, healthcare providers can formulate individual patient intervention programs to overcome factors that hinder patient adherence, by ensuring and nurturing a trusted relationship between the patient and their care team. Pharmacists should consider multifaceted and customised strategies to enhance medication adherence. They should work to simplify, routinize, and standardise the process of taking and refilling medicines in general.

Hence, addressing the barriers and solving them collectively in a multi-targeted approach will improve medication outcome and will reduce the economical healthcare burden that some countries, particularly, developing countries cannot cope with.

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