Original Article

Patient-related factors associated with medication adherence behavior in patients with end-stage renal disease: A systematic review

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ABSTRACT

Objectives: This systematic review aims to identify influencing factors of medication adherence behavior in patients with end-stage renal disease (ESRD), with a special interest in patient-related factors based on the World Health Organization adherence model. **Materials and Methods:** Primary electronic databases comprising PubMed, Scopus, Web of Science, Embase and Cochrane Library, as well as ProQuest (Health and Medical), ProQuest (Psychology), and EBSCOHost (APA PsychARTICLES) were used to search for literature on patient-related factors in medication adherence, from inception till August 31, 2021. **Results:** 479 articles were identified and six articles meeting eligibility criteria were reviewed and remained in this systematic review. The present review found that despite different tools being used to measure ESRD's perception of medication's necessity and beliefs, there was a profound association between perception and beliefs with medication adherence behavior. There is a positive relationship between knowledge, belief, educational level, ethnicity, female, and medication adherence behavior. Mixed finding was reported between perception, age, and medication adherence behavior. However, there were no studies on patients' attitudes and medication adherence behavior as suggested in the WHO adherence model. **Conclusion:** Only a limited number of patient-related factors were available for evaluation in the current systematic review. Additional research is needed to advance the understanding of medication adherence behavior affected by patient-related factors on the medication and illness. However, the findings must be taken with caution because of the limited studies included in this review.

KEYWORDS: *Beliefs, End-stage renal disease, Knowledge attitude, Medication adherence, WHO adherence model*

INTRODUCTION

*C*hronic kidney disease (CKD) is a growing public health concern. Its incidence rate is increasing exponentially across the world affecting more than 750 million individuals worldwide as of 2017 [1,2]. Patients with kidney disease may suffer not only from kidney dysfunction but also comorbidities such as diabetes and hypertension [3,4]. Besides, they may experience psychological disorders such as depression or anxiety as a result of their chronic disease [5,6]. With the comorbidities of diseases and disorders, they are likely to develop complex medication management [7], which may then lead to a medication adherence problem.

In the present systematic review, adherence is defined as the extent to which a person's behavior corresponds with agreed recommendations from a health-care practitioner, such as taking medication, following a diet, or executing lifestyle changes [8]. Thus, medication adherence is simply, the extent to which an individual follows through with taking medication

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prescribed by their health practitioner. Medication adherence is crucial for patients with kidney disease to maintain homeostasis [9] and also to improve health with the decrease in the risk of morbidity and mortality [10]. According to the WHO adherence model [8], five factors affect adherence: first, patient-related factors comprising patients' knowledge, attitudes, beliefs, perceptions, and expectations; second, health-care system-related factors consisting of the system's weak capacity to educate patients, health-care practitioners' lack of knowledge and training, and inadequate health services; third, condition-related factor such as the severity of symptoms, comorbidities; fourthly, treatment-related factor consisting of the complexity of the therapy regimen, treatment duration, and treatment failures; and finally, socioeconomic-related factor comprising employment, level of education, and cost of living. Each of these factors influences the adherence behavior of patients [Figure 1].

There had been several research studies that explored the relationship between various chronic diseases such as the health-care system-related factor [11-13], condition-related factor [14,15], treatment-related factor [16-19], socioeconomic-related factor [20-22], and patient-related factor [23-25]. The findings of these studies suggest that patients' adherence behavior is due to many complex and interrelated factors.

Some of these past researches conducted on patient-related factors and medication adherence in patients with diabetes, hypertension, AIDS, and anxiety-depressive disorders reported unintentional nonadherence to the medication regimen because these patients showed a lack of attentional capacity

or resources [23,26-28]. For instance, they may not remember to administer the medication before/after mealtimes or find it challenging to understand the instructions given. On the other hand, intentional nonadherence is defined as patients' awareness or remembrance of their medication regimen, but intentionally stopping or refusing to follow them because they do not favor it. Ghimire *et al.* [24] suggested that patients' knowledge regarding their medication was crucial as participants' concerns about the effects or purpose of their medicines would influence participants' medication adherence. Ahlawat *et al.* [25] found that the elderly were less adherent to their medication regimen due to forgetfulness. This unintentional non-adherent behavior is commonly found among the elderly group in studies of chronic diseases [26,27].

Mixed results were found in medication adherence behavior between genders. Pagès-Puigdemont *et al.* [23] noted that females were better adherers than males in their medication regimen, whereas other studies showed males as better adherers [29,30]. However, these studies were on patients with myocardial infarction, diabetes, or hypertension and were not in end-stage renal disease (ESRD) patients.

The patient-related factor as in accordance with the WHO adherence model includes patients' knowledge about the medication prescribed to them, their attitude, behavior, beliefs in the management strategy of their illnesses, and expectations regarding the treatment outcomes. Past studies focused predominantly on knowledge and gender only; hence, much less is known about the other aspects of patient-related factors, such as attitude, behavior, and beliefs.

Patients' attitudes were associated with effective treatment and medical outcomes in other patients such as patients with hypertension [31], chronic pain [32], and recipients of kidney transplants [33]. However, scarce reports were found on patients with ESRD where medication adherence in them is closely associated with patients' characteristics in which predicted therapeutic compliance [34]. Thus, among other factors, patient-related shall be given the focus to promote better medication adherence behavior among patients with ESRD.

Thus, this current systematic review aims to unravel past knowledge on patient-related factors in medication adherence behavior of patients with ESRD, in accordance with the WHO adherence model criteria and also in search of a possible additional factor related to the model.

MATERIALS AND METHODS
Protocol registration

This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (registration number: NMRR-20-987-54563), and the Institutional Review Board (SREC 005/2017/ER). The systematic review is also registered with PROSPERO (CRD42020199397). It is conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline [35].
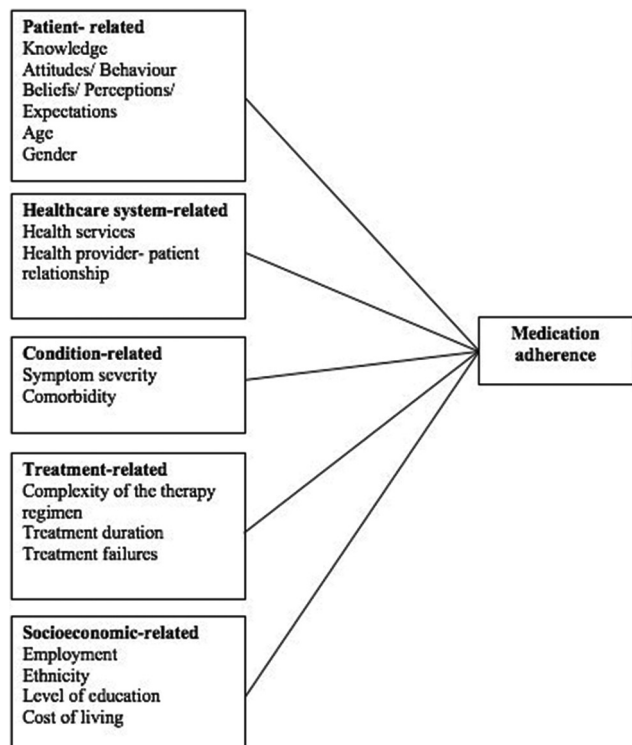

Figure 1: WHO adherence model

Literature search

A computerized literature search was conducted in five major databases: PubMed, Scopus, Web of Science, Embase, and Cochrane Library. Other databases that were used include ProQuest (Health and Medical) and ProQuest (Psychology) and EBSCOHost (APA PsychARTICLES) by the two investigators independently (ALAA and KP) from inception up to August 31, 2021.

Search strategies

The search strategies or search terms used are as follows: (knowledge, patient medication OR medication knowledge, patient OR patient drug knowledge OR drug knowledge, patient OR knowledge, patient drug) AND (attitudes OR opinion OR opinions OR attitude, health OR health attitudes OR health attitudes OR attitudes, health) AND (behaviour, illness OR behaviours, illness OR illness behaviours OR sickness behaviours OR behaviours, sickness OR behaviours, sickness) AND (medication adherence OR medication nonadherence OR medication nonadherence OR medication noncompliance OR medication persistence OR medication noncompliance OR medication compliance OR adherence, medication OR nonadherence, medication OR compliance, medication OR noncompliance, medication) AND (patient nonadherence OR patient noncompliance OR patient adherence OR patient compliance OR patient cooperation OR compliance, patient OR adherence, patient OR patient noncompliance) AND (ESRD OR end-stage renal disease OR disease, end-stage kidney OR renal disease, end-stage OR renal disease OR chronic kidney disease OR kidney disease OR chronic kidney failure OR end-stage renal failure OR renal failure, end-stage OR renal failure, chronic OR renal failure, endstage OR chronic renal failure). An expanded combination of Medical Subject Headings search terms was used [Appendix 1].

Study screening

Initially, relevant articles were identified through the databases mentioned above and were imported into Endnote X9. Imported articles then underwent a process to remove any duplicated articles. Two investigators (ALAA and KP) independently screened the titles and abstracts for the current review suitability based on the inclusion criteria. Furthermore, eligibility and quality assessment of important articles and search for full-text articles were conducted. If any discrepancies of quality assessment on the included studies were found between two investigators (ALAA and KP), a discussion was held and resolved by the senior authors (KWL and PBO) for final consensus before the full text of each relevant article was reviewed.

Inclusion criteria

Studies were included in the systematic review if they met the inclusion criteria below:
a. Studies included adult patients who had been diagnosed with ESRD
b. Studies investigated patient-related factors (e.g., knowledge, attitude, perception/beliefs) on medication adherence behavior
c. Published in English or have an English translation version

d. Peer-reviewed studies and
e. Observational studies only

Titles and abstracts of articles were screened for relevance. Full texts of relevant articles were obtained, and data or information from each article were extracted as described in the next section.

Data extraction

Data extracted from the studies included the last name of the first author, year of publication, place, country, sample size, study design (cross-sectional, cohort, longitudinal), sampling method, screening method, population, instruments used in the studies for adherence measurement and beliefs/perceptions of medication knowledge, demographics (e.g., ethnicities, educational level, marital status, income, and employment), and significant findings. Two investigators (ALAA and KP) individually extracted the data. They assessed the study quality, with discrepancies resolved through a discussion with a moderator (Akshina Dewi Nawoor [ADN]). The outcome measure for medication adherence varied among studies included with some reporting only the odds ratio or means and no consistent results were available for comparison. Therefore, the decision made was to exclude meta-analysis from the current study.

RESULTS

Quality assessment

The Joanna Briggs Institute Critical Appraisal Tools [36] was used as a checklist to assess the quality of the articles. They were assessed by two investigators (ALAA and KP) independently. Any discrepancies were resolved through discussion with two investigators (SCP and PBO). The checklist consisted of 8 items that assess components in analytical cross-sectional studies. To determine the risk of bias, each article's quality was judged according to the following: (1) low risk of bias if studies reached more than 70% score "yes;" (2) moderate risk of bias if "yes" scores were between 50% and 69%; and (3) high risk of bias if "yes" scores were below 49% [36]. "✓" indicates yes, "×" indicates no and "?" indicates unclear [Table 1].

Description of included studies

As shown in Figure 2, in the initial search process, 495 articles were identified in all the databases stated in the identification stage. After removing duplicates, there were 479 studies for the title and abstract screening. Title and abstracts were screened to ensure that it is related to the objective of this study. During the screening process, 337 studies were excluded based on screening of title and abstract to ensure that it is related to the objective of this study, and 142 studies were left for full-text assessment. From the 142 studies, another 136 studies were excluded due to insufficient results (e.g., narrative review articles or not pertaining to patient-related factors). After careful evaluation, only six eligible studies were remained and included for quantitative analysis, and these 6 were in the systematic review with low and moderate risk of bias.

The results yielded by the databases search had a mixed population such as ESRD and CKD patients. Although one

Table 1: Joanna Briggs Institute critical appraisal checklist for analytical cross-sectional studies

Study	Q1[a]	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Percentage yes	Risk
Abd Kadir *et al*. [37]	✔	✔	✔	✔	?	?	✔	✔	75	Low
Aleidi *et al*. [38]	✔	✔	?	✔	✔	✖	?	✔	62.5	Moderate
Chater *et al*. [39]	?	?	✔	✔	✔	✖	✔	?	50	Moderate
Horne and Weinman [40]	✔	✔	✔	✔	✔	✔	✔	✔	100	Low
Kim and Evangelista [41]	✔	✔	✔	✔	✔	✔	✔	✔	100	Low
Neri *et al*. [42]	✔	?	✔	✔	✔	✔	✔	✔	87.5	Low

[a]Q1 - Q8 indicate questions 1 to 8 based on the JBI risk assessment checklist. JBI: Joanna Briggs Institute. ?: Unclear
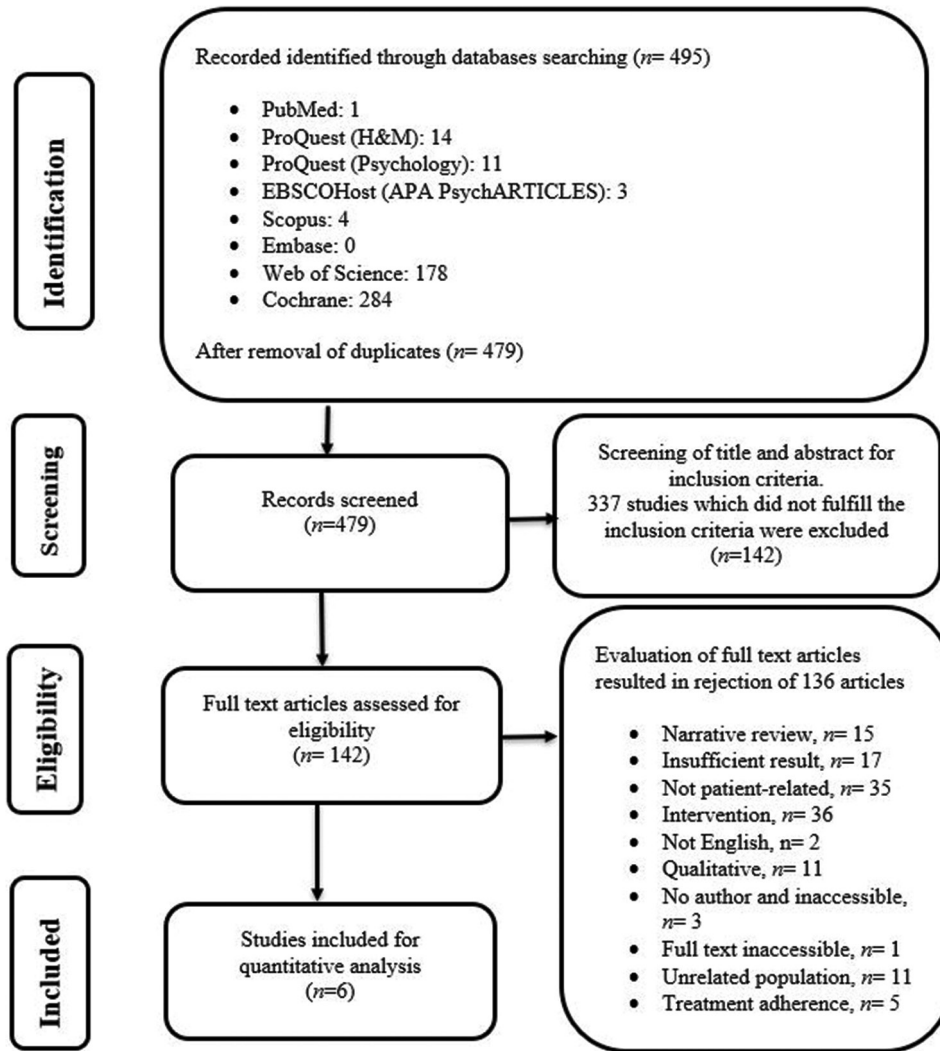
Figure 2: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

study [40] had 4 different populations (asthma, renal, cardiac, oncology), we retained the study and focused on the results yielded for renal patients in the study.

Characteristics of included studies

These six research articles varied in their methods of analysis, patient population, and instruments used for the outcome variable (medication adherence). As a result of the varying methodology being applied in these studies, there was no attempt to combine the results into a meta-analysis. Table 2 summarizes

the details from the 6 studies indicating the sample size, study design, patient population, mean age, gender, race, educational level, the instrument used in the studies, and findings.

A total of 2387 patients with kidney disease were included in the systematic review. The range of the mean age was 49–67 years [Table 2]. Two of the six studies were conducted in the United Kingdom [39,40], one study each in the United States of America [41], Saudi Arabia [38], Malaysia [37], and Italy [42].

Table 2: Characteristic of the included studies

Author (year) and country	Study design	Populations, (*n*)	Mean age (SD)	Gender (%)	Race (%)	Educational level (%)	Instrument used to measure adherence + (beliefs/perception/knowledge)	Results related to patient-related factors associated with medication adherence
Chater *et al.* (2014)[39] United Kingdom	Cross-sectional	Dialysis (renal), (221)	58.1 (14.2)	Male (52.0) Female (43.9) Not stated (4.1)	Caucasian: 82.4 Asian/Asian British: 6.3 black/black/ black British: 2.7 Mixed: 2.7 Other: 1.4 Not stated ethnic: 4.5	High school: 52.5 Higher education: 24 Not stated: 18.1	MARS + (BMQ)	Younger age significantly (OR=0.98, 95% CI=0.54-2.43, *P*<0.01) related to low-intentional adherence but not unintentional Non-caucasian has low adherence (OR=2.36, 95% CI=0.88-6.32, *P*<0.01) intentional adherence (*P*<0.01) but not unintentional (*P*>0.05) as non-Caucasians have higher concerns (Mean=2.57, SD=0.73) compared to Caucasian (Male=2.96, SD=0.92) Low adherence was associated with reduced beliefs in personal need for the treatment (OR=0.34; 95% CI: 0.14-0.83; *P*<0.05), and increased concerns about the treatment (OR=3.17; 95% CI: 1.87-5.37; *P*<0.001)
Horne and Weinman (1999)[40] United Kingdom	Cross-sectional	Renal (dialysis), (47) Asthma, (78) Cardiac, (116) Oncology, (83)	Renal: 49.0 (17.3)	Male (49.0) Female (51.0)	N/A	Renal-Secondary: 59.6 Tertiary: 21.3 Advanced: 19.1	MARS + (BMQ)	Younger patients reported lower adherence Medication beliefs were the strongest predictor for adherence (19% variance) than demographic variables and clinical factors Patients' beliefs about medicine, types of illness and age of the patients influence the adherence rate
Kim and Evangelista (2010)[41] United States	Cross-sectional	ESRD, (151)	51.9 (15.6)	Male (57.6) Female (42.4)	Caucasian: 1.3 African American: 12.6 Asian American: 38.4 Native American: 0.7 Hispanic: 47.0	High school/less: 56.3 Vocational: 4.6 Some college/ uncompleted: 14.6 College graduate/ more: 24.5	ESRD-AQ + (IPQ-R)	Older patients perceived higher chronicity of ESRD by higher scores in the timeline dimension (mean=23.49, SD=4.67) compared to young (mean=20.73, SD=5.32). Thus, higher medication among older patients than young patients In general, six out of the seven patients' illness perception of control dimension do not correlate with adherence, except for "treatment control", which was correlated with non-adherence to treatment (*r*=−0.171, *P*<0.05)
Aleidi *et al.* (2020)[38] Saudi Arabia	Cross-sectional	ESRD, (237)	52.15 (15)	Male (54.0) Female (26.0)	N/A	Illiterate: 28.7 High school/less: 54.4 University level: 15.6 Higher education: 1.7	Patients' responses on the commitment to dose and administration of the drug (time) + (Self-developed questionnaire on knowledge)	Recruitment of younger patients (mean age=52.15 years) lead to good adherence A positive significant correlation between serum phosphate (*P*=0.00); knowledge of dietary control (*P*=0.001) A strong positive correlation between phosphate serum level and the number of phosphate

Contd...

Table 2: Contd...

Author (year) and country	Study design	Populations, (n)	Mean age (SD)	Gender (%)	Race (%)	Educational level (%)	Instrument used to measure adherence + (beliefs/ perception/knowledge)	Results related to patient-related factors associated with medication adherence
								binder tablets administered (P=0.003). Further, a significant negative correlation between phosphate serum level and the use of phosphate binders (P=0.000) Another negative correlation between serum PTH level and the use of phosphate binders (P=0.023) Therapeutic efficacy was affected by other factors such as administration time adherence positively correlated with the serum phosphate level (P=0.00) Adherence to treatment is positive significantly correlated with knowledge of dietary control (P=0.001)
Abd Kadir et al. (2019)[37] Malaysia	Cross-sectional	CKD, (491)	54.5 (14.6)	Male (49.5) Female (50.5)	Malay: 80.4 Chinese: 14.5 Indian: 3.9 Others: 1.2	N/A	Calculate no. of missed doses in past 1 month + (DFIT)	Patients aged >55 years reported to be 2.3 times higher in medication adherence rate Having drug knowledge increased the adherence rate by 8.7 times A lower number of adherence when using individual medication assessments (adherent: n=135, 27.5%; non-adherent: n=356, 72.5%) compared to assessing patients based on a general adherence assessment (adherent: n=404, 82.3%; non-adherent: n=87, 17.7%) (χ^2=40.1, df (1), P<0.01) Common reasons for non-adherence were found to be forgetting to take medications (51.1±24.8%) and complex medication schedule (20.8±25.8%)
Neri et al. (2011) [42] Italy	Cohort	Dialysis (renal), (1238)	Adherent: 66.6 (12.8) Non-adherent: 61.7 (14.5)	N/A	N/A	N/A	MMAS-4 + (BOT)	BOT score was strongly associated to tablet count (β=0.09, P<0.01), age (β=-0.07, P=0.03), female sex (β=0.15, P<0.01), support from healthcare providers (SHC; β=-0.15, P<0.01), dialysis vintage (years; β=-0.09, P<0.01), number of hospitalizations (β=0.07, P=0.03), region of residence (North: β=-0.23, P<0.01) Besides, perceived BOT scores are significantly positively correlated with patient's adherence (OR=0.484, (0.352-0.666) However, patients with low education would have a stronger association with support from healthcare providers (interaction term: β=0.14, P=0.02)

N: Sample size; N/A: Not applicable; ESRD: End-stage renal disease; MARS, Medication Adherence Reports Scale; BMQ: Beliefs about medication questionnaire; IPQ-R: Revised illness perception questionnaire, AQ: Adherence questionnaire; MMAS-4, 4-item Morisky's Medication Adherence Scale; BOT: Perceived burden of oral therapy; DFIT: Assessment of drug dose, frequency, indication, and administration, PTH: Parathyroid hormone, CKD: Chronic kidney disease, SD: Standard deviation, OR: Odds ratio, CI: Confidence interval, SHC: support from healthcare providers

Questionnaires used to measure adherence

There were various medication adherence tools used to assess patients' adherence toward medication such as the Medication Adherence Rating Scale (MARS) [39,40], 4-item Morisky's Medication Adherence Scale (MMAS-4) [42], ESRD adherence questionnaire (ESRD-AQ) [41], number of missed doses reported by patients for the past one month [37], and patients' commitment to dose and time of administration of drugs [38].

Questionnaires used to measure belief, perception, and knowledge

From the six studies, only two of the studies [39,40] used the Beliefs about Medication Questionnaire (BMQ) to measure people's evaluation of medicines in terms of necessity and concerns. The second standardized instrument used to assess cognitive representations of illness was the illness perception questionnaire (IPQ-R), being adopted in one study [41]. Only one study used the Perceived Burden of Oral Therapy (BOT) to measure patients' perceptions of the burden of taking medication [42]. In addition, two studies investigated patients' medication knowledge: one study used the assessment of Drug, Frequency, Indication, and Administration (DFIT) [37] and another study used their self-developed questionnaire to assess patients' knowledge on medication [38].

Patients' medication knowledge, beliefs, illness perception, and adherence

Some conflicting results were seen in studies that used BMQ to measure patients' beliefs on the necessity and concern of medication. Chater *et al*. [39] found that the patients expressed their beliefs as a common necessity and great concern with medication. Moreover, Horne and Weinman [40] reported that patients with renal disease expressed significantly higher necessity than concerns and were more likely to adhere to medication compared to cardiac and oncology patients.

In one study, Kim and Evangelista [41] found that treatment control had a significant correlation with non-adherence, i.e., patients with a higher level of perception of uncontrollability of their illness displayed a higher nonadherence. In addition, three studies investigated patients' medication knowledge and these studies found that patients were more likely to be nonadherent when they have less medical knowledge about the medication, they have been prescribed [37,38,41].

Age, gender, ethnicity, education level, and adherence

Age

Five out of the six studies included in the current systematic review found similar trends for age and adherence toward medication, in that the younger end of the mean age range is less likely to adhere to medication compared to their older counterparts. Chater *et al*., [39] explained that the young people's lack of adherence in their study were more intentional (i.e., I do not want to eat my medication) than unintentional (i.e., I forgot to eat my medication). Younger age also showed more significant concern on the medication than regarding it as a personal need (necessity) according to their scores in the BMQ's necessity and concern domains. Age as a patient-related factor

was inconclusive in Aleidi *et al*.' study [38] as their participants reported a mean age of 52.15 years.

Gender

Only two studies in this systematic review found significant gender differences. Chater *et al*., [39] showed that females expressed more concerns toward medication than males. However, they did not find any association between beliefs and adherence for differing genders. Another study by Kim and Evangelista [41] measured the clearance of urea (K), time (t) over the volume of distribution of urea (V) (Kt/V) and post-SUN levels (levels of vitamin D) of both genders. They revealed that females had significantly lower Kt/V urea (solute removal during hemodialysis) and higher post-SUN (Vitamin D) levels than males. This might suggest that females are less adherent than the males because patients who adhere to the medication would typically have higher Kt/V urea and lower levels of post-SUN.

Ethnicities

One study found differences between patients' ethnicity and its association with adherence behavior [39]. Their findings revealed that non-Caucasians were substantially associated with low medication adherence compared to Caucasians. Non-Caucasians adherence type was most likely to be intentional nonadherence (i.e., I refused to take my medication) because they have greater concerns about the effectiveness of the medication.

Educational level

Three out of six studies reported patients' educational level is associated with adherence behavior.

Neri *et al*. [42] reported that patients with a lower level of education reported a stronger perceived BOT score– i.e., they are bothered more by the number of pills prescribed, the size of the pills, the side effects and also frequency of therapy, and thus reported lower adherence behavior. However, another two studies reported that the patients' education level did not predict patients' medication adherence [40,41].

DISCUSSION

The purpose of this review is to examine patient-related factors (i.e., knowledge, attitudes, beliefs, age and gender) of the WHO adherence model in patients with ESRD and its association with medical adherence behavior. It is also to capture any gaps that have not been explored. Initially, this systematic review aimed to investigate the association between patient-related factors and medication adherence behavior in patients with ESRD. However, further analysis revealed that socioeconomic/demographic trends were also significant and hence it was reported in the review as part of the demographic variables.

Thus, we first discuss the original objective, followed by further analysis.

Main finding: Patients' knowledge, beliefs, illness perception, and adherence

Knowledge

We found that patients were more likely to be nonadherent when they have less knowledge about the medication they

have been prescribed. This was noticeably apparent for the phosphate binder medication as patients were fearful of the adverse effects [37,38], the unpleasant taste [37], and the lack of understanding of the complexity of the role of minerals and electrolytes in the phosphate binder as reported by Aleidi *et al.*, 2020 [38]. Abd Kadir *et al.* [37] found that patients were most adherent to antiplatelets and antihypertensive medication compared to insulin and phosphate binders. Moreover, despite the significant positive correlation between medication knowledge and medication adherence in Aleidi' study [38], 80% of those patients that reported poor knowledge of dietary phosphate control and phosphate binders displayed normal phosphate level. Both studies found that the level of medication knowledge is associated with medication adherence. This is crucial especially for medications such as insulin and phosphate binders.

Belief

Patients believed medication is a necessity, but they also have a high concern about the medication that is prescribed such as the side effects of medication. Although they expressed great concern, the patients were still categorized as high adherers than low adherers via MARS. This may explain that the patients' nonadherence type was unintentional as MARS is a self-reported questionnaire and it was found that these patients who had a high concern about the medication showed high adherence to medication despite that their belief about medication is otherwise. However, patients may show socially desirable characteristics – reporting what is expected by society-in a self-reported survey. From the observation made with Chater *et al.* [39] and Horne and Weinman [40] studies that used BMQ, it may suggest that there are constant changes between the two components of BMQ (necessity and concern) among patients with kidney disease.

Illness perception

Kim and Evangelista [41] found that treatment control had a significant correlation with nonadherence to diet restriction – i.e., the treatment control and diet restriction showed a significant negative correlation. Patients with kidney disease who have negative illness perceptions would rely on medication treatment without adhering to diet restriction. Diet restrictions appear to be an unimportant attribute to their kidney disease. With only one study that used IPQ to assess patients' cognitive representations of their illness, it was difficult to arrive at a conclusive deduction.

As mentioned before there were different types of measuring tools or questionnaires used primarily to measure medication adherence in all the studies included. However, there are some questionnaires used more for measuring beliefs or perceptions such as the BMQ and IPQ.

Some observations were made on BMQ's domain of medication necessity and concern beliefs. One possible reason for BMQ popularity is because the original authors tested on six illness groups (i.e., asthmatic, diabetic, renal, cardiac, psychiatric, and general medical), and hence it may be easily generalized to most illness patient groups, especially chronic illness patients. The questionnaire is easily

accessible from the original construction of the questionnaire paper. The questionnaire consists of 18 questions with four subdomains (Specific-Necessity, Specific-Concern, General-Overuse, and General-Harm).

The IPQ is also a regularly used measuring tool. It is easily accessible, and the components were based on Leventhal's Self-Regulatory Model, which captures both the emotional representation and cognitive dimensions of the illness [43]. There have been two different versions of IPQ, namely the revised IPQ (IPQ-R) and brief IPQ (B-IPQ). The IPQ-R is the improved version of the original IPQ as some of the components such as control/cure and timeline were lower than other domains. New items were added in the control/cure and timeline components to provide better internal reliability in the revised IPQ, and this sums about 54 questions with 11 subdomains. The shorter version, B-IPQ, is easily accessed in the original paper. It only consists of 9 questions with good reliability. The personal control item has been comparatively low in both IPQ-R and B-IPQ. They found that the personal control item in B-IPQ is better than IPQ-R because they obtained a significant correlation with two different types of illness groups (i.e., diabetes and asthma). Contrarily, IPQ-R only obtained a significant correlation with one type of illness group (i.e., asthma) [44]. The original set of IPQ-R is a lengthy questionnaire to complete as it has 54 questions in total. Therefore, the use of either B-IPQ or IPQ-R depends on researchers' choice and suitability for their study aim.

One study included in the systematic review used the assessment of Drug Dose, Frequency, Indication, and Administration (DFIT) [37] and Aleidi's study developed their questionnaire with Cronbach's alpha of 0.80 [38]. The DFIT [37] rated the participants' medications knowledge and abilities to read and understand the medication instructions based on their correct answers. The higher the score, the better the medications knowledge. In Aleidi's study, the self-developed instrument was used to measure the patient's knowledge of phosphate dietary control and adherence levels toward the control of hyperphosphatemia. Participants were rated as having good knowledge levels (11-7 points), moderate knowledge level (7-4 points), or poor knowledge level (0-4 points).

Secondary finding: Socioeconomic/demographic and adherence

Our review revealed that age, gender, educational level, and ethnicities are closely related to patient-related factors as it is associated with the individuals' perception of their overall healthcare [45]. Thus, the authors deemed it necessary to include educational level and ethnicities in our present review and report. In addition, the present review only found studies reported on patients' knowledge, beliefs, and perceptions; there were no studies found on ESRD patients' attitudes as suggested in the WHO adherence model. Patients' attitudes, not only influence medication adherence, are the key elements to effective treatment and self-management strategies. Any treatment strategies shall assess the patients' attitudes and integrate the findings into the clinical process to improve medical and treatment adherence.

Age, gender, ethnicity, education level, and adherence

All the studies included in the current systematic review reported that younger patients are less likely to adhere to medication. Similar trends of age and medication adherence behavior were also found in studies of other illness groups such as HIV, diabetes [28,46,47], cardiovascular illness [48], and hypertension [49-51]. Their findings revealed that older age patients tended to adhere to medication better than younger age patients. This evidence from other chronic illness groups (e.g., hypertension, diabetes) substantiate the finding of the current systematic review on age differences and medication adherence behavior. However, some studies find otherwise, where older adults are less adherent toward the medication regimen than the young [52,53]. This suggests that age may be the best predictor for medication adherence in patients with ESRD.

Only two studies in this systematic review found significant gender differences. Chater *et al*., [39] showed that females expressed more concerns toward medication than males. However, they did not find any association between beliefs and adherence for differing genders. Another study by Kim and Evangelista [41] measured the clearance of urea (K), time (t) over the volume of distribution of urea (V) (Kt/V) and post-SUN levels (levels of vitamin D) of both genders. They revealed that females had significantly lower Kt/V urea (solute removal during hemodialysis) and higher post-SUN (vitamin D) levels than males. This might suggest that females are less adherent than the males because patients who adhere to the medication would typically have higher Kt/V urea and lower levels of post-SUN.

Kim and Evangelista [41] also found that females scored significantly higher for identity dimension (i.e., perceived more physical symptoms such as fatigue, loss of strength, and dizziness) than males. Moreover, females experienced more emotional disturbances associated with ESRD as they substantially scored greater emotional representation dimension compared to males. Contrarily, females adhered more to medication taking than males. In support of this, studies also found that the female gender adheres better than males [23,54].

In terms of ethnicity, non-Caucasian's adherence type was most likely to be intentional nonadherence (i.e., I refused to take my medication) because they have greater concerns about the effectiveness of the medication [39]. A similar study by Constantiner *et al*., [55] found that Blacks and Hispanics (non-Caucasians) reported significantly more barriers to consuming immunosuppressant medication than Caucasians. However, there were no apparent differences in controllable barriers (e.g., "I miss a dose of my immunosuppressant medication (s) as I think there may be side effects") in Constantiner's study. Only uncontrollable barriers (e.g., "I get confused about how to take my immunosuppressant medication") were significant for Hispanics compared to Caucasians but not significant for Blacks or other ethnicities. Therefore, this indicates that ethnicity differences and medication adherence behavior may play a part, especially in the adherence type (intentional or unintentional).

For education level and medication adherence, Kim and Evangelista [41] found that patients with higher educational levels (above high school) scored low in the personal control dimension in IPQ-R, suggesting that the patients perceived their actions of taking medication or not has no consequences on the outcome of their illness. This finding implies that individuals with high levels of education might have less adherence rate. Moreover, studies revealed that patients with lower educational levels were strongly associated with their health-care practitioners' support, thus suggesting that they are likely to adhere to a medication when there is strong support from their health practitioners [42]. However, some past studies do not concur with the findings above and reported that low educational levels would have low medication adherence [26,56-60]. Therefore, the results for levels of education and adherence behavior should take into caution for generalizability.

Measuring adherence behavior

This systematic review reveals that various adherence tools were used in the studies of patients' medication adherence behavior. MARS may not be suitable for measuring tools to use to capture adherence behavior for patients with kidney disease as it is targeted to chronic mental illness patients especially schizophrenia [61,62]. There are only slight differences in the types of domains or subdomains they are attaining from each of the measurements. Appendix 2 summarizes the measuring tools concerning their strengths and limitations, as well as the Cronbach alpha of these tools.

Consequently, researchers could also adopt a more objective approach in measuring medication adherence such as the one used in Abd Kadir *et al*.' study [37] (i.e., calculated no. of missed doses for the past one month) and Aleidi *et al*.' study [38] (i.e., patient's responses on the commitment to dose and the time for administration of the drug, and these were compared with the record of serum phosphate levels of each patient). This could capture rich data as it would have less human error compared to a self-reported questionnaire, where there could be a high influence of demand characteristic or forgetfulness from patients.

Strengths and limitations

There are several limitations in the current systematic review. It is unavoidable to have a selection bias or publication bias, as many research articles have been published on medication adherence. However, the present authors tried their best to reduce the bias by including and reporting differing results found and critically review each study. Furthermore, a meta-analysis was not feasible to run as the questionnaires varied across studies and there is no consistency in reporting the odds ratio or means of the results, particularly in measuring adherence. Although the number of included articles was small ($n = 6$), most of the studies included are at with low and moderate risk of bias. Moreover, the present review only found studies on knowledge, beliefs, and perceptions; there were no studies found on patients' attitudes as suggested in the WHO adherence model. With the resources available, the current systematic review could only focus, mainly, on patient-related factors such as beliefs and attitudes of medication adherence and medication knowledge in patients with ESRD.

Despite the limitations, this systematic review presented some strengths where rigorous comparisons between measuring tools were conducted and the extraction of trends in the sociodemographic factors (educational level and ethnicities) in all the six included studies were also examined. In addition, age plays a crucial role in affecting adherence behavior in patients with ESRD and from the findings, it is worth starting the education process of why medication adherence is essential in dealing with any form of chronic diseases-even before a young "potential" patient becomes a patient. Prevention campaigns and initiatives shall be drawn and organized based on this-i.e., awareness and prevention at early years.

Conclusions

This systematic review identified the importance of patient-related factors in promoting medication adherence behavior. Patients' perception and beliefs with the treatment reported the most profound association with medication adherence behavior as there were consistent findings from all the studies. With this discovery, it would be beneficial for education and intervention programs on medical adherence to start addressing patients' perceptions and beliefs as it affects patients' efficacy in consuming the medication. In addition, it is also important to promote higher health literacy in patients' knowledge about medication adherence as knowledge plays a role between treatment compliance and medication adherence. Attitude, as a factor under the patient-related factor, was not included nor reported in the past six studies although attitude could influence the medical and treatment outcomes. The finding would be important and helpful to counsellors, psychologists, and clinicians in managing their patients' or clients' beliefs and knowledge to promote better adherence behavior.

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Conflicts of interest

There are no conflicts of interest.

References

1. Bikbov B, Perico N, Remuzzi G, on behalf of the GBD Genitourinary Diseases Expert Group. Disparities in chronic kidney disease prevalence among males and females in 195 countries: Analysis of the global burden of disease 2016 study. Nephron 2018;139:313-8.

2. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1789-858.

3. Tonelli M, Wiebe N, Guthrie B, James MT, Quan H, Fortin M, et al. Comorbidity as a driver of adverse outcomes in people with chronic kidney disease. Kidney Int 2015;88:859-66.

4. Fraser SD, Roderick PJ, May CR, McIntyre N, McIntyre C, Fluck RJ, et al. The burden of comorbidity in people with chronic kidney disease stage 3: A cohort study. BMC Nephrol 2015;16:193.

5. Moreira JM, Bouissou Morais Soares CM, Teixeira AL, Simões E Silva AC, Kummer AM. Anxiety, depression, resilience and quality of life in children and adolescents with pre-dialysis chronic kidney disease. Pediatr Nephrol 2015;30:2153-62.

6. Ozcan H, Yucel A, Avşar UZ, Cankaya E, Yucel N, Gözübüyük H, et al. Kidney transplantation is superior to hemodialysis and peritoneal dialysis in terms of cognitive function, anxiety, and depression symptoms in chronic kidney disease. Transplant Proc 2015;47:1348-51.

7. St. Peter WL, ed. Management of polypharmacy in dialysis patients. Seminars in dialysis. Wiley Online Library; 2015;28:427-32.

8. World Health Organization. Adherence to long-term therapies: Evidence for action. World Health Organization; 2003.

9. Tangkiatkumjai M, Walker DM, Praditpornsilpa K, Boardman H. Association between medication adherence and clinical outcomes in patients with chronic kidney disease: A prospective cohort study. Clin Exp Nephrol 2017;21:504-12.

10. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ 2006;333:15.

11. Adams AS, Uratsu C, Dyer W, Magid D, O'Connor P, Beck A, et al. Health system factors and antihypertensive adherence in a racially and ethnically diverse cohort of new users. JAMA Intern Med 2013;173:54-61.

12. Sarkar U, Lyles CR, Parker MM, Allen J, Nguyen R, Moffet HH, et al. Use of the refill function through an online patient portal is associated with improved adherence to statins in an integrated health system. Med Care 2014;52:194-201.

13. Demian MN, Shapiro RJ, Thornton WL. An observational study of health literacy and medication adherence in adult kidney transplant recipients. Clin Kidney J 2016;9:858-65.

14. Adefolalu AO, Nkosi ZZ. The complex nature of adherence in the management of HIV/AIDS as a chronic medical condition. Diseases 2013;1:18-35.

15. Saadat Z, Nikdoust F, Aerab-Sheibani H, Bahremand M, Shobeiri E, Saadat H, et al. Adherence to antihypertensives in patients with comorbid condition. Nephrourol Mon 2015;7:e29863.

16. Phillips LA, Leventhal H, Leventhal EA. Physicians' communication of the common-sense self-regulation model results in greater reported adherence than physicians' use of interpersonal skills. Br J Health Psychol 2012;17:244-57.

17. Xie L, Frech-Tamas F, Marrett E, Baser O. A medication adherence and persistence comparison of hypertensive patients treated with single-, double- and triple-pill combination therapy. Curr Med Res Opin 2014;30:2415-22.

18. Carbone L, Zebrack B, Plegue M, Joshi S, Shellhaas R. Treatment adherence among adolescents with epilepsy: What really matters? Epilepsy Behav 2013;27:59-63.

19. Sontakke S, Budania R, Bajait C, Jaiswal K, Pimpalkhute S. Evaluation of adherence to therapy in patients of chronic kidney disease. Indian J Pharmacol 2015;47:668-71.

20. Peltzer K, Pengpid S. Socioeconomic factors in adherence to HIV therapy in low- and middle-income countries. J Health Popul Nutr 2013;31:150-70.

21. Hodeib M, Chang J, Liu F, Ziogas A, Dilley S, Randall LM, et al. Socioeconomic status as a predictor of adherence to treatment guidelines for early-stage ovarian cancer. Gynecol Oncol 2015;138:121-7.

22. Kim TH, Lee MJ, Yoo KB, Han E, Choi JW. Association of demographic and socioeconomic factors with risk factors for chronic kidney disease. J Prev Med Public Health 2015;48:170-7.

23. Pagès-Puigdemont N, Mangues MA, Masip M, Gabriele G,

Fernández-Maldonado L, Blancafort S, et al. Patients' perspective of medication adherence in chronic conditions: A qualitative study. Adv Ther 2016;33:1740-54.

24. Ghimire S, Castelino RL, Jose MD, Zaidi ST. Medication adherence perspectives in haemodialysis patients: A qualitative study. BMC Nephrol 2017;18:167.

25. Ahlawat R, Tiwari P, D'Cruz S. Prevalence and predictors of medication non-adherence in patients of chronic kidney disease: Evidence from a cross sectional study. J Pharm Care Health Syst 2016;3:1.

26. Al-Ramahi R. Adherence to medications and associated factors: A cross-sectional study among Palestinian hypertensive patients. J Epidemiol Glob Health 2015;5:125-32.

27. Ramli A, Ahmad NS, Paraidathathu T. Medication adherence among hypertensive patients of primary health clinics in Malaysia. Patient Prefer Adherence 2012;6:613-22.

28. Ahmad NS, Ramli A, Islahudin F, Paraidathathu T. Medication adherence in patients with type 2 diabetes mellitus treated at primary health clinics in Malaysia. Patient Prefer Adherence 2013;7:525-30.

29. Eindhoven DC, Hilt AD, Zwaan TC, Schalij MJ, Borleffs CJ. Age and gender differences in medical adherence after myocardial infarction: Women do not receive optimal treatment – The Netherlands claims database. Eur J Prev Cardiol 2018;25:181-9.

30. Billimek J, Malik S, Sorkin DH, Schmalbach P, Ngo-Metzger Q, Greenfield S, et al. Understanding disparities in lipid management among patients with type 2 diabetes: Gender differences in medication nonadherence after treatment intensification. Womens Health Issues 2015;25:6-12.

31. Bajorek B, Lemay K, Magin P, Roberts C, Krass I, Armour C. Patients' attitudes and approaches to the self-management of hypertension: Perspectives from an Australian qualitative study in community pharmacy. High Blood Press Cardiovasc Prev 2017;24:149-55.

32. Vanhaudenhuyse A, Gillet A, Malaise N, Salamun I, Grosdent S, Maquet D, et al. Psychological interventions influence patients' attitudes and beliefs about their chronic pain. J Tradit Complement Med 2018;8:296-302.

33. Rebafka A. Medication adherence after renal transplantation – A review of the literature. J Ren Care 2016;42:239-56.

34. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. Ther Clin Risk Manag 2008;4:269-86.

35. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Reprint-preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Phys Ther 2009;89:873-80.

36. JB IJATJBI, The University of Adelaide. Joanna Briggs Institute Reviewers' Manual: 2014 Edition/Supplement; 2014. Available from: http://joannabriggs.org/sumari.html. [Last accessed 2015 Sep 25].

37. Abd Kadir T, Islahudin F, Abdullah MZ, Ibrahim N, Bing PK. Assessing individual medication adherence among chronic kidney disease patients: A multi-centered study. JPRI 2019;31:1-11.

38. Aleidi AM, Alayed NJ, Alduraibi HM, Alqassimi NS, Ismail AA. Phosphate binders usage, patients knowledge, and adherence. A cross-sectional study in 4 centers at Qassim, Saudi Arabia. Saudi Med J 2020;41:1076-82.

39. Chater AM, Parham R, Riley S, Hutchison AJ, Horne R. Profiling patient attitudes to phosphate binding medication: A route to personalising treatment and adherence support. Psychol Health 2014;29:1407-20.

40. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. J Psychosom Res 1999;47:555-67.

41. Kim Y, Evangelista LS. Relationship between illness perceptions, treatment adherence, and clinical outcomes in patients on maintenance hemodialysis. Nephrol Nurs J 2010;37:271-80.

42. Neri L, Martini A, Andreucci VE, Gallieni M, Rey LA, Brancaccio D,

et al. Regimen complexity and prescription adherence in dialysis patients. Am J Nephrol 2011;34:71-6.

43. Leventhal H, Nerenz DR, Steele DJ. Illness representations and coping with health threats. Routledge; In Handbook of Psychology and Health 2020;4:219-52.

44. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J Psychosom Res 2006;60:631-7.

45. Arpey NC, Gaglioti AH, Rosenbaum ME. How socioeconomic status affects patient perceptions of health care: A qualitative study. J Prim Care Community Health 2017;8:169-75.

46. Aflakseir A. Role of illness and medication perceptions on adherence to medication in a group of Iranian patients with type 2 diabetes. J Diabetes 2012;4:243-7.

47. Awodele O, Osuolale JA. Medication adherence in type 2 diabetes patients: Study of patients in Alimosho General Hospital, Igando, Lagos, Nigeria. Afr Health Sci 2015;15:513-22.

48. Cohen MJ, Shaykevich S, Cawthon C, Kripalani S, Paasche-Orlow MK, Schnipper JL. Predictors of medication adherence postdischarge: The impact of patient age, insurance status, and prior adherence. J Hosp Med 2012;7:470-5.

49. Kang CD, Tsang PP, Li WT, Wang HH, Liu KQ, Griffiths SM, et al. Determinants of medication adherence and blood pressure control among hypertensive patients in Hong Kong: A cross-sectional study. Int J Cardiol 2015;182:250-7.

50. Lo SH, Chau JP, Woo J, Thompson DR, Choi KC. Adherence to antihypertensive medication in older adults with hypertension. J Cardiovasc Nurs 2016;31:296-303.

51. Siegel D, Lopez J, Meier J. Antihypertensive medication adherence in the Department of Veterans Affairs. Am J Med 2007;120:26-32.

52. Park JH, Shin Y, Lee SY, Lee SI. Antihypertensive drug medication adherence and its affecting factors in South Korea. Int J Cardiol 2008;128:392-8.

53. Pasina L, Brucato AL, Falcone C, Cucchi E, Bresciani A, Sottocorno M, et al. Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. Drugs Aging 2014;31:283-9.

54. Castellucci LA, Shaw J, van der Salm K, Erkens P, Le Gal G, Petrcich W, et al. Self-reported adherence to anticoagulation and its determinants using the Morisky medication adherence scale. Thromb Res 2015;136:727-31.

55. Constantiner M, Rosenthal-Asher D, Tedla F, Salifu M, Cukor J, Wyka K, et al. Differences in attitudes toward immunosuppressant therapy in a multi-ethnic sample of kidney transplant recipients. J Clin Psychol Med Settings 2018;25:11-9.

56. Alikari V, Tsironi M, Matziou V, Tzavella F, Stathoulis J, Babatsikou F, et al. The impact of education on knowledge, adherence and quality of life among patients on haemodialysis. Qual Life Res 2019;28:73-83.

57. Jin H, Kim Y, Rhie SJ. Factors affecting medication adherence in elderly people. Patient Prefer Adherence 2016;10:2117-25.

58. Lemay J, Waheedi M, Al-Sharqawi S, Bayoud T. Medication adherence in chronic illness: Do beliefs about medications play a role? Patient Prefer Adherence 2018;12:1687-98.

59. Abdul-Sattar AB, Abou El Magd SA. Determinants of medication non-adherence in Egyptian patients with systemic lupus erythematosus: Sharkia Governorate. Rheumatol Int 2015;35:1045-51.

60. Uchmanowicz B, Chudiak A, Uchmanowicz I, Rosińczuk J, Froelicher ES. Factors influencing adherence to treatment in older adults with hypertension. Clin Interv Aging 2018;13:2425-41.

61. Dobbels F, Berben L, De Geest S, Drent G, Lennerling A, Whittaker C, et al. The psychometric properties and practicability of self-report instruments to identify medication nonadherence in adult transplant patients: A systematic review. Transplantation 2010;90:205-19.

62. Lam WY, Fresco P. Medication adherence measures: An overview. Biomed Res Int 2015;2015:217047.

Appendix 1: Search terms used for final search on August 31, 2021

Search	Search items	PubMed	Scopus	Web of Science	Embase	Cochrane Library	ProQuest (health and medical)	ProQuest (Psychology database)	APA psycharticles
#1	Knowledge, patient medication OR medication knowledge, patient OR patient drug knowledge OR drug knowledge, patient OR knowledge, patient drug	230	1353	25,816	0	11,637	1769	1234	41
#2	Attitudes OR opinion OR opinions OR attitude, health OR health attitudes OR health attitudes OR attitudes, health	232,677	36,982	471,560	9093	33,316	14,699	29,101	11,823
#3	Behaviour, illness OR behaviours, illness OR illness behaviours OR sickness behaviours OR behaviours, sickness OR behaviours, sickness	81,671	106	18,966	0	8905	1432	2645	681
#4	Medication adherence OR medication nonadherence OR medication non-adherence OR medication noncompliance OR medication persistence OR medication non-compliance OR medication compliance OR adherence, medication OR non-adherence, medication OR compliance, medication OR noncompliance, medication	15,528	7514	35,454	922	34,781	2477	2438	255
#5	Patient nonadherence OR patient non-compliance OR patient adherence OR patient compliance OR patient cooperation OR compliance, patient OR adherence, patient OR patient noncompliance	16,399	45	123,963	275	70,153	8414	5850	470
#6	ESRD OR end-stage renal disease OR disease, end-stage kidney OR renal disease, end-stage OR renal disease OR chronic kidney disease OR kidney disease OR chronic kidney failure OR end-stage renal failure OR renal failure, end-stage OR renal failure, chronic OR renal failure, endstage OR chronic renal failure	165,379	3092	241,285	13,509		17,257	4519	52
#7	#1 OR #2 OR #3	309,980	38,073	512,225	9093	44,130	17,612	32,569	12,438
#8	#4 OR #5	31,052	7546	134,228	1194	82,667	9064	6655	608
#9	#6 AND #7 AND #8	1	4	178	0	284	14	11	3

ESRD: End-stage renal disease

Appendix 2: Comparison between different measurement tools for adherence behavior

Tools	Strengths and limitations	Cronbach/reliability test	Population
MARS	Consists of 10 questions with subdomains of forgetfulness, adverse effects, the value of medication, behavior, and attitudes	Cronbach alpha=0.75	Chronic mental illness especially schizophrenia
	Simplistic scoring		
	Strong positive correlation		
	Limited generalizability		
ESRD-AQ	46 questions with subdomains of general information, HD treatment, medication, fluid restriction, dietary restriction	No Cronbach alpha reported but very strong test-retest reliability, ICC score ranging from 0.83-1.00	ESRD patients only
	Questions and scores are available in the original paper (easily access)		
	Targeted to only one illness group		
	Limited generalizability		
MMAS-4	4 questions of forgetfulness, medication-taking behavior, adverse effects, and problems	Cronbach alpha=0.61	All validated conditions
	Higher validity and reliability in patients with chronic diseases than MAQ		
	Abundant research has used this measurement tool		
	Require to pay for access (not easily accessible)		

MARS, Medication Adherence Reports Scale, ESRD: End-stage renal disease, AQ: Adherence questionnaire, MAQ: Medication adherence questionnaire, ICC: Interclass correlation coefficient, HD: Hemodialysis