

The Pharmacist Role In Improving Medication Adherence In Dialysis Patients: A Systematic Review

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ABSTRACT

End-stage renal disease (ESRD) is a worldwide concern in this latest generation as the prevalence had been in an increasing trend. This research aims to evaluate the impact of pharmacist interventions on medication adherence and factors related to medications non-adherence among hemodialysis (HD) patients. A literature search was conducted using search engines PubMed, Cochrane Library and ScienceDirect to identify studies that investigate the pharmacist interventions on medication adherence and factors related to medication non-adherence among HD patients. Based on the study objective a qualitative assessment of the final selected articles was made. The quality of the included studies was assessed using the Newcastle-Ottawa scale. Seven studies met the inclusion criteria. The summed overall quality using the Newcastle-Ottawa scale of all the selected paper was good. The majority of the studies were conducted as prospective study design. More than half of the studies (71%) utilized subjective measure which is self-reporting with a validated questionnaire such as Medication Adherence Report Scale (MARS), Brief Medication Questionnaire (BMQ) and Morisky 8-item Medication Adherence Scale (MMAS-8) to measure participants' adherence. The selected papers have shown that poor medication knowledge as the main factor for non-adherence towards medications. The most common reported pharmaceutical care done by the pharmacist to improve medication adherence is by providing medication counselling. All the studies demonstrate the positive impact of pharmacist involvement in HD patients to enhance medication adherence. All identified studies prove that clinical pharmacists could play an important role in educating patients which helps them to have a positive attitude towards medications.

Keywords: Hemodialysis, Medication non-adherence, Pharmacist

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INTRODUCTION

Pharmacist as one of the healthcare professionals in the healthcare team always has different roles from physician and nurses. Pharmacists work in a different type of healthcare facilities mainly in hospitals, pharmacies and industries. The main role of a clinical pharmacist is to dispense prescription medications to the patients and offer expertise in the safer use of medications. Besides dispensing medicines with key information such as side effects and contraindication, pharmacists are trained to collaborate with other healthcare professionals, ensure patients' safety, counsel patients regarding medications use, educating patients on drug therapy.

End-stage renal disease (ESRD), which is the final stage of chronic kidney disease (CKD) has become a popular public health problem across the world due to the increasing number of incidence and prevalence annually as well as significantly high cost in treatment. National Health and Morbidity Survey (NHMS) had done a sub-study on the estimation of the prevalence of CKD in West Malaysia and the results showed the prevalence had been increased from 9.1% in the year 2011 to 15.5% in the year 2018. Studies had been shown that diabetes mellitus and hypertension are the leading cause of ESRD in Malaysia with 65% of all ESRD cases in the year 2016 were due to diabetes mellitus¹. CKD and hemodialysis cause a burden due to its high cost in treatment. US Renal Data System (USRDS) reported that the total spending for CKD and ESRD was nearly \$100 billion in the year 2015². In the year 2015, the total cost of dialysis provision in Malaysia is RM1.5 billion¹. Renal replacement therapy (RRT) is the safest and the common treatment planned for ESRD patients that have only 10-15% of kidney function left.

Renal replacement therapy can be applied intermittently or continuously using extracorporeal (hemodialysis) or paracorporeal (peritoneal) methods. Malaysian Dialysis and Transplant Registry reported that there were 39,711 patients on dialysis by the end of the year 2016 in Malaysia¹. Studies show that men associated with a higher risk of the need for renal replacement therapy compared to women³. Hemodialysis can be done either at the dialysis center or at home according to the patient's preference. As stated in National Kidney Foundation, hemodialysis usually is needed to be done 3 times per week for about 4 hours each time while dialysis treatment can be done more frequently with shorter hours each time if patients prefer to do hemodialysis at home. Patients who require maintenance hemodialysis usually have co-morbidities that need to fulfil complex drug regimens causing a need for them to take an average of 10-12 medications per day⁴. However, poor medication adherence in hemodialysis patients is a common patient care issues that have never been resolved by healthcare professionals. Examples of undesirable consequences resulted from non-adherence to dialysis are bone demineralization, metabolic disorders and pulmonary oedema which then lead to the development of cardiovascular disorders and, finally, death⁵. Although deaths caused by nonadherence are hard to measure, the estimate of 125,000 deaths per year is widely cited in the literature⁶. A study done by Ghimire *et al.*, 2017, shows that 56.7% of participants who were undergoing hemodialysis had low medication adherent⁷. They then explored hemodialysis patients' behaviour towards medication adherence and the factors associated with it identified that medication non-adherence may be

due to 5 different factors such as patient factors, healthcare team factors, therapy-related factors, social factors and condition-related factors. However, patient-related factor such as insufficient and poor understanding of prescribed medication and healthcare team factor such as lack of time for medication counselling are the two main factors that should be focused on by pharmacist's care to improve medication adherence in a hemodialysis patient. According to the definition of adherence, healthcare providers should establish a relationship and partnership with the patient that draws on the abilities of each as an important determinant of adherence.

Pharmacist, a member of the healthcare team who exposes more to medication and patients. Hence, pharmacists should play an important role in improving patients' adherence towards treatments to improve their quality of life. Studies show that medication adherence has a correlation with medication knowledge⁸. Hence, the pharmacist should provide appropriate knowledge about drug use to dialysis patients that would provide a better understanding for patients and improve clinical outcomes.

METHODS

Literature search

The elements of this systematic review of medication adherence in hemodialysis patients included several electronic literature searches to identify (a) journal articles related to improving medication adherence in hemodialysis patients, (b) factors identified that contributed to medication non-adherence among hemodialysis patients, and (c) pharmacist involvement to impact medication adherence.

Data sources and searches

Systematic searches were conducted with 4 search engines which are PubMed, ScienceDirect, EBSCOhost and Cochrane Library. Reference list resulted from these search engines were downloaded through EndNote to identify further studies for inclusion and ensure that the searches are relevant to all 3 elements of the review. Common keywords were used throughout the literature search journey to identify and narrow further to include only studies that fulfill the criteria of this review. Keywords "pharmacist", "medication adherence", "non-adherence", "compliance", "non-compliance" and "hemodialysis" are used to determine and identify studies that predict pharmacist involvement in improving medication adherence in hemodialysis patients.

Inclusion and exclusion criteria

All articles were regarded as legible if the results reported were from a cohort, cross-sectional or randomized controlled trials studies. While all articles subjected to a case study, case report, case-control, non-peer-reviewed, reviews and editorials, reviews containing vague literature and systematic literature review were excluded.

Study selection

Two researchers independently reviewed the titles and abstracts of all potential research articles that met the inclusion and exclusion criteria. Any differences were resolved through discussion or by a third reviewer. Full texts of the eligible research articles were retrieved and screened for eligibility by the researcher independently. Any differences were resolved through discussion by the third reviewer.

Data Extraction

After completion of the literature search, the researcher reviewed the titles and abstracts of all identified studies and determine which articles are suitable for further consideration, and then obtain the full records. Authors

independently extract data from each identified study and record them on a standardized data extraction form. Disagreements were resolved by discussion and by mutual consensus.

Quality of reporting

All 7 selected articles are assessed with the Newcastle-Ottawa scale to ensure the quality of papers being used. Among 7 papers, 3 of them deserve full 9 stars, 3 of them have 8 stars while 1 of them have 7 stars. Hence, all 7 articles are rated as good quality as all of them have 3 to 4 stars in the selection domain, 1 to 2 stars in the comparability domain and 2 to 3 stars in the outcome domain.

Strategy for data synthesis

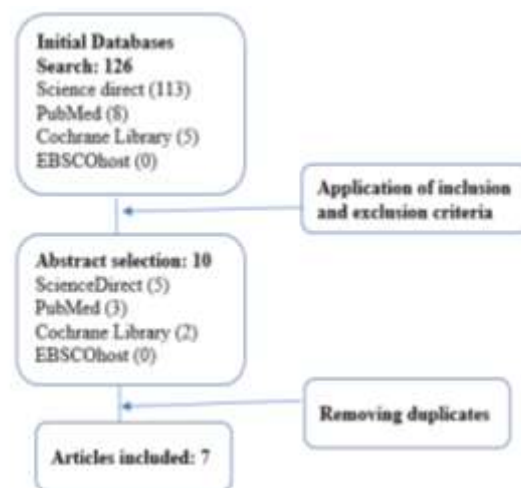
Data were extracted by the researcher into a dataset for analysis. Qualitative analysis was carried out keeping in view the study objectives.

RESULTS

Description of included studies

A total of 126 journal articles are identified through the use of Science direct, Pub med, Cochrane library and EBSCOhost initially. After screening for inclusion criteria and removing duplicates, only 7 potentially relevant papers were identified and evaluated in this systematic review. All 7 included studies fulfilled all inclusion criteria and fit the objectives of this study. All the included citations had similarity in their objectives which were to assess and investigate the impact of their pharmacists' interventions in pharmaco-adherence in hemodialysis patients. The details of literature search is shown in figure 1 below.

Figure 1: PRISMA flow diagram



Quality assessment

All 7 selected articles were assessed with the Newcastle-Ottawa scale to ensure the quality of papers being used. Among 7 papers, 3 of them deserve full 9 stars, 3 of them have 8 stars while 1 of them have 7 stars. Hence, all 7 articles are rated as good quality as all of them have 3 to 4 stars in the selection domain, 1 to 2 stars in the comparability domain and 2 to 3 stars in the outcome domain

General Study Characteristics

All included papers were conducted in various countries which give the benefits of gathering relevant information from different countries and cultures. Among 7 of the studies, 3 of the studies were conducted in India while one

study each was performed in Iran, Indonesia, Norway and Saudi Arabia. Most of the included studies (n=4) were a prospective study in design, 2 were conducted in a randomized controlled trial design and 1 was carried out in a cross-sectional survey design. Other than that, the sample size varied in all studies from a minimum of 45 participants to a maximum of 153 participants. Furthermore, most of the studies had more male participants than female in their studies. However, some of them did not include gender into considerations while choosing their participants' characteristics. Next, the age group selected in all studies vary but the median age concluded from all papers ranging from 51 to 72 years old. Among all 7 papers, all of them invited ESRD patients who are receiving hemodialysis treatment as the participants of their studies. Besides, 4 out of 7 selected research articles performed their studies in hospital settings of HD wards whereas 2 of the studies conducted their studies in outpatient settings. There was only 1 research was carried in both inpatient and outpatient settings among all.

Studies assessing medication adherence

All the included journal articles assessed medication adherence as one of the outcomes in their studies. However, there is not a specific strategy to measure medication adherence thus different methods are used in various studies to assess their endpoint of medication adherence. More than half of the studies (n=5) utilized subjective measure which is self-reporting with a validated questionnaire to measure participants' adherence. The validated questionnaire used in the studies is the Medication Adherence Report Scale (MARS), Brief Medication Questionnaire (BMQ) and Morisky 8-item Medication Adherence Scale (MMAS-8). One out of seven studies carried out a cross-sectional survey and assessed medication adherence with a non-validated questionnaire which is a face-to-face patient satisfaction survey form. Furthermore, two studies assessed medication adherence with both validated questionnaire and biochemicals as biochemicals measurement could be the most supportive evidence to prove the accuracy of subjective measures of a

validated questionnaire. Among them, one study assessed medication adherence by measuring both serum phosphate level and the changes in the number of medications between self-report and medications recorded in electronic healthcare record (EHR) while another study measured medication adherence with Morisky 8-item Medication Adherence Scale and get supported by the objective measure of laboratory results such as haemoglobin levels, interdialytic weight gain and blood pressure.

Factors associated with non-adherence

This systematic review had pinpointed the main factors involved in all included studies. Among factors associated with medication non-adherence, the majority of the included papers reviewed that most of the ESRD patients are lack knowledge and understanding regarding medications and patient usually on highly prescribed medications or a complex medication regimen. Other than that, studies also showed that patient's belief and myth, frequent medication adjustments, lack of funds, lack of trust in patient's perception, poor relationship with the doctor and lack of family support are other factors contributed to poor medication adherence. Among these factors, they can be classified into different main factors. Firstly, elements that are classified in patient-related factor are lack of medication knowledge, beliefs and myths regarding drugs, lack of trust and family support. Next, ESRD patients on hemodialysis need to be complied with their complex medication regimens and deal with a high number of prescribed medications every day. These therapy-related factors lead to patient poor adherent. Furthermore, there are other 2 factors which are healthcare team-related factor and socioeconomic-related factor also associated with medication non-adherence. ESRD patients who had a poor relationship with doctors and other healthcare professionals will lead to poor medication-taking behaviour³. Besides, as patients on hemodialysis always have a heavy burden on accessing their medications and therapy thus lack of funds contributed to socioeconomic-related factor

Table 1: Summary of studies assessing medication adherence

Author, Year, Country	Study design and number of patients	Factors Associated with non-adherence	Pharmacist's intervention & Method to assess adherence	Adherence outcome
Al-Abdelmuhsin <i>et al</i> ⁹ (2020), Saudi Arabia	Cross-sectional survey n= 138	Lack of medication knowledge, Highly prescribed medications	Medication counselling Method to assess adherence: Face to face patient satisfaction survey	There is 81.2% of HD patients think that providing a hotline for medication counselling can improve medication adherence. 64.5% among the HD showed that they have interest in obtaining more knowledge about their prescribed medications.
Hjemås BJ <i>et al</i> ¹⁰ (2019), Norway	Interventional, single arm, pre-post study (Prospective) n= 53	Lack of medication knowledge, Medication belief	Half-hour one to one personalized medication counselling Method to assess adherence: Change in serum phosphate levels, Medication Adherence Report Scale (MARS-5)	There is a positive change as medication counselling increased in the probability of serum phosphate being below the target threshold value 1.80 mmol/L (5.58mg/dL), although

			and Brief Medication Questionnaire (BMQ)	it is not statistically significant
Rodrigues ¹¹ <i>et al.</i> (2019), India	Randomization controlled clinical trial n= 100	Lack of medication knowledge, Require multiple medications, Lack of funds	Medication counselling using patient information leaflet Method to assess adherence: Morisky 8-item Medication Adherence Scale (MMAS-8)	Comparison of pre and post medication adherence scores in the test group P-value lesser than 0.05 indicates that there is a significant difference between the means of the two groups thereby indicating that the pharmacist intervention caused a significant change in the medication adherence. Comparison of pre and post medication adherence scores in the control group ▪ P-value greater than 0.05 indicates that there is no significant difference between the means of the two groups thereby indicating that absence of pharmacist intervention caused no significant change in medication adherence.
Rani <i>et al</i> ¹⁵ (2013), South India	Prospective study, self-reporting n= 85	Lack of understanding medication knowledge, The complexity of medication regime, Polypharmacy, Frequent medication adjustments	Medication counselling Method to assess adherence: Brief Medication Questionnaire (BMQ)	The study proved that patient counselling significantly associated with medication adherence (p=0.0000). Mean MKAQ score was a statistically significant increase from the baseline of 14.30±6.97 to 19.32±6.61 at the end of the sixth week of counselling (**p=0.000) and to 33.62±7.76 at the end of the twelfth week of patient counselling (**p= 0.000).
Hanifa <i>et al</i> ³ (2019), Indonesia	Prospective interventional study with the quasi-experiment method, self-reporting n= 45	Highly prescribed medicines Frequent dosing changes Lack of trust in patient perceptions Poor relationship with a doctor Lack of patient medication knowledge Lack of family support	Home pharmacy care Method to assess adherence: Medication Adherence Report Scale (MARS)	The mean results of an average test of the compliance value in HD patients increased from 6.62 to 8.38 (*p<0.05). Home pharmacy care significantly improved adherence drug used after an intervention (**p= 0.000)
Mateti <i>et al</i> ¹⁸ . (2018), India	Randomized controlled trial n= 153	Lack of medication knowledge Patient's myth and beliefs	WHO-FIP Pharmaceutical care model Method to assess adherence:	There was a significantly increased in medication adherence

			Morisky 8-item Medication Adherence Scale (MMAS-8) and assessment of haemoglobin levels, interdialytic weight gain (IDWG) and blood pressure (BP).	rate scores in the pharmaceutical care group (PCG) compared to the usual care group (UCG) in academic hospital and government hospital data of HD patients. However, the overall medication adherence rate of HD patients was moderate PCG group significantly reduced (*P<0.05) its IDW and BP compared with UCG when analyzed by repeated measures of ANOVA. PCG also have significant increased (*P<0.05) in hemoglobin levels compared to UCG when analyzed by repeated measures of ANOVA.
Ismail <i>et al</i> ¹² , (2019), Iran	Prospective study with a quasi-experimental, self-reporting n= 72	Highly prescribed medicines	Medication review using Medication Therapy Management (MTM) and Motivational Interviewing (MI) Method to assess adherence: Pre- and post-HD serum phosphate levels and the differences in number of medications between patients' self-report and medication records at Electronic healthcare record (EHR).	Mean pre-HD phosphate levels decreased after the intervention, but it is not statistically significant (p=0.682). The change in pharmaco-adherence was also not statistically significant (p=0.348).

From the table 1 above, most pharmacist interventions studies with a medication adherence outcome showed improvements in adherence, although a few of them did not achieve a significant statistic in the improvement. Despite the difference of used for pharmacists' intervention in all studies, six out of seven citations involved patient education regarding their medications and lifestyle modification in the interventions given whereas all studies proved that patient education brought positive impact towards patients' adherence to their medication and treatment plan. Other than assessing medication adherence, four studies also assessed the change in laboratory results before and after interventions. Mainly changes in serum phosphate are measured among these studies to demonstrate that pharmacist intervention help in achieving serum phosphate at the threshold value. A study by Ismail *et al.* (2019) proved that mean pre-HD serum phosphate levels decrease after the intervention, where initially 53% of the patients who were hyperphosphatemia decreased to 43%

at the follow up after receiving pharmacist's interventions¹².

DISCUSSION

This systematic review summarized 7 recent findings from various countries to investigate the factors associated with medication and therapy non-adherence in hemodialysis patients. Besides, it also synthesized evidence on the impact of pharmacist's involvement in improving medication adherence in ESRD patients on hemodialysis. Factors influencing patient's adherence to medication taking and therapy are complicated and multifaceted. Hence, the prevalence of non-adherence in hemodialysis patients has been on a rising trend. Non-adherence to medications, lifestyle modification and therapy could lead to bad consequences. A study was done to evaluate the correlation between non-adherence to conventional hemodialysis and all-cause mortality resulted in showing non-adherence increases the risk of mortality rate and increase cardiovascular disease rate¹³. Besides that, missing dialysis session was independently associated

with higher mortality risk and increase hospitalisations¹⁴. All the consequences of a patient's non-adherence lead to a final outcome which is lower the quality of life¹². However, we have pointed out a higher proportion of included studies identifying the two main outcomes which are disease-oriented outcomes and patient-oriented outcomes. As mentioned in the factors of medication non-adherence, medication adherence is closely associated with medication knowledge thus the most patient-oriented outcomes from beneficial from pharmacist's intervention is improving medication-related knowledge. Among seven studies assessing medication adherence, five of them have pharmacist intervention to improve medication knowledge as one of the outcomes of their studies. Other than that, patient-satisfaction towards healthcare professional and the differences in medications reported are other examples of patient-oriented outcomes concluded from the studies. From an evidence-based point of view, a few studies are measuring disease-oriented outcomes to provide stronger evidence on the role of pharmacists in the care of ESRD patients on hemodialysis. Disease-oriented outcomes are those that directly reflect the control of disease with medication taking, which are those measuring patient's laboratory results and vital signs. According to 3 studies that had proved the correlation between disease-oriented outcomes and medication adherence as one of their results, they measured mainly serum phosphate level, interdialytic weight gain, blood pressure, haemoglobin level and et cetera. This is because ESRD patients who are on hemodialysis always come with a lot of complications such as hyperphosphatemia, anaemia and altered bone metabolism. Despite the complications and consequences of being non-adherence in hemodialysis patients, factors contributed to patient's non-adherence is still continuously explored to optimize healthcare. Prioritization of medications due to poor understanding, perceived necessity and concerns were the major patient-related factors for non-adherence⁷. Hemodialysis patients are extremely poor in medication knowledge such as the name, indication and dosage regimen of their medications¹¹. Hence, they have no idea on the importance of being medication adherent and the consequences of non-adherence which lead to their poor medication-taking behaviour such as low self-efficacy, demotivated and forgetfulness. Patients who are aware of the consequences of non-adherence was found to be more motivated to have adhered to their medications⁷. This systematic review proved the implementation of pharmacist interventions of various studies focused mostly on patient-related factor. Moreover, ESRD patients on maintenance hemodialysis are prone to several chronic comorbidities, which necessitate them to deal with various types of medications thus increase the risk of non-adherence behaviour¹². The study also proved that adherence to medications and therapy decreases as the complexity and duration of the regimen increases¹⁵. Another therapy-related factor that contributed to medication non-adherence is frequent adjustments made on dosage and dosing regimen. This could cause ESRD patient to get confused about the correct medications that are required to take. Hence, they may miss the dose intentionally or unintentionally more easily. The patient who was unassured with their recent changes in their medication regimen will lead to high tendency to forget to take the altered medications which caused non-adherent⁷. The burden added to ESRD patients usually summed up from physical burden such as disease complications, mental burden such as depression and also

socioeconomic burden such as the huge amount of costs of medications. In Malaysia, the costs per patient per year were RM39,790.58 for haemodialysis¹⁶. Therefore, lack of funds and the number of daily medications are usually the most common factor contributed to non-adherence^{11,15}. As shown by our results, various interventions had been implemented by the pharmacist to improve medication adherence. The greatest number of studies (n=4) aims to improve medication knowledge with the use of the validated questionnaire. Research has consistently demonstrated the patient's understanding of their conditions and medications is positively related to adherence¹⁵. A cross-sectional survey reported that around 64.5% of the hemodialysis patient showed their interest in obtaining more knowledge about their prescribed medications⁹. Hence, the most common intervention implemented is medication counselling. Providing counselling for patients who required to take medications routinely will help to create awareness and adherence which lead to an improve in the results of therapy by optimizing the use of the correct drugs³. Medication counselling can increase the patient's knowledge regarding the control of their phosphate level and the reason for the necessity to take their phosphate binder¹⁰. Furthermore, patients also reported their challenges met during medication counselling which can further help in identifying the factors associated such as forgetfulness, denial necessity and social embarrassment¹⁰. Among other pharmacist interventions other than medication counselling, patient education also plays a main role in-home pharmacy care and the WHO-FIP pharmaceutical care model. Giving counselling continuously to patients at their own home where they feel comfortable can increase the level of patient's adherence rate in medications taking, boost trust, patient safety and improving patient's poor behaviour³. Medication counselling can be carried out in both inpatient and outpatient setting through a different platform such as phone call and face-to-face counselling. On the other hand, the pharmacist also provides medication review using patient-centred approach strategies such as Medication Therapy Management (MTM) and Motivational Interviewing (MI) which pharmacist participate in disciplinary monthly rounds and make therapeutic recommendations to the team monthly. As proved in the results, most of the interventions improved medication adherence in hemodialysis patients after the implementation of the patient's education, which is the most important factor of non-adherence. Most of our included articles show a positive impact of pharmacist intervention in medication adherence in ESRD patient on hemodialysis. This systematic review proved that pharmacist intervention helps hemodialysis patients in improving medication knowledge and achieving desired laboratory results. By concluding from our 7 included studies, pharmacists play an important role in optimizing drug therapy regime, identify factors to medication non-adherence and educate patients on medication-related knowledge. Pharmacist as a member of the multidisciplinary team should involve in the systems of patient care which can lead to an outcome of improving medication adherence and reduce hospital admissions¹⁷.

Strengths and Limitations

This study evaluates whether pharmacist interventions can improve medication adherence effectively. As literature is scarce on the role and impact of pharmacist services for the population among hemodialysis patients, this study summarizes the available evidence regarding

the role and impacts of pharmacist interventions in improving medication adherence and clinical outcomes. Other than that, this systematic review focuses mainly on haemodialysis patient which only a few studies had been done in the past. However, this systematic review only limited to research articles that were published in the English language. Besides, the results of this paper are less generalized to hemodialysis patients in Malaysia as all of the studies took place in other countries. Furthermore, this systematic review focuses mainly on patients on hemodialysis thus it may not be applicable when extrapolating these findings to peritoneal dialysis patients. Other than that, medication adherence in all included studies was measured through a variety of methods which brought the possibility of bias outcome and limit the internal validity of the findings.

Implications of future research

With the aid of collected information from data and literature search in this systematic review, this paper may help to optimize pharmacist's intervention based on patients' perspectives to medication adherence in the future. Hence, pharmacists are more feasible to predict and improve medication adherence in patients. Besides that, a new model of patient centred pharmaceutical care could be redesigned after investigating and collaborating both factors of medication non-adherence and results of pharmacists' interventions that were concluded in this systematic review. As patients' medication adherence to their medications and treatments improve, they can have a better quality of life by decreasing the medical costs and the occurrence rate of consequences towards non-adherence.

CONCLUSION

This systematic review provides evidence on the role of the pharmacist in ESRD patients on haemodialysis to improve medication adherence. Factors associated with medication non-adherence are identified by overall and analysis of studies to create awareness and support other healthcare professionals to achieve the similar goal and optimal treatment targets. Furthermore, these studies also prove the effectiveness of various pharmacist interventions implemented in improving medication adherence among hemodialysis patients by assessing medication adherence through various strategies.

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CONFLICT OF INTEREST

There is no conflict of interest regarding to the publication of this article.

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