

Factors Influencing Medication Adherence among Patients with Hypertension: A Systematic Review

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ABSTRACT

Hypertension is known to affect around the world with steadily upward prevalence. Due to the nature of unpresented signs and symptoms, adherence to medication treatment for hypertension is poor in many countries. The impacts of uncontrol hypertension are explainable by increasing numbers of people with stroke, heart disease, and chronic kidney disease, well-known complications of hypertension. Promotion patients' adherence to medication regimen needs understanding of factors contributing to the adherence. This systematic review aims to describe the factors influencing medication adherence among patients with hypertension. A total of 29 peer-reviewed studies published between 2010 - 2020 were included for the final review following a PRISMA guideline. Factors influencing antihypertensive medication adherence are categorized as the socio-demographic, patient-related, treatment-related, disease-related, and healthcare service-related. Inadequate knowledge and improper perception of patients regarding hypertension, and forgetfulness, insufficient healthcare services and medications supply, quality shortage of health services and lack of social support especially for older adult, are the most significant factors influencing the antihypertensive drug adherence. These factors can be applied in improving medication adherence programs, non-communicable disease control program in an extensive setting by involving patients, family members and public broadly. Additionally, quality building programs for health care providers and implementing universal health care coverage for the patients can be strengthened since both are related to quality of service and accessibility of health care system that are initial parts of medication adherence. Finally, short message service (SMS) by Ministry of Health as a reminder for medication as well as awareness should be applied.

Keywords: Antihypertensive Treatment, Drug Adherence, Hypertension, Medication.

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INTRODUCTION

Hypertension (HTN) is diagnosed if, when it is measured on two different times, the systolic blood pressure on both times is ≥ 140 mmHg and/or the diastolic blood pressure on both times is ≥ 90 mmHg.^[1] HTN is one of the most leading cause of death among non-communicable diseases and causes a lot of serious cardiovascular complications such as stroke, coronary heart diseases and renal complications. There were 1.13 billion people who had HTN worldwide in 2015.^[1] Globally, about 26% of the world's population (972 million people) are estimated to have HTN, and the prevalence will become to 29% by 2025.^[2]

Currently, around one-third of people with HTN are not diagnosed, and of those diagnosed, approximately half of them is not taking antihypertensive medicine.^[3] High blood pressure directly or indirectly causes death of at least nine million people globally every year according to estimation of the World Health Organization (WHO). Moreover, target organs are damaged (TOD) since patient was diagnosed as prehypertension.^[3] Medical control and adherence to medication treatment are key points. However, study showed that hypertensive patients usually take only 50% to 70% of the prescribed dose, about 50% of patients do not continue the antihypertensive therapy within the first year of treatment. Therefore, up to 75% of patients do not get the BP control.^[4] Among the hypertensive patient in Middle Eastern, the adherent percentage to antihypertensive medication is only 55.9 %.^[5] Across South Asia, more than 50% of patients don't know their conditions of having HTN and low adherence to medication are occurred up to 80% of those patients.^[6]

The adherence to medication is the process of taking the prescribed medications by the patients. Adherence includes three process of initiation, implementation, and persistence.^[7] Medication adherence is the essential healthy behaviour for getting a treatment success and this behaviour is changing over time.^[8] Long-term cardiovascular risks can be reduced obviously by maintaining persistence with anti-hypertensive treatment.^[9] The risks of HTN related mortality from stroke and acute myocardial infarction were significantly lower in patients with good and excellent adherence.^[10] In contrast, patients with poor medication adherence had worse mortality from cardiovascular diseases: IHD, cerebral haemorrhage, and cerebral infarction. Higher risk of hospitalization and mortality rate for certain cardiovascular diseases were associated with poor medication adherence.^[11] Furthermore, patients with acute conditions are typically higher in adherence rates than those with chronic conditions like HTN. Persistence of patients with chronic diseases is poorly low, and it has been falling most significantly after the first six months of therapy.^[12]

Therefore, it is necessary to describe the factors influencing the medication adherence of patients with HTN. Although there were similar reviews conducted in chronic diseases,^[46, 47] and HTN,^[30] the previous reviews cannot fully identify the associations between religious faiths, beliefs about disease control and knowledge of disease and medication adherence.^[47] The range of countries in previous reviews was limited for only resource-limited and developing countries, not including developed countries.^[30, 46] Moreover, medication adherence rate in resource-limited countries was sub-

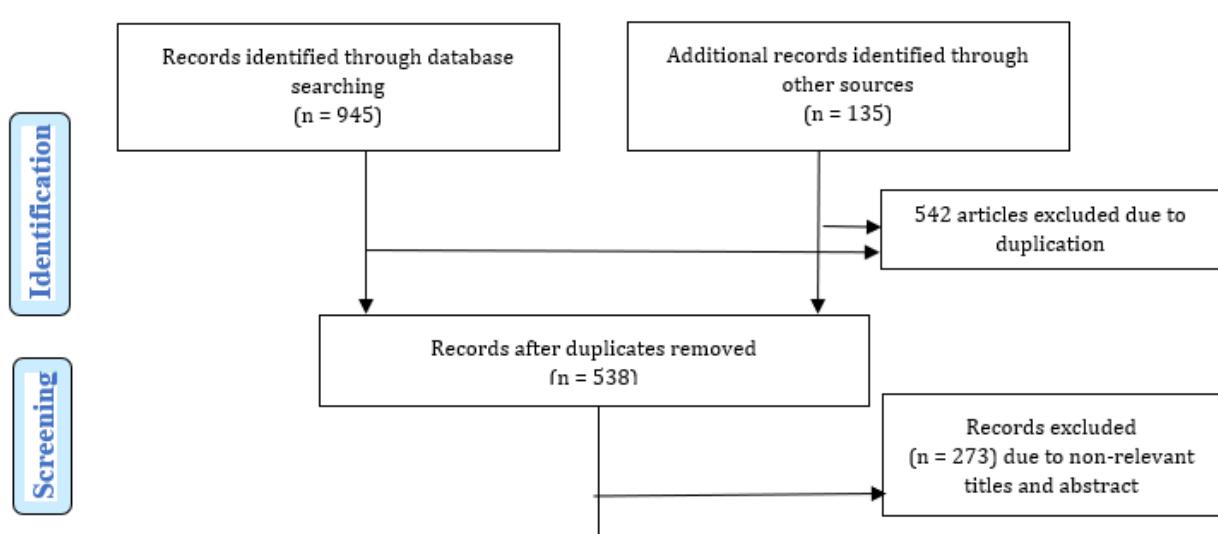
optimal and showed very similar results with resource-rich countries.^[46] Therefore, it is necessary to identify any difference in adherence rate among these countries and to explore various influencing factors on it. Furthermore, there is no previous review involving the patients with HTN in the developed countries and there is globalization and economically increasing nowadays. The level of adherence to anti-hypertensive medications may vary from country to country and factors related to drug adherence may also be different. Until now, a more comprehensive review of reasons why patients with HTN are poor in adherence of anti-hypertensive medication cannot be found, so this review was done to guide future research, and interventions to promote medication adherence that takes into account the relevant factors produced different successful outcomes. The review of factors contributing to different adherence will demonstrate all factors related to drug adherence and improve understanding among health care providers to develop appropriate intervention.

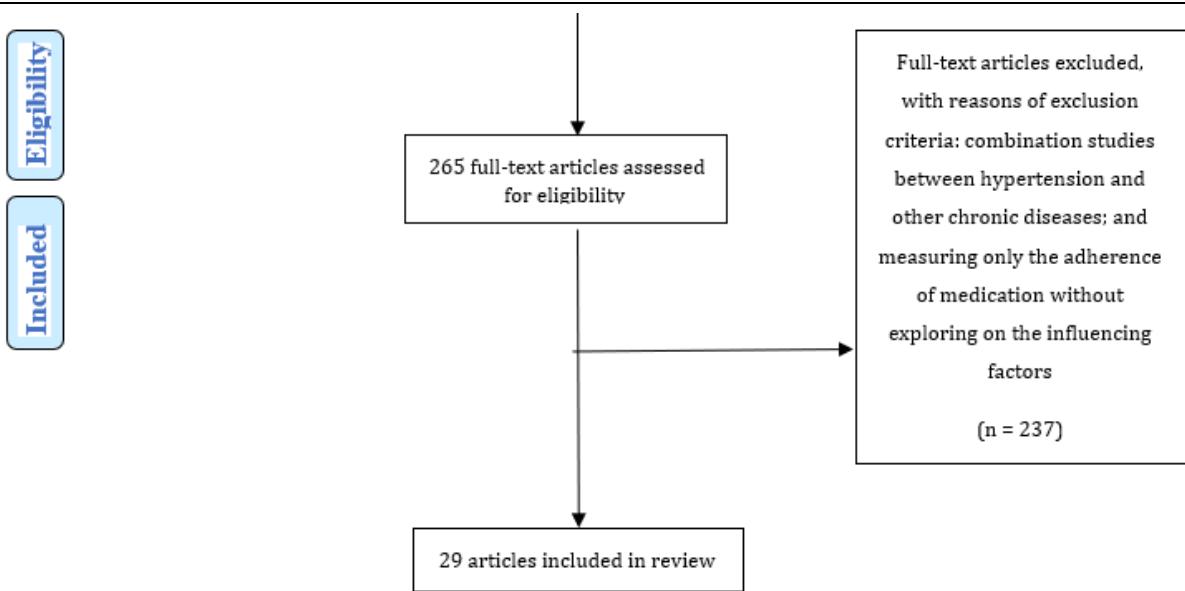
MATERIALS AND METHODS

The researchers conducted this systematic review following the standardized critical appraisal instruments from the Joanna Briggs Institute (JBI) methodology for systematic reviews. The processes are included search strategy, study selection, assessment of methodological quality, data extraction, and data analysis/synthesis.^[13] A systematic review of published studies within the period of 2010 to 2020 was done by searching six electronic databases: PubMed, Science Direct, Medline, ProQuest and Google Scholar, as well as manual journal searches. Peer-reviewed full text articles published only in English on hypertensive adults and older adults that measured adherence level of antihypertensive drugs and their associated factors were eligible for inclusion. The PRISMA reporting and analytical guidelines of systematic reviews was followed for this review.^[14] The search strategy included the following terms: medication adherence OR determinants of adherence AND influencing factors OR related factors OR associated factors OR compliance OR persistence AND hypertension OR high blood pressure.

The selection criteria for this review include 1) the articles reporting a study or project on the measuring the adherence to antihypertensive medications and identification of influencing factors on medication adherence of hypertensive patients on the antihypertensive medication 2) a peer-reviewed full-text article published in English 3) participants involved all adults and older adults age over 18 years and above. Exclusion criteria were 1) combination studies between HTN and other chronic diseases and 2) measuring only the adherence of medication without exploring on the influencing factors.

Initial search found 1,080 studies. After reviewing the abstracts and titles by two independent reviewers for assessment against the inclusion criteria, the total 29 articles are left: 24 were quantitative studies, three were qualitative studies, and two were mixed methods study. All 29 articles were included for appraisal of methodological quality and were determined to be of adequate quality, reporting adequately at least 50% of the applicable questions with an answer of "yes" from the JBI critical appraisal tools. The overall quality of all these 29 original/initial studies was considered acceptable for inclusion. The methodological quality of the quantitative and qualitative studies was assessed by using JBI critical appraisal tools,^[13] and the rest by using Mixed Methods Appraisal Tool (MMAT) by a modified e-Delphi study.^[51] The standardized data extraction tool from JBI was used to record the citation details, methodology and objectives, and main findings of each paper. The following information was extracted and tabulated by author name, study design, variables that were being investigated, assessment of medication adherence, sample size, setting and any statistical information (95% CI, p-value, correlation coefficients).^[13] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty of evidence criteria were applied to assess the quality of the evidence. Based on the methodological quality assessment and GRADE criteria, there were no important limitations to the included studies. The results consisted high and moderate certainty of the evidence in the reviewed studies.^[52] A summarized information of the studies reviewed was given in Table 1.





“Figure 1: PRISMA FLOWCHART of the review process”

RESULTS AND DISCUSSION

Results: Factors influencing medication adherence
This review involved different study designs including quantitative, qualitative and mixed method. It also contained the studies conducted in various countries of Ethiopia (3), India (3), Nigeria (3), Bangladesh (2), Brazil (2), Iran (2), Malaysia (2), Pakistan (2), Poland (2), China (1), Ghana and Nigeria (1), Hong Kong (1), Myanmar (1), Palestine (1), Serbia (1), USA (1), and Vietnam (1) from 2010 to 2020. This review has the total sample of 39,488 patients and has the methodological and theoretical relevancy. The data collection methods in this review were application of questionnaires in 23 studies, patient interviews for four studies, and patients' self-reports with observing medical records in two studies. The measurements for medication adherence used in the reviewed studies were eight-item Morisky Medication Adherence Scale (MMAS-8), 4-Item Morisky Medication Adherence Scale (MMAS-4), Drug Attitude Inventory-10 scale (DAI-10), Four-Item Morisky Green Levine Medication Adherence scale, Modified Morisky Green test, Morisky-Green Test, and the Hill-Bone Compliance scale. Besides, the most of use was MMAS-8 and this was discussed in 11 published articles.^[15, 16, 17, 19, 20, 21, 27, 40, 44, 49, 50] The most cut off point for medication non-adherence for MMAS-8 scale was the scores less than six, MMAS-4 scale was less than one, DAI-10 was any negative score less than zero rated as poor adherence where the scores were ranging from a maximum of 10 to a minimum of -10, Four-Item Morisky Green Levine Medication Adherence Scale was 2 points or less, Modified Morisky Green test was 3 points or less, Morisky-Green Test was less than two, the treatment compliance in Hill-Bone compliance scale was interpreted as higher the score, the poorer adherence, and patients' self-reports in some studies applying a threshold of 80% as adherence. For the patient interviews, non-adherence to antihypertensive medication was described as medication discontinuation for the period of interview, after receiving treatment at initial diagnosis, by categorizing into 'yes' and 'no'. The rate of non-adherence to anti-hypertensive medicine varied from 25.88% to 85%. The results for each after using these measurement scale were described in the following table 1. The factors influencing the medication adherence of hypertensive

patients are categorized as the socio-demographic, patient-related, treatment-related, disease-related, and healthcare service-related factors.

1. Sociodemographic factors

There were 25 studies confirmed that sociodemographic factors play important roles on medication adherence. These socio-demographic factors included age, occupation and medication cost, family support, co-morbidities, place of residence, and distance from health care, gender, education level, convenience of medication filling, family history, type of family, religion, ethnicity, marital status and availability of medicine. We found 10 studies showed age as a significant factor for drug adherence,^[15, 16, 17, 18, 19, 20, 21, 22, 23, 49] eight studies for occupation, lack of employment and cost of medicine,^[15, 18, 20, 23, 32, 39, 44, 49] seven for family support,^[23, 27, 31, 32, 34, 39, 50] six for comorbidities,^[15, 16, 18, 24, 27, 28] five for place of residence, and distance from health care,^[15, 16, 23, 27, 41] five for sex,^[15, 23, 24, 25, 49] three for education level,^[17, 23, 32] two for convenience of medication filling,^[39, 44] two for family history,^[15, 26] two for type of family,^[21, 26] two for religion,^[37, 38] one for ethnicity,^[25] one for marital status,^[15] and one for availability of prescribed drugs.^[37] The age influences on medication adherence showed different findings of contradictory results. Younger age was significantly associated with non-adherence of hypertensive medications in India (≤ 57 years),^[21] Hong Kong,^[20] Myanmar,^[49] Palestine,^[16] Ghana and Nigeria,^[17] but another study in Serbia found in older adults age more than 65 years.^[19] Adherence to medication regimen was found more likely in female patients,^[24, 25] but more in male.^[15] The occupation concerned with medical cost, and payment mode, mainly lack of employment,^[15, 18, 20, 23, 32, 39, 44, 49] and family history made more influence on medication adherence,^[15] and especially during check-ups for conditions related to HTN.^[26] For the ethnic group, Chinese patients were twice as more likely (95% CI: 1.14-3.6; $P < 0.05$) to drug adherence, compared to Indian.^[25] For comorbidity factors, medication adherence is associated with having obesity (physical), *angina, heart attack, or stroke*,^[24] of other chronic diseases (comorbidity),^[18, 28] and presence of cardiovascular comorbidities can promote the adherence to antihypertensive medication. Social support contains

inadequate family support, poor family cohesion in Bangladesh, and absence of a person who can accompany to go to the hospital/physician.^[31] For type of family, having family members to take care of the patient was important for better medication adherence,^[21, 26] also having a spouse or living partner was associated with better adherence.^[15] Higher educational level,^[17, 23, 32] and living closer to the healthcare facilities,^[15, 16, 23, 27, 41] were related to higher adherence. The religious belief also influenced on the medication adherence by making changes of medication regimen such as faith healing.^[38] Drugs availability was influenced by drugs exhaustion, financial problems for replacement leading to skipping appointments/being unable to refill prescription.^[37]

2. Patient-related factors

There were 23 studies confirmed that patient-related factors are influencing on drug adherence. The patient-related factors included knowledge, beliefs and perception on health status and disease management, lifestyles, personal habits, attitude, awareness, forgetfulness, understanding about treatment, psychological condition, and physical ability. It was found for patients' related factors including 10 studies for knowledge as a significant factor for medication adherence,^[16, 17, 25, 32, 33, 36, 37, 39, 40, 41] 10 for beliefs/perceptions of hypertension and its management,^[15, 17, 26, 31, 34, 35, 39, 40, 49, 50] four for lifestyles: diet, physical exercise, and BMI,^[15, 18, 35, 44] three for psychological condition: depression,^[17] dementia,^[23] memory,^[39] and three for personal habits,^[15, 24, 35] two for attitude,^[34, 39] two for awareness,^[15, 22] two for forgetfulness,^[16, 37] and two for self-perceived health status,^[16, 20] one for understanding level of disease and the medical recommendations,^[18] and one for physical ability.^[23]

Inadequate knowledge relating about disease and treatment, especially drugs for dosage and frequencies of prescribed medication leading to the fear of getting used to medication, adverse effect, and dissatisfaction with treatment,^[16] the medication and lifestyles recommendations including necessary of long-term treatment,^[33] had a statistically significant association to poor medication adherence.^[16] Medication adherence can also be influenced by personal habits: alcohol consumption,^[15, 24] tobacco chewing,^[15] and smoking.^[15, 24, 35] Respondents with sedentary lifestyle and smoking were less adherent to anti-hypertensive medication than those with regular physical activity and non-smokers, and these may be due to respondents' inadequate knowledge about cardiovascular disease impaired the adherence to medicine intake.^[35] These means disease-management behaviors of patients are also influenced not only psychosocial factors and also by habits and beliefs. These can produce the habitual/subsequent actions for their behaviors. Also, poor adherence was associated with not only knowledge but also understanding and beliefs about disease and treatment recommendations.

The disease understanding about HTN and treatment including the absence of signs and symptoms and chronicity of disease, difficulties in accepting and adapting to continuous use of prescribed drugs, and ignorance of the name of antihypertensive medication^[18] was associated with drug adherence. Then, adherence was influenced by the beliefs about disease such as not a curable disease,^[32] the severity of complications,^[31, 50] and disease management of HTN,^[32] and also by their perceptions on disease and treatment: perceived barriers,^[15, 49] inadequate perceived susceptibility and perceived benefit,^[35] perceived severity,^[35, 50] and beliefs

about HTN is curable by using orthodox and traditional medicines.^[31] Adherence was also influenced by the awareness regarding sodium intake reduction by using salt substitutes and products for healthier meals composition, exercise.^[38] Finally, physical ability,^[23] and mental diseases,^[17, 23, 39] can influence on drug taking behavior.

3. Treatment-related factors

There were 16 studies confirmed that treatment related factors are influencing to drug adherence. The treatment-related factors included the followings of irregular follow-up and number of making appointment with health care personal, poor BP control and adverse effects of antihypertensive drugs, number of drugs taken currently, frequent blood pressure measurements, use of herbal preparation, not using non-Western prescription medication complex drug therapy, continued use of medication, and non-pharmaceutical treatment. Adherence to anti-hypertensive treatment is significantly associated with regular follow-up or number of making appointment with health care personal in six,^[15, 23, 25, 26, 31, 36] poor BP control and adverse effects of antihypertensive drugs in five,^[16, 19, 34, 37, 39] number of drugs taken currently in five,^[15, 16, 25, 40, 41] frequent blood pressure measurements in two,^[40, 45] use of herbal preparation, not using non-Western prescription medication in two,^[17, 31] complex drug therapy in one,^[36] continued use of medication in one^[18], and non-pharmaceutical treatment in one study.^[40] Use of non-Western prescription medication or traditional medicines can stop using anti-hypertensive medications, but choice of drugs was mainly based on their beliefs.^[31] Appointment keeping can lead to better blood pressure levels monitoring and getting more access to health information and can serve as the basis for adherence to antihypertensive medication management.^[31, 36] Good adherence was found significantly in patients who have regular BP measurements,^[40, 45] high level of non-pharmaceutical hypertension treatment,^[40] and in those either receiving, or taking medicine once per day.^[15, 16, 25, 40, 41] Non-adherence to medication was due to complexity of drug therapy,^[36] having side effects of drugs and blood pressure control.^[16, 19, 34, 37, 39]

4. Disease-related factors

There were 15 studies confirmed that disease related factors are influencing to drug adherence. The disease-related factors include duration of disease, the presence or absence of the disease symptoms, level of disease control, current disease seriousness and quality of life, complications, and previous disease experience. We found disease related factors for duration of HTN as a significant factor of drug adherence in eight,^[15, 19, 20, 23, 26, 40, 45, 49] the absence of disease symptoms in three,^[21, 37, 38] blood pressure level control in three,^[17, 25, 40] spot blood pressure and complications in one,^[27] and previous disease experience in one study.^[44]

Respondents who did not have disease symptoms of HTN (OR, 0.414:95%CI, 0.192 to 0.892) were more like to be in the high adherent category compared to those who reported experiencing such symptoms.^[21] More non-adherent patients had more disease symptoms,^[21] and the absence of symptoms made more non-adherence to drugs.^[37] Non-adherence was associated with HTN related complications and high blood pressure and poor control^[27]. Previous history of admission to emergency services due to hypertensive crisis made more adherence to drugs.^[44] Patients with antihypertensive agents for longer duration reported better adherence than those with shorter duration for ≥5 years,^[15, 26] and ≥3 years.^[49]

5. Healthcare service-related factors

There were nine studies confirmed that factors related to healthcare services influenced drug adherence. The factors related with health care services are patients' satisfaction on the services they got, having health insurance, and the quality of health care services. These barriers to non-adherence are found in four studies regarding disappointment with the health services provided and treatment as a significant factor,^[16, 26, 36, 38] three studies for fewer interaction with physicians,^[32, 34, 39] two studies for having health insurance,^[17, 38] one study for inadequate information from health care center, and another study for HTN diagnosed by unqualified providers.^[24] Healthcare team and system-related factors include the availability of professional guidance, cost and coverage of medications,^[39] deficiencies in information from service provider and government hospital^[32] and insured participants.^[17, 38] According to Odusola *et al.* (2014), there are barriers of medication adherence by patients trust in orthodox "western" medicines, trust in doctor and dreaded dangers of HTN and patients' satisfaction inconvenient operating hours of clinic, long waiting period, and under-dispensing of prescriptions.^[38]

DISCUSSION

This review has substantial heterogeneity in methods and populations across studies, however, over half of the studies including in this review were quantitative methods. Most of the sampling techniques were purposive and consecutive sampling method and all eligible hypertensive patients were selected widely from clinics/hospitals or communities as study participants. Thus, the results may be necessarily generalizable. A large number of influencing factors related to medication adherence of HTN were consistently identified across different countries and various factors influenced on the medication adherence of hypertensive patients including socio-demographic factors, patients-related factors, treatment related, disease related, and health care services related. Therefore, a comprehensive adherence promotion programs can be implemented based on these findings.

Nonadherence was related with low household income and socioeconomic status in this review. These effects on the cost of medication were also found in the study conducted among cardiovascular patients.^[43] Also, poor knowledge and negative perceptions about medication and side effects are linked with non-adherence to cardiovascular medications in resource-limited settings. Medication adherence remained constantly in different geographic settings, urban versus rural area, or the regimen complexity of medicines that was different from this review.^[46] Furthermore, adherence to medication regimes was associated with perception of illness according to the study about the impact of personal and cultural beliefs on medication adherence of patients with chronic illnesses: a systematic review done by Shahin *et al.* (2019).^[47] Additionally, adherence to medication in chronic illness can be predicted by their degree of automatic/ habitual behavioral repetition according to Phillips *et al.* (2016).^[48] Besides, the following findings are similar to the systematic review of factors influencing medication adherence to anti-hypertensive treatment in the developing countries conducted by Dhar *et al.* (2017). They found that low household income and socioeconomic status; knowledge and beliefs of hypertension and its management; avoiding adverse effects of medications; cost of medication; use of herbal preparations; absence of

symptoms; irregular follow-up; and dissatisfaction with the treatment and health services provided are especially occurring in this study.^[30] In this review, the following factors were influencing on the adherence of anti-hypertensive medication additionally; ethnicity, religion, marital status, convenience of medication filling and ran out of prescribed drugs as socio-demographic factors; lifestyles, and physical ability as patient-related factors; frequent blood pressure measurements as treatment-related factors; spot blood pressure and previous disease experience as disease-related factors; and having health insurance as health-service related factors. Therefore, these findings can be helpful for hypertensive patients in improving medication adherence in the future more comprehensively, in which may prevent possible HTN related complications. This review has the similar results with the review about factors affecting adherence by Dwajani *et al.* (2018). Better adherence observed in patients who have social support and good relationship of doctor-patient. Poor adherence was found in lack of family or social support, limitation in accessing health care facilities, inability or difficulty to access pharmacy, lack of financial resources, medication cost, cultural and lay beliefs about illness, treatment and burdensome work schedules, improper communication regarding the benefits of taking medication, and usage instructions and adverse effects of medications, especially in older patients with memory problems. Furthermore, patients with chronic disease and few or no symptoms, physical impairments such as hearing, visual, cognitive and swallowing problems, and poor knowledge about the disease, were less adherent to drugs. Complex medication regimen, and inadequate understanding about the medicine: its importance, apprehension about possible adverse side effects, absence of motivation, and substance abuse, made the patients poor medication adherence.^[42] According to this review, perceiving less importance of taking treatment is most of the patient-related barriers of medication adherence by forgetfulness to take medication and carelessness. Consequently, a person's perception about his or her ability to perform a specific behavior or patients' self-efficacy or perception about control/cure: personal and treatment control, illness representation especially timeline and emotional dimensions and knowledge levels of hypertensive patients on adherence to treatment plan, have the impact on adherence to medication.^[40] Furthermore, perceptions of hypertension are major contributing factor for medication adherence. Patients who accurately perceive the seriousness of and complications of disease becoming more adherence to medications. Hesitation of hypertensive patients to take anti-hypertensive medicines continuously can cause more non-adherence due to fear of medication side effects and unsure of the benefits of continuous medication use.^[33, 34] Especially, knowledge and perceptions of a person are interrelated to each other, good knowledge background makes perfect perception, and that right perception can support proper knowledge application for medication adherence. Moreover, occupation is related with distance from home and forgetfulness, such as- business professionals who are leaving home early and late returning due to their tight work schedule and long distance from home that can result in tiredness.^[37] Besides, medication adherence was jointly influenced by age and place of residence,^[16] and also by age and working status.^[24] Disappointment with the health services provided and treatment became a barrier for medication adherence.^[16, 36, 38] Therefore, the underlying reasons of

dissatisfaction such as workload of health care personal, time limitation or inadequate facility, and the quality health services should be considered as an important issue for getting disease control. In this review, the medication adherence rate was different between developed and developing countries. It was quite lower in developed countries that was opposed to the systematic review done by Bowry *et al.* (2011).^[46] Moreover, the level of drug adherence in the developed countries was ranging from 45.8 to 65.9%,^[16, 20, 23, 40] but higher rate in developing ones for more than 70,^[19, 24, 26, 27, 28, 41] and also vary from region to region in the same country.^[15, 21, 26] Based on the adherence rates, the health care systems especially in the developing countries should consider about the health coverage of the citizens because the financial burden can affect the medication adherence,^[15, 18, 32, 39, 44, 49] however, self-concern and monitoring should be paid more attention by developed countries.^[16, 20, 40]

In conclusion, the most five significant influencing factors for drug adherence are 1) patients' disease knowledge, 2) perception and forgetfulness, 3) required health care services and drug supply, 4) health information from health care personals, and 5) social support especially for older adults. Because these are the comprehensive factors for getting medication adherence and also rely on each other, these should be paid more attention. Without one of the above factors, the fully adherence to medicine cannot be obtained.

LIMITATIONS

This review was limited to the studies published in international journal and online accessible information during the years 2010 to 2020. It cannot cover all the studies published in other languages and non-online publication. The majority of the studies relied mainly on self-reported adherence, which may be subjective presentation and may have recall bias. Among the selected quantitative studies, mostly are cross-sectional studies. Therefore, longitudinal assessment can be better for differentiation of whether chronic or occasional non-adherence, and associated barriers that may lead to non-adherence. This review cannot describe about the health care delivery especially for treatment recommendations. Moreover, there is no clear explanation about the relations between lifestyle factors and medication adherence that is also necessary for getting better adherence to anti-hypertensive medications and can be applied more clearly in the adherence promotion implementation programs.

CONCLUSIONS

In conclusion, medication adherence of hypertensive patients was influenced by various factors including socio-demographic factors, patients-related factors, treatment related, disease related factors and health care services

related factors. These five groups of significant factors can serve as a basic foundation for interventional studies for improving their adherence of hypertensive patients to reduce considerably morbidity, mortality and avoidable health care costs for non-adherence.

Practical implications and future research: Anti-hypertensive medication adherence is very important for getting blood pressure control and preventing the impacts on the public. Healthcare providers, especially physician, nurse, and pharmacist, should implement non-communicable disease control program and health promoting strategies by taking consideration of all of the influencing factors and encouraging healthy lifestyles to lessen these barriers. Engaging patients and their family members in medication adherence improving interventions are needed since they can help self-monitoring and elevate self-concerning of drug adherence. Suggested interventions are such as health talk and nursing interventional programs to improve knowledge and concern of medication adherence. Promoting regular appointment and lifestyle modification are also important. Planning adequate medicines and medication deliverable system should be also paid more attention for distance area and lack of social support patients. Moreover, treatment related barriers and disease related barriers can be minimized by putting special attention on regular follow-up, frequent blood pressure measurement, and clarifying the drug therapy regimen while providing health care services. The regular short message service (SMS) to the patients should be applied by Ministry of Health as a reminder for taking anti-hypertensive medications as well as improving awareness of the treatment recommendations. Additionally, right time referral for the patients with uncontrolled BP to prevent the complications timely is needed. The patients, their partners, family members or attendance should involve in these programs of promoting medication adherence because social support is very important for drug adherence, especially among older adults with HTN. Moreover, appropriate health resources: man, money, material and time should be established to get medication adherence. Finally, the barriers related to health care services can be resolved by the involvement of the whole health care system especially by implementing universal health care coverage for the poor financial status and quality building training for the health care providers. Future studies need to address detailed cultural barriers and reasons of health care system barriers such as inadequate staff quality, staff over workload and inadequate health care settings. Moreover, this review demonstrated the need for further well-designed studies to better understand the related factors of medication adherence and also other age groups of juvenile hypertensive patients.

"Table 1: A summary of the reviewed studies"

No.	Author and Study design	Variables being investigated and statistical information	Measurement of medication adherence, results	Setting and sample size	Level, Certainty of evidence
1.	Ali <i>et al.</i> (2014). ^[27] Prospective cross-sectional	Family support (AOR = 0.170, 95%CI = 0.030-0.905), spot blood pressure (AOR = 0.052, 95%CI = 0.003-0.242), place of patients' residence (AOR = 0.184, 95%CI = 0.024-0.597) and HTN complications (AOR = 21.737, 95%CI = 1.568-418.428)	MMAS 8-Item adherence scale, 73.6% of patients had drug adherence and one-fourth of patients, 26.4% were non-adherent to treatment.	121 hypertensive patients from outpatients of two referral hospitals, Ethiopia	Level 4.b ⊕⊕⊕○ MODERATE ^a

2.	Teshome <i>et al.</i> (2017), ^[41] cross-sectional study	urban residence (adjusted odd ratio [AOR]=2.10, 95% confidence interval [CI]: 1.15, 3.85), taking less than two drugs per day (AOR=3.04, 95% CI: 1.53, 6.06), and having knowledge about HTN and its treatment (AOR=8.86, 95% CI: 4.67, 16.82) while age >60 years negatively (AOR=0.33, 95% CI: 0.11, 0.98)	four-item Morisky-Green-Levine Scale, three-quarters (75.1%) of the participants were adherent to their medication therapy.	337 hypertensive patients, Debre Tabor General Hospital, northwest Ethiopia	Level 4.b ⊕⊕⊕○ MODERATE ^a
3.	Tsadik <i>et al.</i> (2020), ^[50] institution-based cross-sectional study	having family support (AOR: 1.65; 95% CI = 1.23, 2.22), high perception about consequences of hypertension (AOR: 1.51; 95% CI = 1.17, 1.95), and high perception about the severity of the disease (AOR: 1.42; 95% CI = 1.09, 1.86)	MMAS-8 Scale, 36.0% were high adherence, 31.7% medium adherence, and 32.3% low adherence.	A total of 989 hypertensive patients in 4 public hospitals, Central Ethiopia	Level 4.b ⊕⊕⊕○ MODERATE ^a
4.	Ahmad (2015), ^[15] descriptive study	Socio-demographic (sex (more in male than female, OR=1.25), age ($p < 0.001$), marital status ($p = 0.015$), socioeconomic status ($p < 0.001$), family history ($p = 0.008$), awareness ($p < 0.001$), comorbidities ($p < 0.001$)), lifestyles (diet ($p < 0.001$), physical exercise ($p = 0.018$), smoking ($p < 0.001$) and habits of alcohol consumption ($p = 0.026$), health care facility (distance from UHTC, conveyance, frequency of check-up) ($p = 0.001$), treatment (number of drugs ($p < 0.001$), cost of medicine ($p < 0.001$), duration of treatment ($p < 0.001$)), treatment outcome (health perception ($p = 0.002$), treatment perception ($p < 0.001$), blood pressure ($p < 0.001$))	Morisky 8-Item Medication Adherence Questionnaire, Good adherence was found in 191 patients (57.2%) and poor in 143 (42.8%).	334 hypertensive patients from Urban Health and Training Centre (UHTC), North India	Level 4.b ⊕⊕⊕○ MODERATE ^a
5.	Bhandari <i>et al.</i> (2015), ^[26] Cross-sectional	Duration of HTN for \geq 5-year (OR = 2.98; 95% CI = 1.73-5.14), hypertension was detected during check-ups for conditions related to HTN (OR = 2.35; CI = 1.25-4.39), living with \leq 4 family members (OR = 2.01; CI = 1.52-3.50), those with a family income of \geq Rs 3000 (OR = 2.56; CI = 1.47-4.45), getting free (OR = 4.16; CI = 1.36-12.69), perceived BP under control (OR = 2.23; CI = 1.17-4.26) and satisfied with current treatment (OR = 3.77; CI = 1.32-10.76)	patient self-reports plus reviewing medical records, the adherence rate (adherence \geq 80%) was 73% (95% CI = 68%-78%). (non-adherence was 27%)	348 hypertensive patients living in a selected urban slum Dwellers in Kolkata, India	Level 4.b ⊕⊕⊕○ MODERATE ^a
6.	Nagarkar, <i>et al.</i> (2013), ^[21] cross sectional	Age (95% CI: 3.348 (1.665-6.732), $p = 0.001$), family type (95% CI: 2.670 (1.378-5.175), $p = 0.004$) (living in nuclear family setup) and experience of symptoms of HTN (95% CI: 0.414 (0.192-0.892), $p = 0.024$) (not experience of symptoms)	MMAS-8, 23.4% were high adherent and 76.5% showed low drug adherence.	among 205 hypertensive patients, in the state government's civil hospital located in the urban parts of Pune District in the state of Maharashtra, India	Level 4.b ⊕⊕⊕○ MODERATE ^a
7.	Campbell <i>et al.</i> (2014), ^[37] Cross-sectional	Forgetfulness (OR 14.8, 95%CI: 3.9-54.8, $p = 0.000$), ran out of prescribed drugs (OR 1.3, 95%CI: 0.1-0.4, $p = 0.000$), avoiding side effects (OR 3.0, 95%CI: 1.4-6.7, $p = 0.006$) and absence of symptoms (OR 3.3, 95%CI: 1.3-8.0, $p = 0.010$), religion ($X^2 = 5.0068$, df=1, P-value=0.025), and knowledge ($X^2 = 6.6848$, df = 1, P-value= 0.00972, F-exact Test= 0.0184)	Modified Morisky Green test, Majority 196 (74.81%) of the respondents were not compliant to anti-hypertensive treatment while only 66 (25.19%) complied.	262 hypertensive patients from outpatients of a HTN clinic, Nigeria	Level 4.b ⊕⊕⊕⊕ HIGH

8.	Odusola <i>et al.</i> (2014), ^[38] Qualitative	Affordability of care (through health insurance), trust in orthodox "western" medicines, trust in doctor, dreaded dangers of hypertension, and use of prayer to support efficacy of pills, inconvenient clinic operating hours, long waiting times, under-dispensing of prescriptions, side-effects of pills, faith motivated changes of medication regimen, herbal supplementation/ substitution of pills, and ignorance that regular use is needed, local practices and norms.	a semi-structured interview guide	40 hypertensive patients from a rural primary health care Nigeria	Level 4.d HIGH
9.	Osamor <i>et al.</i> (2011), ^[31] Survey and qualitative interviews	Regular clinic attendance ($p < 0.0001$), not using non-western prescription medication ($p < 0.0001$), support from family members, friends concerned about the respondent's HTN and helpful in reminding the respondent about taking medication ($p < 0.0001$), belief about HTN ($p = 0.001$): feeling better, forget to take medication and cost	Survey questionnaire for medication compliance (how frequently people missed as: 'high 'medium' and 'low'). Over one-half (50.7%) of the respondents had high self-reported compliance with treatment whereas 41.5% had poor self-reported compliance.	N = 440 and 8 focus groups. Consecutive sampling method was used to recruit participants from a list of hypertensive patients of a poor urban community Nigeria	Level 4 HIGH
10.	Hussain <i>et al.</i> (2011), ^[32] Cross-sectional	Lower level of education (OR-6.34, 95% CI: 1.65 24.41), low family income (OR- 1.75, 95% CI: 0.52 5.90), poor knowledge levels (OR-24.50, 95% CI: 6.28 95.58) regarding management and consequence of untreated HTN, believes and understanding of disease (OR-12.90, 95% CI: 1.65 100.63), lack of accompanying person to go to the physician/hospital (OR- 3.54, 95% CI: 1.04 11.99), deficiencies in information from service provider and government hospital (OR- 5.16, 95% CI: 1.13 23.66).	Adherence Questionnaire, Only 15% of patients had adherence to drugs and eighty five percent (85%) were non-adherent.	120 hypertensive patients of inpatient departments of a medical college and a private clinic, Bangladesh	Level 4.b MODERATE ^a
11.	Khanam <i>et al.</i> (2014), ^[24] Cross-sectional	Sex (male) (OR 1.74, 95% CI: 1.48–2.04), hypertension diagnosed by unqualified providers (OR 1.52, 95% CI: 1.31–1.77), and patients with cardiovascular comorbidity (OR 0.79, 95% CI: 0.64–0.97)	Interviewing, non-adherence to antihypertensive treatment, 74% of patients had drug adherence and 26% discontinued the use of medication.	29,960 Stratified two stage sampling from the population of three rural sites, Bangladesh	Level 4.b MODERATE ^a
12.	Barreto <i>et al.</i> (2014), ^[36] cross sectional study	Complex drug therapy ($p = 0.02$), poor knowledge about the disease ($p = 0.00$) and dissatisfaction with the healthcare service ($p = 0.00$)	Medication Adherence Questionnaire (MAQ-Q), 57.4% of patients had drug adherence, and 42.6% did not adhere.	422 hypertensive people at the Primary Healthcare Service in a city located in the South region of Brazil	Level 4.b MODERATE ^a
13.	Demoner <i>et al.</i> (2012), ^[18] quantitative, descriptive exploratory study	Sociodemographic variables (youngest age group ($p = 0.0143$), working ($p = 0.0254$)), diseases (other chronic disease ($p = 0.0061$)), continued use of medication ($p = 0.0011$)), body mass index (BMI) ($p = 0.0056$) (presenting with overweight or obesity)	Morisky-Green Test, 36% of patients were adherent and 64% were nonadherent to antihypertensive therapy.	432 patients with HTN in a primary care unit, Brazil	Level 4.b MODERATE ^a
14.	Behnood-Rod <i>et al.</i> (2016), ^[44] cross-sectional study	Overweight/obesity ($B = -0.52$, $P = 0.02$), previous history of admission to emergency services due to hypertensive crisis ($B = -0.79$, $P = 0.001$), and getting medication directly from drugstore without refill prescription in hand ($B = -0.51$, $P = 0.04$)	MMAS-8, About half of the sample 141 cases (50.4%) showed good adherence and 139 cases (49.6%) showed low adherence	280 hypertensive patients in tertiary referral centre of university-affiliated hospital, private cardiology office,	Level 4.b MODERATE ^a

			pharmacy, and private general practitioner office in the cities of Tehran, Karaj, Kermanshah, and Bafgh, Iran.	
15.	Kamran <i>et al.</i> (2014), ^[35] cross sectional	Sedentary lifestyle ($P < 0.01$) and smoking ($P < 0.01$, OR = 1.9, 95% CI = 1.3–2.9), inadequate perceived susceptibility ($p <0.01$), perceived severity ($p <0.001$), perceived benefit ($p <0.01$), and poor lifestyle factors ($p <0.001$).	MMAS 4-Item, Only 24% (161/671) of the study population had adherence. (non-adherence was 76 %)	671 hypertensive patients in a rural area of the Ardabil city, Iran.
16.	Ramli, <i>et al.</i> (2012), ^[25] Cross-sectional	Sex (Female more than male) (OR-1.46 [95% CI]: 1.05–2.04; $P <0.05$), ethnic (Malay and Chinese than the Indian) (95% CI: 1.14–3.6; $P <0.05$), number of drugs (OR-0.84, 95% CI: 0.76–0.92, $P =0.000$), medication knowledge (OR- 1.03, 95% CI: 1.01-1.04, $P= 0.001$), daily dose frequencies of the medications (OR- 0.74, 95% CI: 0.61-0.89, $P= 0.002$), blood pressure control (A poor adherence rate was found to negatively affect blood pressure control) (For SBP, $135.83 \text{ mmHg} \pm 15.79$; $t [618] = 2.815$, 95% CI: 1.126–6.217; $P < 0.05$ and for DBP, $83.56 \text{ mmHg} \pm 7.26$; $t [600] = 2.521$, 95% CI: 0.347–2.792; $P < 0.05$).	Modified Medication Adherence Scale, Good adherence was observed in 53.4% of the 653 patients sampled. (non-adherence was 46.6%)	653 hypertensive patients from 7 primary health care clinics, Malaysia
17.	Shima <i>et al.</i> (2014), ^[34] Qualitative	Side effects or fear of the side effects of antihypertensive medication, patients' attitudes, lack of information from health care professionals and insufficient social support.	A rough interview guide	25 hypertensive patients Malaysia
18.	Arshad (2015), ^[28] cross-sectional study	Co-morbid conditions (OR=4.238; 95% CI 1.161, 15.468)	4-Item Morisky Medication Adherence Scale, 75 patients (70.75%) had good compliance and poor compliance (scores ≤ 2) was present in 31 (29.25%) patients.	106 hypertensive patients, at 1-Mountain Medical Battalion, Pakistan
19.	Saleem <i>et al.</i> (2011), ^[33] Cross-sectional observational	Knowledge scores of HTN and adherence level ($p < 0.001$).	Drug Attitude Inventory (DAI-10), 249 (64.7 %) were categorized as poor adherent. No patient was considered as good adherent in the study.	385 Eligible hypertensive patients from two tertiary care hospitals, Pakistan
20.	Jankowska-Polańska <i>et al.</i> (2016), ^[40] descriptive study	Knowledge ($\beta=0.208$; $P=0.001$), non-pharmaceutical treatment ($\beta=0.182$; $P=0.006$), and frequent blood pressure measurements ($\beta=0.183$; $P=0.004$). The most significant factor in MMAS was knowledge in the "drug adherence" ($p=0.303$; $P,0.001$).	MMAS-8, 65.9% of patients had drug adherence and 34.1% had poor adherence.	233 hypertensive patients in the Kosmonautów health centre in Wroclaw, Poland
21.	Uchmanowicz <i>et al.</i> (2019), ^[23] a cross-sectional study	Coexistence of frailty syndrome in aging patients ($p <0.05$): physical (weight, daily life, walking, hearing, vision, strength, and tiredness) ($p<0.001$), psychological (memory, mood, anxious, and coping with problems) ($p= 0.007$), and social components (living alone, people around, and support) ($p= 0.001$)	the Hill-Bone Compliance, the mean score obtained was 20.24 ($SD = 4.01$) and ranged from 14 to 32 points, the median was 19.5 points, among the total scores ranged between 14- and 56-points,	160 hypertensive patients aged 65 to 78 hospitalized at the University Clinical Hospital, Poland

			half of the participants obtained less, and half obtained more than 19.5 points.		
22.	Hu <i>et al.</i> (2013), ^[45] a cross-sectional survey	The duration of HTN (adjusted OR, 3.31; 95% CI, 1.91 – 5.72; P < 0.001), frequency of performing BP measurements (adjusted OR, 2.33; 95% CI, 1.42 – 3.83; P < 0.001)	A questionnaire survey developed by the researchers, 195 (61.3%) has adherence to medication.	318 hypertensive patients in a rural community in Beijing, China	Level 4.b ⊕⊕⊕ HIGH
23.	Boima <i>et al.</i> (2015), ^[17] cross sectional	Formal education (p = 0.001), younger age (p = 0.000), concern about medications ($r = -0.0347$, p = 0.002) and knowledge of hypertension ($r = 0.14$, p = 0.006), depression ($r = -0.208$, p < 0.001), use of herbal preparation (p = 0.014), insured participants (p = 0.032) and poor BP control (p = 0.006).	MMAS 8-Item adherence scale, 33.3% of patients were adherent and MNA was found in 66.7%.	357 hypertensive patients from four hospitals, Ghana and Nigeria	Level 4.b ⊕⊕⊕○ MODERATE ^a
24.	Lee <i>et al.</i> (2013), ^[20] cross-sectional study	Younger age (p< 0.001), shorter duration of antihypertensive agents used (p= 0.006), job status being employed (p= 0.001), and poor or very poor self-perceived health status (95% CI: 0.647 (0.422–0.991), p= 0.045) were negatively associated with drug adherence (all p values≤ 0.05).	MMAS-8, 725 patients (65.1%) had good adherence to antihypertensive agents. (44.9% was non-adherence)	1114 hypertensive patients in an outpatient clinic located in the New Territories Region of Hong Kong	Level 4.b ⊕⊕⊕○ MODERATE ^a
25.	Han <i>et al.</i> (2015), ^[49] A hospital-based cross-sectional study	younger age (adjOR=3.03, 95%CI=1.15-7.99), male patients (adjOR=1.84, 95%CI=1.01-3.37), low household income (adj OR=2.39, 95%CI=1.17-4.85), longer duration of hypertension (adjOR=4.00, 95%CI=1.87-8.59 for those within 1-3 years and adjOR=2.63, 95%CI=1.12-6.20 for those with more than 3 years compared to those less than 1year)) and higher level of perceived barriers (adjOR=2.55, 95%CI=1.27-5.09).	Morisky Medication Adherence Scale (MMAS-8), Only 50% of hypertensive patients were reported as good adherence to anti-hypertensive medication.	216 hypertensive patients who recruited by convenient sampling method at tertiary hospitals in Yangon, Myanmar	Level 4.b ⊕⊕⊕○ MODERATE ^a
26.	Al-Ramahi, (2015), ^[16] Cross-sectional	Younger age (p= 0.006), living in a village (p= 0.001), forgetfulness (OR 5.12, 95% CI: 3.12–8.41), dissatisfaction with treatment (OR 2.93, 95% CI: 1.22–7.02), side effects (OR 4.58, 95% CI: 1.87–11.25), fear of getting used to medication (OR 8.00, 95% CI: 2.44–26.19), and evaluating health status (p= 0.012) as very good (OR 5.58, 95%CI: 1.83–17.04) Good(OR 5.40, 95%CI: 1.78–16.32), Poor (OR 4.55, 95%CI: 1.44–14.41), lower income (p=0.035), receiving a higher number of antihypertensive tablets (p= 0.001), a higher dosing frequency (p<0.0001) and having no other chronic disease (p= 0.009).	MMAS-8, 206 patients (45.8%) had good adherence and low adherence in 244 (54.2%) of the patients.	450 hypertensive patients in outpatient clinics of governmental primary healthcare centres, Palestine	Level 4.b ⊕⊕⊕○ MODERATE ^a
27.	Lalic <i>et al.</i> (2013), ^[19] cross sectional	Age ($\chi^2 =21.3$; p<0.01; OR=6.0 95%, CI 2.76-13.04), duration of therapy ($\chi^2 =5.12$; p< 0.05; OR=2.50 95%CI 1.18-5.30 and side effects of drugs ($\chi^2 =4.99$; p< 0.05; OR=3.78 95%CI 1.28-11.13).	MMAS-8, Good adherence was observed in 74.12% of the 170 patients sampled and 25.88% non-adherent.	170 hypertensive patients treated in a primary health care outpatient, Serbia	Level 4.b ⊕⊕⊕○ MODERATE ^{a,b}
28.	Holt <i>et al.</i> (2013), ^[39] a Qualitative Study	in older adults, including memory, knowledge, attitudes and beliefs, side effects, social support, interaction with health care providers, and cost and convenience of medication filling, patient (Individual-level) (Memory and forgetfulness), Family, Friends, and Community (Interpersonal relationships, specifically, support from family and friends, and peer or community groups), Health care system (Participants spent a substantial amount of time discussing their	A structured interview guide	25 older hypertensive patients in focus group sessions, a large managed care organization (MCO) in south-eastern Louisiana, USA	Level 4.d ⊕⊕⊕ HIGH

		interactions with their health care providers), Environmental and policy level (The cost and coverage of medications).			
29.	Nguyen et al. (2017), ^[22] mixed method, prospective design in Quantitative method	Each one-year increase in age resulted in patients being 1.036 times more likely to be compliant (95% CI: 1.002 to 1.072). Awareness of complications related to HTN was given as the main reason for adherence to therapy (12 patients reported forgetfulness to take medicine)	Patient self-report plus reviewing medical records and In-depth interviews, 49.8% of the patients were adherent	315 subjects for Quantitative and 18 subjects for Qualitative study in rural mountainous communes in the North of Vietnam	Level 4 HIGH
JBI Levels of evidence					
Level 4 – observational-descriptive study					
Level 4.b – Cross-sectional study					
Level 4.d- Case study					
GRADE Working Group Grades of Evidence for certainty of evidence					
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different is low.					
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different is moderate.					
Low: This research provides some indication of the likely effect. The likelihood that it will be substantially different (a large enough difference that it might have an effect on a decision) is high.					
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different (a large enough difference that it might have an effect on a decision) is very high.					
Explanations					
a. risk of bias (low, unclear, high)					
b. consistency (consistency, inconsistency, unknown/non applicable)					
c. directness (direct, indirect)					
d. precision (precise, imprecise)					

CONFLICTS OF INTEREST

There is no conflict of interest regarding the publication of this paper.

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