REVIEW ARTICLE

A Review of the Effectiveness of Interventions on Medication Adherence Among Hypertension Patients

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ABSTRACT

A majority of hypertensive patients will end up suffering uncontrolled hypertension, which is partly due to poor medication adherence. This paper aimed to review a range of interventions that could improve anti-hypertensive medication adherence. Literature search was conducted using PubMed, Scopus, Medline, and Science Direct databases, with publication dates confined to between October 2009 and October 2019. Eventually, only 11 studies were used for this study. It was found that interventions that are based on or include patient education, patient interviews, patient reminders, self-management and behavioural modifications have the potential to improve patients' adherence to anti-hypertensive therapy. Most successful interventions involve patient reminder, self-management and behavioural intervention.

Keywords: Medication adherence, Anti-hypertensive drugs, Health promotion

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INTRODUCTION

In Malaysia, as well as in Europe, hypertension is defined as a persistently raised blood pressure (i.e. systolic blood pressure ≥ 140mmHg and/or diastolic blood pressure ≥ 90 mmHg) (1, 2). The American Heart Association (AHA), however, classifies a person to be hypertensive if the blood pressure is more than 130/80 mmHg (3). Hypertension is a global chronic disease. The prevalence of patients with hypertension is projected to be more than 1.56 billion in 2025 (4, 5), and the majority of them will end up suffering uncontrolled hypertension (6). This, in turn, could lead to other morbidities, including cardiovascular diseases and renal insufficiency; thereby increasing health and economic burdens (7).

One of the leading causes of uncontrolled hypertension is poor medication adherence (8-10). Previous studies have estimated that 31.2% to 83.7% of the hypertensive population did not adhere to their anti-hypertensive drugs as prescribed (11). According to a recent study in Malaysia, adherence to anti-hypertensive drugs was 53.4% (12), which is relatively low when compared to that for anti-lipid therapy, where the prevalence of adherence was reported to be 82.4% (13).

As such, researchers have conducted trials to investigate strategies to improve drug adherence among hypertensive patients. Previous reviews have summarised several adherence-improving interventions. However, these reviews have limitations as they only synthesise blood pressure outcomes. They did not directly analyse the level of drug adherence (14). In addition, some authors limit their reviews of intervention effects to a specific type of adherence measurement method (15), while others restrict their reviews to specific types of interventions, for instance, including only interventions conducted by clinicians (16, 17). Hence, this review aimed to provide a more comprehensive review of interventions that could improve medication adherence among hypertensive patients.

METHODS

Identification of Studies

The focus of our study is to determine strategies that can improve drug adherence among patients suffering from hypertension. Hence, the literature search was done using a broad search string (interventions OR strategies) AND (adherence OR compliance) AND (hypertension) AND (medication OR drug) from databases belonging to Pubmed, Scopus, Medline, and Science Direct, with the publication dates restricted to between October 2009 and October 2019.

Inclusion and Exclusion Criteria

Individual studies were included if: 1) the reported intervention aimed to improve anti-hypertensive drug adherence among adult and elderly populations; 2) the

intervention was adequately described by the authors; 3) anti-hypertensive drug adherence was measured as one of the outcomes of the intervention; and 4) the study reported clearly the method of adherence measurement.

Articles were excluded if they: 1) contain unpublished studies; 2) did not provide sufficient data for measuring anti-hypertensive agents adherence; 3) was inaccessible due to the lack of full texts; 4) written in languages other than English; 5) studied adherence using qualitative methods; and 6) any comment OR editorial OR letter OR protocol paper that did not report the result of the interventions on drug adherence.

A total of 1,113 literatures were obtained from the initial search, of which 198 were retrieved from PubMed, 337 (Scopus), 284 (Medline), and 294 (Science Direct). Out of these records, 68 duplicates were eliminated. Subsequently, the titles and abstracts of the 1,045 remaining reports were reviewed in order to exclude irrelevant topics. After the exclusion of articles with irrelevant topics, only 52 articles were downloaded for further assessment (Fig. 1).

Included Studies

Fifty-two articles with findings on interventions to improve drug adherence among hypertensive patients were assessed. Out of these 52 studies, 42 of them were excluded as they failed to meet the necessary criteria. Hence, only 11 articles were used for the final review.

Data Extraction

After the initial search, two independent authors (YSQ and NHZ) assessed all the selected papers, and whatever areas of disagreement that arose were resolved through discussions. The relevant data (authors, publication year, study location, population characteristics, study method, interventions, and outcomes) from each study was then extracted and keyed into a spreadsheet. Any discrepancies found were, again, resolved through discussions, with reference to the full text of the relevant papers.

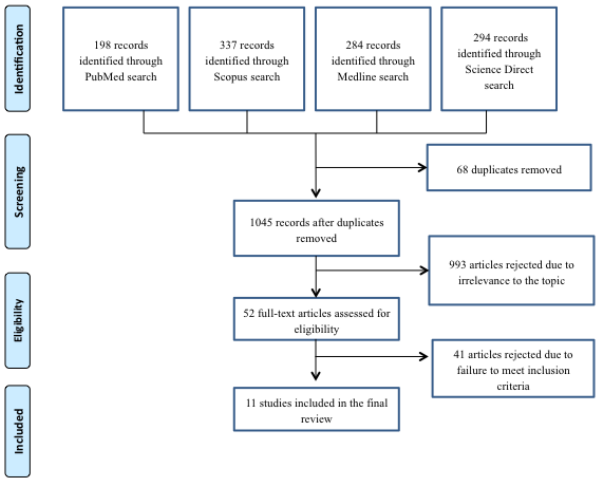

Fig 1: Flowchart of articles through the review process

RESULTS

The most common research design was randomised controlled trial (n = 7), followed by quasi-experimental studies (n = 2), community trial (n = 1), and case-control study (n = 1) (Table I).

Sample sizes ranged from 116 to 28,924. Almost half of the respondents selected for the studies were elderly people (≥ 60 years old) (5, 18-21). The highest mean age was 66.7 years old (21). A majority of the studies were conducted in the United States (n = 4) (10, 19, 22, 23) and Australasia (n = 4) (20, 21, 24, 25), followed by South America (n = 2) (5, 18) and Europe (n = 1) (26).

Interventions were delivered through reminder text messages, telephone counselling, mailed packagings, medication-time devices, provision of handouts or educational materials, and discussions or teaching sessions. But several studies assessed different combinations of interventions (5, 10, 20, 21).

The settings where interventions were delivered varied across the studies. Most of the interventions were conducted within community pharmacies (n = 7), followed by in a clinic setting (n = 4). Follow-up periods ranged between 2 months (18) and 3 years (5) from baseline. The longest, continuous study period was 3 years (5).

Two studies sought to improve drug adherence through patients' initiative (i.e. the patients themselves play active roles in their treatment outside the healthcare centres) (19, 22), six sought to improve adherence through healthcare professionals' effort (i.e. strategies provided by trained personnels in healthcare settings) (5, 18, 20, 23-25), and the remaining three involved interventions that combined both approaches (10, 21, 26).

Level of adherence was measured with self-administered adherence questionnaires (n = 5), pill counts (n = 2), medication event monitoring system (mems)(n = 1) and proportion of days covered by medication (n = 2). Only one study used four measures of adherence, namely medication possession ratio, proportion of days covered by medication, refill time, and time to medication discontinuation (5). Adherence self-reporting utilisation of anti-hypertensive agents was often based on the Morisky Medication Adherence Scale (5, 20, 21). Other validated self-administered scales were used, such as the Drug Attitude Inventory (25), Questionnaire on Adherence to Systemic Hypertension Treatment (QATSH) (18), and Tool for Adherence Behaviour Screening (21). Of these studies, only two literatures reported the validity and reliability of the self-administered questionnaires (5, 20).

All articles included in this review applied non-pharmacological interventions, which includes patient

Table I: Individual studies on interventions to improve antihypertensive drugs adherence

Studies	Location	Population Characteristics	Methods	Interventions	Classification of Intervention	Outcomes
De Souza (18)	Brazil	• Sample size, N = 116 • Male = 21.56% • Female = 78.44% • Mean age = 64.58 ± 10.87 years old	• Study design: Quasi-experimental study • Randomisation: No • Blinding: No • Follow-up: 2 months	• Intervention: Received flipchart education (contained 11 pictures and 11 script sheets). • Control: Received standard care. • Interventions were provided by nurses, physical educators, and undergraduate students in nursing and physical education.	• Patient education	• Adherence measurement: Questionnaire on Adherence to Systemic Hypertension Treatment (QATSH) score. • The average baseline QATSH score improved by 2.68 ($p < 0.001$) from 98.03 ± 7.08 at baseline to 100.71 ± 6.88 two months after the intervention.
Dupclay (19)	United States	• Sample size, N = 9266 • Cases = 4633 • Control = 4633 • Mean age = 62 years old • Male = 38% • Female = 62%	• Study design: Case-control study • Randomisation: No • Blinding: No • Follow-up: 11 months	• Case: Patients who received antihypertensive drugs with reminder packaging. • Control: Patients who received antihypertensive drugs without reminder control. • Cases were obtained from the Walmart pharmacy dataset, while controls were obtained from the SourceLx (Wolters Kluwer) database.	• Patient reminder	• Adherence measurements: Medication possession ratio, proportion of days covered, time to refill, and time to discontinuation. • The medication possession ratio among patients who received reminder packaging was 80% compared to 73% among the control group ($p < 0.001$). • The proportion of days covered among patients who received reminder packaging was 76% compared to 63% among the control group ($p < 0.001$). • Refill timing was 10 days for patients who received reminder packaging compared to 16 days for control group ($p < 0.001$). • The time to discontinuation for the patients who received reminder packaging was 196 days compared to 174 days in the control group ($p < 0.001$).
Hosseininasab (24)	Iran	• Sample size, N = 196 • Male = 39.3% • Female = 60.7% • Intervention = 98 • Control = 98 • Mean age = 59.6 years old	• Study design: Randomised controlled trial • Randomisation: Yes • Blinding: Not reported • Follow-up: 24 weeks	• Intervention group: Received wrist self-monitoring device and were educated to measure and document their BP daily during the study. • Control group: Received usual care. • Interventions were provided by a team that consisted a cardiologist, a general practitioner and a staff nurse.	• Self-management	• Adherence measurement: pill counting (no. of consumed pills divided by the no. of total prescribed pills for each antihypertensive drug). • The pill counts of patients in the intervention group was 99.0% compared to 97.8% in the control group ($p = 0.04$).
Leslie (22)	United States	• Sample size, N = 28,924 • Intervention = 24,000 • Control = 75,000 • Age = ≥18 years old	• Study design: Quasi-experimental study • Randomisation: No • Blinding: No • Follow-up: 2 years	• Intervention group: Received a 90-day refill component (prescriber-directed fax program) and a refill reminder component (reminder sent to members who are late to refill). • Control group: Received standard care	• Patient reminder	• Adherence measurement: the improvement in proportion of days covered by medications (proportion of days covered by medications post follow-up – proportion of days covered by medications pre follow-up). • For the intervention group, the proportion of days covered by medications increased by 2.6%, while the proportion of days covered by medications in control group decreased by 1.3% ($p < 0.001$).
Obreli-Neto (5)	Brazil	• Sample size, N = 194 • Intervention = 97 • Control = 97 • Mean Age = 65.3 years old	• Study design: Randomised controlled trial • Randomised: Yes • Blinding: Double-blinded (investigators and participants) • Follow-up: 36 months	• Intervention group: Received pharmacotherapy workup (consisted of assessment on non-adherence problem, discussion on role of medication to health status, suggestion to physician concerning new drug regiments, orientation to correct use of drugs, visual reminder that a medication was taken) and educational group activities (which discussed themes on adherence, dangers of self-medication, and correct storage of medicines). • Control group: Received usual care. • Interventions were offered by primary healthcare unit (medical and nurse consultancies).	• Patient education • Patient interview	• Adherence measurement: improvement in adherence according to Morisky-Green test and computerised dispensed medication history. • According to the Morisky-Green test, the intervention group showed improvement of adherence by 33% ($p < 0.001$) while that of control group was not significant ($p = 0.565$). • According to the computerized dispensed medication history, the intervention group showed improvement of adherence by 30.9% ($p < 0.001$) while no significant changes were observed in the control group (0.564).
Ogedegbe (10)	United States	• Sample size, N = 256 • Intervention = 128 • Control = 128 • Mean age = 58 ± 12 years old	• Study design: Randomised control trial • Randomisation: Yes • Blinding: Not reported • Follow-up: 12 months	• Intervention group: Received patient education (consisted of education workbook, behavioural contract and bimonthly telephone calls), enhanced with positive-affect induction (patients asked to identify small things in lives that invoke positive feelings, and they also received unexpected small gifts mailed to them to induce positive feelings), and self-affirmation induction (patient was asked to remember their core value and proud moments whenever they encounter situation that make it difficult to take medications). • Control group: Received patient education only.	• Patient education • Patient reminder • Behavioural modification	• Adherence measurement: electronic pill monitors. • Medication adherence was higher in intervention group (42%) versus the control group (36%), where $p = 0.049$.

(Continued.....)

Table I: Individual studies on interventions to improve antihypertensive drugs adherence (continued)

Studies	Location	Population Characteristics	Methods	Interventions	Classification of Intervention	Outcomes
Oser (23)	United States	• Sample size, N = 734 • Age = 18 years old and above	• Study design: Community trial • Randomisation: No • Blinding: No • Follow-up: 3 years	• Intervention group: Received community brief consultation on medication management, change in lifestyle and BP control, as well as patient-education material. • Control group: Not included in the study. • Interventions were given by community pharmacists.	• Patient education	• Adherence measurement: proportion of days covered by prescription claims as 80% or greater. • The percentage of patients who adhered to medication improved from pre-intervention to post-intervention (from 73% to 89%).
Pladevall (26)	Spain	• Sample size, N = 877 patient, 79 physician • Age = 50 years old and above	• Study design: Multicenter cluster-randomised trial • Randomisation: Yes • Blinding: Single-blinded (investigators) • Follow-up: 39 months	• Intervention group: Received counting pills during physician visits, designated family member to support adherence behaviours and an information sheet. • Control group: Received standard care. • Physician gave the intervention during patient hospital visit.	• Behavioural modification	• Adherence measurement: medication event monitoring system. • Intervention patients were more likely to be adherent compared to control group (92.2% vs. 89.0%, respectively; p = 0.002) and were more likely to be at least 80% adherent (OR 1.91; 95% CI 1.19, 3.05).
Saleem (25)	Pakistan	• Sample size, N = 385 • Male = 265 • Female = 120 • Control = 192 • Intervention = 193 • Mean age = 39.0 ± 6.5 years old	• Study design: Randomised control trial • Randomisation: Yes • Blinding: Not reported • Follow-up: 9 months	• Intervention group: Received health education pertaining on medication counselling by pharmacist. • Control group: Received standard care • Intervention was given by trained pharmacists.	• Patient education	• Adherence measurement: Drug Attitude Inventory (DAI-10) • The DAI-10 score of the patients in intervention group was (3.2 ± 0.9) was significantly higher than those of the control group (-1.9 ± 2.1), where p < 0.001.
Steward (21)	Australia	• Sample size, N = 395 • Male = 202 • Female = 193 • Intervention = 207 • Control = 188 • Mean age = 66.7	• Study design: Cluster-randomised trial • Randomisation: Yes • Blinding: No • Follow-up: 6 months	• Intervention group: Received package comprising BP monitor, training on BP self-monitoring, motivational interviewing, medication use review, prescription-refill reminders. • Control group: Received standard care. • Interventions were provided by community pharmacists.	• Patient education • Patient interviews • Patient reminders • Self-management • Behavioural modification	• Adherence measurement: Morisky scale and the Tool for Adherence Behaviour Screening (TABS). • The proportions adherent (Morisky score) increased in both groups, intervention group from 60% to 73.5% (P = 0.003) and control from 57.2% to 63.6% (P = 0.1). • The proportions of participants adherent based on the TABS differential score remained relatively consistent (<5% change) from baseline to 6 months within both groups.
Wong (20)	Hong Kong	• Sample size, N = 274 • Male = 86 • Female = 145 • Intervention = 113 • Control = 161 • Mean age = 62.4 ± 9.35 years old	• Study design: Randomised controlled trial • Randomisation: Yes • Blinding: No • Follow-up: 6 months	• Intervention group: Received community-based medication counseling service and free-of-charge telephone consultations. • Control group: Received standard care • Interventions were provided by community pharmacists.	• Patient education • Patient interview	• Adherence measurement: increase in Morisky Medication Adherence Scale 8-item (MMAS 8) scores. • The increase of the MMAS-8 score was greater in the intervention group (from 5.07 ± 1.21 to 6.63 ± 1.31) than the control group (from 5.12 ± 1.01 to 6.49 ± 1.23). However, there was no significant difference between the MMAS-8 scores at the end of 6 months follow-up between the two groups (p = 0.199).

education (e.g. counselling, discussion and providing information materials), consultation, motivation techniques (e.g. follow-up interviews and reminders) and vital-sign monitoring (e.g. self blood pressure measurement).

Only one study (18) utilised a theoretical framework to guide the adherence-improving intervention, in which the "Teaching patients with low literacy skills" was used to develop an educational flipchart to enhance medication adherence. A majority of the articles reported statistically significant improvement in drug adherence, with one study being the exception (20). Most of the interventions were based on one or more than one of the following strategies: patient education (n = 7), patient interviews (n = 3), patient reminders (n = 4), self-management (n = 2), and behavioural modifications (n = 3).

Out of the seven patients' education-based strategies, six reported significant improvement in anti-hypertensive medication adherence (5, 10, 18, 21, 23, 25). Two out of three studies that were based on patient interviews reported significant results on medication adherence (20, 21). Improvements in drug adherence were also seen in strategies that were based on or included patient reminders (10, 19, 21, 22). All studies involving self-management (21, 24) and behavioural modifications (10, 21, 26) showed significant improvement in anti-hypertensive medication adherence.

DISCUSSION

The current review identified a wide range of potentially effective interventions. We noted that interventions that are based on patient education, patient interviews, patient reminders, self-management and behavioural modifications are valuable at improving anti-hypertensive therapy adherence.

Patient education has been widely used to enforce medication adherence (27-29). To our knowledge, patient education is effective in improving adherence in anti-hypertensive drugs as it allows healthcare providers to educate patients by adequately explaining the method of taking medication, by discussing any difficulties

while taking medicines, exploring patients' knowledge and beliefs about their treatments (30). It is crucial to inform patients regarding their disease and treatment as an effort to adopt the principles of patient-centered care and sharing of decision-making.

Patient interviews comprise of collaborative method of communication and information exchange between healthcare providers and patients, which is used to assess a patient's readiness to act on a specific behaviour. It respects the patient's autonomy and facilitate patient confidence and decision-making (31). Effective patient interviews by healthcare workers ensure knowledge about the benefits and risks of the treatment being communicated to allow patients to make informed decisions (32). This is because patients and clinicians often have different perceptions of risk (33). Nevertheless, our review shows inconsistent results in the effectiveness of patient interviews in improving anti-hypertensive drug adherence. This might be due to insufficient follow-up periods, as seen in one of the studies (20). Hence, it could be argued that the effects of the intervention could not be evident on a short-term.

Patient reminder also helps to improve adherence via reminder text messages, phone calls, video calls, reminder packaging, and interactive voice response (IVR) systems (34). Often, hypertensive patients, especially the elderly ones, do not adhere to their medication due to their forgetfulness to refill their medication (i.e. non-intentional non-adherence). Hence, providing patient reminder can reverse this phenomenon. Various studies have also suggested that patient reminders are helpful at improving drug adherence (35, 36).

In this review, we discovered that self-management is effective in increasing drug adherence among hypertensive patients. Self-management refers to one's ability to manage his or her own symptoms and lifestyle changes with the assistance of family, community, and healthcare professionals (37). It incorporates the concepts of self-care and self-monitoring, which is aimed at empowering the patients to play a more active role in the treatment of their diseases (38). In addition, providing knowledge and basic skills to hypertensive patients may minimise their dependence on healthcare services and, subsequently, the associated medical costs (39, 40). Not limited to the management of hypertension, self-management inter¬ventions have also resulted in higher medication adherence rate for other chronic diseases, such as diabetes mellitus and osteoarthritis (41).

Behavioural modifications are meant to modify patients' behaviours toward treatment. These usually include cognitive behavioural therapy, motivational components and therapies focussing on dysfunctional behaviours, cognitions and emo¬tions to promote positive changes and healthy lifestyles (42). In this review, behavioural interventions were found to be effective at improving anti-hypertensive drug adherence. For instance, the behavioural component as seen in Pladevall et al (26) included a pill-counting session done in front of the patients. This resulted in better adherence in the interventional group as compared to the control group, which only received routine clinical practice. This can be explained by the fact that the pill-counting component could generate the "Hawthorne effect" (43) (sometimes referred to as the "observer effect"). As such, the participants in the interventional group modified their behaviours in response to their awareness that they were being observed by their healthcare providers.

Strengths

While other reviews examined the adherence-improving interventions across multiple morbidities (44-46), the current review focuses specifically on hypertension therapy. Such specificity is a major strength as the effects of intervention cannot be generalised across various therapeutic areas. Hence, limiting our scope to interventions that improve anti-hypertensive drugs adherence provides an important focus, given the heavy burden of having hypertension.

Not only were randomised controlled trials included, but other study designs such as case-control and cohort studies were reviewed. Using a more heterogeneous set of study designs would lead to more generalisable findings. Thirdly, our study focused on newer studies, those published after 2008; thus it is more relevant to the current situation.

Limitations

Several limitations were noted in this review. Firstly, the development of a majority of the adherence-improving interventions were not based on conceptual frameworks of the determinants of drug adherence. Hence, this limits the reproducibility of interventions that showed benefit. Since determinants of drug adherence have been described extensively in various studies (47, 48), we would expect the developers of adherence-improving interventions to design their intervention based on these frameworks so as to maximise the chances of establishing efficacy in their interventions. Unfortunately, such information was not provided in all of the studies (49).

Furthermore, the measurement of medication adherence was not consistent across various studies. The measurement varied from self-reported questionnaire to a more quantitative, continuous measures, such as medication refill time and medication possession ratio. The difference between the various components of drug adherence was not adequately accounted for (49). Among the self-reported questionnaires, many were not validated; hence, their reliability and validity are a concern.

Furthermore, some studies examined a combination of

interventions (i.e. utilised more than one interventional strategies to improve adherence), causing difficulties in interpreting whether the improvement of adherence arosed as a result of a single intervention or due to the combined inputs of the multiple strategies used. This is an important aspect to be considered as some researchers argued that interventions for medication adherence in hypertension tend to be multi-factorial, and there is often no single effective intervention (50).

Lastly, it is well known that the effectiveness of interventions in improving drug adherence may vary according to age, gender, socioeconomic status, income and educational level. Regrettably, these factors were not considered when analysing the studies selected for this review.

CONCLUSION

Interventions that are based on or include patient education, patient interviews, patient reminders, self-management and behavioural modifications can improve patients' adherence to anti-hypertensive therapy. Most successful interventions can be seen in patient reminders, self-management and behavioural modifications.

In the absence of a recent, well-conducted meta-analysis, this review can serve as a summary of the effectiveness of non-pharmacological interventions to improve adherence in hypertension therapy, as well as a guide to draw up health-promotion programmes and health-related policies.

We recommend future studies to use established theoretical frameworks to design adherence-improving interventions, and to measure adherence level and clinical outcomes by using validated tools and evidence-based guidelines.

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