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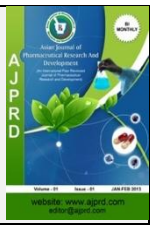

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Review Article

A Systematic Review of Chronic Disease and Medication Adherences with Special Focus on Diabetes Mellitus and Hypertension.

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A B S T R A C T

Adherence to chronic disease management is critical to achieving improved health outcomes, quality of life, and cost-effective health care. As the burden of chronic diseases continues to grow globally, so does the impact of non-adherence. Mobile technologies are increasingly being used in health care and public health practice (mHealth) for patient communication, monitoring, and education, and to facilitate adherence to chronic diseases management. Tight glycaemic control is essential, and good adherence is associated with a lower risk of all-cause mortality and hospitalization in people with T2D. A significant number of people with T2D do not take medication as prescribed and therefore have poor outcomes. The key factors for not achieving targets include therapeutic inertia and adherence. Reasons for poor adherence include perception of treatment, complexity of treatment and adverse effects. Nonadherence is a common reason for treatment failure and treatment resistance. No matter how it is defined, it is a major issue in the management of chronic illnesses. There are numerous methods to assess adherence, each with its own strengths and weaknesses; however, no single method is considered the best. Nonadherence is common in patients with hypertension, and it is present in a large proportion of patients with uncontrolled blood pressure taking three or more antihypertensive agents. Availability of procedure-based treatment options for these patients has shed further light on this important issue with development of new methods to assess adherence. There is potential for mHealth tools to better facilitate adherence to chronic disease management, but the evidence supporting its current effectiveness is mixed. Further research should focus on understanding and improving how mHealth tools can overcome specific barriers to adherence.

KEYWORDS: Patient Adherence, Chronic Disease, Diabetes Mellitus, Compliance, Treatment-Resistant Hypertension.

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INTRODUCTION

Chronic diseases are the most common causes of death and disability worldwide. Chronic disease management often requires a long-term care plan. Adherence to chronic disease management is critical to achieving improved health outcomes, quality of life, and cost-effective health care. A World Health Organization review of adherence behaviors noted that, "increasing adherence may have a greater effect on health than improvements in specific medical therapy". With an average adherence rate of only 50% among patients with chronic diseases, non-adherence is a serious challenge to chronic disease management [1]. The extent of non-adherence is even higher in developing countries. The long-term nature and frequent need for continuous monitoring in chronic disease management gave rise to early developments in telehealth and telemonitoring. These innovations, which seek to improve chronic disease management and prevent death and disability, are improved by ongoing technological advancements.

The treatment of most chronic illnesses is often characterized by long-term pharmacological interventions, which have been shown to be effective through a series of rigorous clinical trials. These pharmacological interventions are only effective if patients follow medical advice on the prescribed treatment

regimen. Suboptimal or nonadherence is common; on average, around 50% of all prescribed medications for chronic conditions are not taken as prescribed [2]. Non adherences have serious health and socioeconomic implications. Adherence to medications is associated with improved health benefits and patient outcomes. A meta-analysis has shown that adherence to prescribed beneficial medication, including a placebo, is associated with significantly lower mortality compared with suboptimal adherence [3].

There is no consensus on the threshold to define adherence and nonadherence. Traditionally, a cut-off value of 80% has been used to dichotomise adherence; healthcare usage and costs in many chronic conditions including hypertension, diabetes, hyperlipidaemia, and schizophrenia are noted to be reduced in patients where medication adherence exceeds 80%. In hypertension consumption, >80% of the prescribed medications have been shown to maintain blood pressure control.

Diabetes is a chronic disease affecting 463 million people worldwide in 2018 and has been reported to be in the top 10 causes of death globally. In the financial year 2018/2019 there were 55 million items prescribed for diabetes, with a total net cost of over £1 billion. Type 2 diabetes (T2D) is a progressive disease with loss of beta-cell function and insulin resistance leading to a failure of glycaemic control. In the UK the National Institute for Health and Care Excellence (NICE) advises glycated haemoglobin (HbA1c) targets of <6.5% (<47.5 mmol/mol) in newly diagnosed patients and <7.5% (<58 mmol/mol) in patients on two or more therapies. NICE suggests reaching these targets by use of glucose-lowering drugs (GLDs), management of other risk factors such as blood pressure and lipids and lifestyle changes. However, they also recommend relaxing target HbA1c levels in certain individuals, such as those who are frail, those who are at risk of hypoglycaemic events which could lead to high-risk consequences and those unlikely to achieve longer term risk reduction benefits [4].

The impact of these mHealth tools on adherence to treatment regimens may be overlooked, as mHealth promoters are eager to demonstrate their effect on clinical outcomes. Adherence to treatment, and specifically adherence to treatment of chronic diseases, is a critical link that connects the promise of mHealth to the ultimate goal of improved clinical outcomes. This enables us to consider mHealth tools at all stages of development and gauge the effectiveness of mHealth interventions across a range of

Technologies and chronic diseases, many of which have overlapping treatment regimens and require similar adherence behaviors. This review aims to evaluate the effectiveness of mHealth in supporting adherence of patients to chronic disease

Management which we call “mAdherence” and the usability, feasibility, and acceptability of mAdherence tools and platforms for chronic disease management [5].

The chronic diseases included are diabetes mellitus (DM), cardiovascular diseases (CVDs), and chronic lung diseases (CLDs). CVDs include hypertension (HTN), coronary artery disease, and congestive heart failure. CLDs include asthma and chronic obstructive pulmonary disease (COPD). These chronic diseases were chosen based on their high global burden. Our definition of mHealth was adopted from the Global Observatory for eHealth definition: “medical and public health practice supported by mobile devices”. We use the term “mAdherence” to refer to any use of mHealth tools by patients and health care providers to improve adherence to chronic disease management. Given the comprehensive nature of chronic disease management, this review goes beyond defining adherence as compliance with a treatment regimen and includes a wide range of interventions, such as medication reminders, symptom monitoring, educational tools, and facilitated patient-provider communication [6, 7].

Definitions of adherence, concordance, compliance and persistence

A number of terms are often used interchangeably to describe a patient’s medication-taking behaviour including adherence, concordance, compliance and persistence. However, use of the term ‘compliance’ is declining as it suggests lack of patient involvement.

Adherence- The extent to which a person's behaviour (taking medication, following a diet, and/or executing lifestyle changes) corresponds with agreed recommendations from a healthcare provider.

Concordance- Joint agreement between the prescriber and the patient regarding therapeutic decisions, including using prescribed medication in a given way.

Compliance- The extent to which the patient’s behaviour matches the prescriber’s recommendations.

Persistence- The duration of medication use by the patient.

Adherence to T2D management [8]

The World Health Organization stated that, in developed countries, adherence to medication in chronic conditions is only around 50%. Decreased levels of adherence are normally seen in patients with chronic conditions compared with those with acute conditions, and this leads to poorer health outcomes and also has a substantial impact on healthcare costs. The management of T2D firstly comprises lifestyle changes such as a decrease in calorie intake, increase in physical activity and weight loss followed by use of GLDs. Monotherapy with metformin is indicated for most patients, with the addition of further GLDs if the individualised glycaemic treatment goal is not achieved within 3 months of metformin plus lifestyle interventions. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Consensus Report recognises the significance of diet and exercise throughout all stages of T2D. There is strong evidence for the advantages of exercise; however, Praet and van Loon15 found that adherence to long-term exercise programmes still varies between 10% and 80%. They suggest adherence may improve if exercise interventions include motivational strategies as well as taking account of time constraints and providing patients with feedback on physical activity levels [9, 10].

The prevalence of non-adherence to GLDs differs greatly in studies. Cramer carried out a retrospective analysis, which showed adherence to oral hypoglycaemic agents (OHAs) varied between 36% and 93% in patients who continued on treatment for 6–24 months. Rozenfeld *et al* found an inverse relationship between taking a prescribed OHA and the HbA1c

level. This study also showed that each 10% increase in adherence to OHA was correlated with a decrease of 0.1% in HbA1c. They also concluded that, of 2,741 patients with T2D who had recently commenced OHA treatment, general adherence was 81% and 65% had good adherence (defined as ≥80% of medication). In another study of electronic records for a range of OHAs in 8,191 patients, 53% of whom had an HbA1c of ≥7% (53 mmol/mol); only 39.6% had persisted with treatment after 24 months. An additional study assessing self-reported compliance of 11,896 patients taking one or two OHAs observed that only 46% had ideal compliance. [11]

People with T2D commonly have multimorbidities. A number of individual studies have shown adherence to be poorer amongst patients with multimorbidities and those on polypharmacy or twice-daily therapies compared with monotherapies and once-daily regimens, respectively. Cramer's retrospective analysis also showed adherence to insulin treatment among patients with T2D was 62–64%.7 a study of 1,099 people reported that the average adherence to insulin treatment was 71% and showed that good adherence was associated with better glycaemic control. Another study found that, from a sample of 144 adults, 59% forgot to take their insulin and 46% reported non-adherence. The French population-based ENTRED study of 3,637 patients with T2D using both OHAs and insulin showed that 39% of patients reported good medication adherence, 49% medium adherence and 12% poor adherence. A systematic review of adherence to pen device insulin therapy found that adherence to vials and syringes varied from 13% to 90% and from 22% to 92%, respectively. [12]

Table 1 Common reasons for poor adherence to glucose-lowering drugs

Perception of treatm	Misunderstanding treatment ben Fear of treatment side effects
Complexity of treatn	Polypharmacy Dosing frequency
Adverse effects	Hypoglycaemia Gastrointestinal side effects Weight gain
Insulin-specific	Inability to regulate dosing Time consumption Impact on social life Pain at injection site Trypanophobia

Factors contributing to poor adherence to T2D treatment

Despite evidence and recommendations, guidelines are not translated into practice. One study showed that, in the UK, one-third of patients with T2D fail to achieve HbA1c levels ≤7.5% (58 mmol/mol). There are a number of possible explanations as to why patients do not always take their medication as prescribed, and often more than one factor contributes to lack of adherence. Some of these reasons cannot be changed, while others are often modifiable. Common reasons for poor adherence to GLDs are shown in Table 1.

Patient adherence to treatment is more likely to improve if they are able to understand that their regimen is having a positive and relative immediate influence on their outcome. A systematic review of a wide range of chronic diseases found that medication adherence is correlated with perceived need and that patients are more likely to be adherent, the more they believe the prescribed medication is actually required. Another study showed that, in patients with T2D, 32.8% felt medication would lead to unwanted side effects and 13.9% felt it may cause weight gain, attributing to decreased adherence. In patients with newly prescribed insulin, 35% were found to be non-adherent with their regime.Reasons for this included feeling that insulin would lead to harm, concerns regarding their inability to regulate the dosing of insulin, the impact on their social life and work, the pain of the injection, side effects and that the advantages and disadvantages of insulin had not been sufficiently clarified. In one study of people with T2D and type 1 diabetes, reasons for non-adherence to insulin included reactions at injection sites, fear of hypoglycaemia, time consumption, interference with physical activity and lack of instructions. A qualitative meta-synthesis of the different perspectives of medication non-adherence between patients and healthcare professionals found that medication administration is a significant barrier to adherence. The authors stated that patients predominantly had trypanophobia (fear of needles), fear of the effects of inaccurately administering insulin and fear of the pain of injection or blood testing. [13, 14]

Consequences of poor adherence

Poor adherence leads to inadequate glycaemic control, which in turn increases the risk of diabetic complications and mortality. In a retrospective cohort study of 11,532 patients, Ho *et al* showed that medication non-adherence to OHAs, antihypertensives and statins was associated with higher HbA1c, blood pressure and low- density lipoprotein cholesterol levels. In multivariable analysis, med- ication non-adherence was associated with an increased risk of all-cause hospitalisation (OR 1.58, 95% CI 1.38 to 1.81; p<0.001) and higher all-cause mortality (OR 1.81, 95% CI 1.46 to 2.33).

One recent meta-analysis explored the association between adherence to T2D medication and the risk of cardiovascular disease, all-cause mortality and hospitalisation.6 Eight observational studies were included (n=318,125 patients). The mean rate of poor adher- ence was 37.8%. The study showed that good medication adher- ence (>80%) compared with poor adherence was associated with a 38% reduction in all-cause mortality (RR 0.72, 95% CI 0.62 to 0.82) and a 10% reduction in hospitalisation (RR 0.90, 95% CI 0.87 to 0.94) (15).

Curtis *et al* assessed the association of adherence to GLDs and the resulting outcomes in patients with T2D. They found that acute care costs and outpatient costs were significantly lower for adher- ENT patients. Adherence was also associated with significant im- provements in acute care outcomes as measured by the probability of a hospitalisation (17.65% vs 22.71%; p<0.0001), the probability of an emergency department visit (38.47% vs 45.61%; p<0.0001), the number of hospitalisations (0.27 vs 0.40; p<0.0001), the num- ber of emergency department visits (0.83 vs 1.23; p<0.0001) and the length of stay in hospital (1.25 vs 2.16 days; p<0.0001).

Interventions to improve adherence [16]

The World Health Organization has stated that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments". Overall, there are a number of factors that are key to medication adherence. There is evidence to suggest that education and monitoring is important in medication adherence, with pharmacist-based interactions being successful in improving glycaemic control. Monitoring via messaging and digital interventions including mobile applications have also proved effective. Currently these are costly; however, if they are able to improve long-term outcomes, they may prove to be cost effective for patients with difficulties managing their condition. Psychological support for patients may also be necessary to reduce fears and anxiety in those who are not adhering to management plans or for those who require additional support with their condition.

Medication adherence in clinical trials [17]

Achievement of optimal adherence in a randomised controlled trial is important. Level of adherence influences the magnitude of observed treatment effect; greater adherence increases the effect size, and poor adherence may fail to distinguish the two treatments. Furthermore, nonadherence to a treatment with worse adverse effects profile may falsely prove to be of similar safety when compared to treatment with a favourable adverse effects profile. Adherence is also an important indicator of how readily a treatment is accepted by patients. Despite its importance, adherence is underreported in clinical trials, with only 33–46% of published randomised controlled trials (RCTs) reporting adherence rates. On the other hand, reported rates of adherence are often remarkably high in these RCTs, resulting in potential overestimation of adherence due to underreporting. This may be related to the extra attention received by study patients, patient selection, and the observer effect altering patient behaviour.

Medication nonadherence and apparent treatment-resistant hypertension

In medicine, the term 'resistant' implies a condition that fails to respond to usual medical therapy. In hypertension, there are eight different classes of antihypertensive medications available namely, thiazide/thiazide-like diuretics, renin angiotensin system inhibitors, calcium channel antagonists, alpha-adrenergic receptor blockers, beta-adrenergic receptor blockers, central vasodilators, aldosterone receptor antagonists, and miscellaneous. The recommended three first-line antihypertensive agents include calcium channel antagonists, renin angiotensin system inhibitors, and thiazide diuretics. There is emerging evidence that the preferred fourth-line antihypertensive agents are aldosterone receptor antagonists when compared with beta-adrenergic receptor blockers and alpha-adrenergic receptor blockers [18].

Patients need to sufficiently adhere to the prescribed therapy for it to be considered to have failed. Therefore, assessment of adherence is a crucial aspect of management of patients with chronic conditions such as hypertension. Furthermore, increasing the number of antihypertensive medications may lead to increased risk of adverse effects and possible drug interactions. Medication adverse effects negatively impact patients' adherence and uncertainty on the part of the physician as to whether or not to intensify treatment. This 'clinical inertia' is detrimental to patients with true TRH given the high risks of morbidity and mortality associated with uncontrolled blood pressure. Assessment of adherence may help to overcome this inertia. Studies reporting rates of nonadherence in patients with TRH and the methods used to assess adherence.

Observational cohort or cross-sectional reports from specialist hypertension centres or general hospitals form the mainstay of studies describing the prevalence of nonadherence amongst TRH patients. Ceral et al. used liquid chromatography with mass spectrometry (LC–MS) to detect antihypertensive drugs in sera of 84 patients with apparent TRH.38 All of the evaluated antihypertensive drugs were present in (34.5%) patients, no drugs were detected in the same number, and the remaining (31%) had some of their antihypertensive drugs in their sera. Jung et al. concluded that low adherence was the commonest cause of poor blood pressure control amongst 375 patients referred with uncontrolled blood pressure. After excluding white-coat effect, secondary causes of hypertension, and optimisation of antihypertensive therapy, 76 patients remained in whom LC–MS was carried out on urine samples. They found that (47%) were adherent and (53%) were nonadherent, of which 12 (30%) had complete nonadherence. [19, 20]

Direct observation has often been used as a surrogate marker for adherence. A sustained reduction in blood pressure following observed ingestion of tablets indicates prior nonadherence although any blood pressure reduction observed could be attributable to blood pressure variability, white-coat effect, or regression of blood pressure to the mean. Grassi et al. showed that 32% of patients presenting to emergency department with a systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg had a drop of least a 20 mmHg in basal systolic blood pressure and/ or a 10 mmHg reduction in basal diastolic blood pressure after a 30-minute-period of rest where patients were seated in a comfortable and quiet room without talking or active listening. Some of these limitations can be minimised by using standardised and guideline-recommended blood pressure measurements and ABPM prior to commencing the directly observed therapy to exclude white-coat effect and reduce visit-to-visit blood pressure variability and regression to the mean.

Prevalence of treatment-resistant Hypertension [21, 22]

TRH has been defined as uncontrolled blood pressure where at least a diuretic and two other different classes of antihypertensive medications, taken at maximum tolerated doses, are unsuccessful in controlling clinic blood pressure to a target less than 140 mmHg systolic and or 90 mmHg diastolic. The publication of SPRINT trial has challenged the well-established target blood pressures for diagnosis and treatment of hypertension. In light of its findings, the American College of Cardiology/American Heart Association has updated its hypertension guidelines with a radical change in the blood pressure targets used for diagnosis and treatment of hypertension; lowering the level of blood pressure to 130/80 mmHg also affects the definition of treatment-resistant

hypertension. The American definition has retained the second element of the definition, which includes patients with controlled blood pressure taking four or more antihypertensive medications.

Management of nonadherence to Antihypertensive medication [23, 24]

There is no proven intervention that has been shown to significantly improve adherence. It is important to have a careful consultation with the patient to identify and address the potential causes of suboptimal adherence. The risks and consequences of nonadherence and the resultant uncontrolled blood pressure should be explained using simple language and visual aids. Patients should be asked how they are managing their drugs in regards to dosing frequency, pill burden, and side effects. It may be necessary to change the medication regimen to fewer daily doses and even monotherapy, but frequent changes in medication regimen should be avoided. It may also be necessary to negotiate a reduction in the number of drugs aiming for a higher and more realistic blood pressure target. The importance and effectiveness of lifestyle modifications in lowering blood pressure should be emphasized. Up to 75% of patients with hypertension require more than one antihypertensive agent to achieve blood pressure control. Single-pill fixed-dose combinations have been recommended, for patients requiring more than one antihypertensive agent, to help improve adherence and consequently blood pressure control. A meta-analysis has shown that fixed-drug combinations improve adherence and persistence in hypertensive patients with nonsignificant beneficial trends in blood pressure and adverse effects compared with free drug combinations. A cohort study of 13,350 patients comparing fixed-drug with free-drug combinations also showed that the fixed-drug combination group had superior adherence rates of 70% compared to 42%, and a significantly lower risk of composite clinical outcomes including death or hospitalisation for acute myocardial infarction, heart failure, or stroke. More recently, the use of low-dose fixed triple drug combination antihypertensive pills has been shown to improve blood pressure control compared to usual care in patients with mild to moderate hypertension. This low-dose fixed-drug combination (FDC) treatment is being suggested as the initial therapy compared to the currently accepted practice of monotherapy. Apart from reducing pill burden, it may be associated with reduced adverse effects and consequently increased acceptability by the patients due to the lower doses of individual agents used. Furthermore, targeting of different pathways by different antihypertensive agents may improve efficacy. A pilot study has shown that a single-pill fixed triple drug combination achieved a mean reduction of 22.8/13.6 mmHg in clinic blood pressure and 9.3 mmHg reduction in 24-hour mean arterial pressure after 18 weeks in 13 patients with TRH. Further larger studies are warranted in patients with TRH to assess the effectiveness of FDC and their impact on patients' medication-taking behaviour. [30, 31]

Self-monitoring of blood pressure, where patients monitor their own blood pressure at home, has been used as an intervention to show improvements in blood pressure and adherence. Patients self-monitoring their blood pressure at home consulted less often with their primary care physician who helps to bring the costs of self-monitoring on par with usual care. Self-monitoring on its own, however, may not be enough to improve blood pressure control. Complex interventions, including systematic medication titration by doctors, pharmacists, or patients; education; or lifestyle counselling, in conjunction with self-monitoring lead to clinically significant blood pressure reduction, which persists for at least 12 months. A recent randomised controlled trial has shown that self-monitoring, with or without telemonitoring, when used by primary care physicians to titrate antihypertensive treatment in individuals with uncontrolled hypertension, significantly lowers blood pressure compared with titration guided by clinic readings. However, the efficacy of self-monitoring of blood pressure in lowering blood pressure in individuals with TRH has not yet been demonstrated. Motivational interviewing has a robust evidence base to increase motivation and facilitate change across a range of health-related behaviours. A meta-analysis of hypertension studies, involving seven underpowered randomised controlled trials, shows that motivational interviewing has a significant effect on systolic blood pressure both after intervention and at follow-up. However, most studies had small sample sizes limiting statistical power, and motivational interviewing was often used as one component of multiple interventions. Although there is lack of robust evidence for its efficacy in apparent TRH, it is a low-cost, easy-to-administer intervention that may be tried in this situation [25, 26].

A recent study suggests that repeated biochemical urine and serum analyses for antihypertensive agents may be used as a therapeutic approach to improve blood pressure control in nonadherent hypertensive patients. In this study, from two hypertension centres in Europe (UK and Czech Republic), discussing results of urine (UK) and serum (Czech Republic), antihypertensive assays with nonadherent patients resulted in improvements in adherence and blood pressure control – an average reduction of 19.5/7.5 mmHg in one centre and 32.6/17.4 in the other. However, this was a retrospective study with unclear follow-up period, and, by the authors' own admission, white-coat adherence effect could not be ruled out. [27, 28]

Finally, a recent randomised controlled trial tested if a smartphone app to increase patient engagement would improve medication adherence and blood pressure control in 411 patients with uncontrolled hypertension. There was a small improvement in self-reported adherence in the intervention group, but there was no difference in the blood pressure control between the intervention and control groups. [29]

CONCLUSION

This review found that the usability, feasibility, and acceptability of mHealth tools for chronic disease management adherence were generally high among both patients and providers. Innovative mAherence tools could unintentionally increase health disparities due to unequal access to technology. Vulnerable, hard-to-reach, or otherwise high-risk patient populations were the target audiences for several mAdherence interventions. There is a clear recognition that mHealth tools have the potential to impact patients who are less inclined to engage traditional health services.

MAdherence offers a way to address barriers to care and to reduce health disparities. There is also some recognition that unequal access to, use of, and knowledge of information and communication technology can influence the uptake and use of mHealth tools. These inequalities and the needs of the target user group should be taken into consideration early in the design and development of the mAdherence tool. However, none of the studies included in this review addressed systematic differences in usability between diverse patient groups. Future research can be designed to better understand these differences and to encourage the development of mAdherence tools that address the needs of diverse patient groups.

T2D is a progressive disease and, along with diet and exercise, pharmacological therapies are needed to sustain glycaemic control and reduce complications. However, non-adherence is common and can lead to adverse outcomes. There are a number of factors that contribute to lack of adherence such as misperception of treatment benefits, complexity of treatment and adverse effects. It is therefore evident that healthcare professionals may need to focus on improvement of adherence prior to considering additional therapies, particularly in the current climate of cost-effective prescribing. A large proportion of patients with apparent treatment-resistant hypertension are nonadherent to prescribed treatment. Availability of urine assays for antihypertensive drugs and metabolites in the recent years has made it easier to identify nonadherence, which has significant detrimental consequences.

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