**ADHERENCE THERAPY FOR HYPERTENSION**

**By**

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**ABSTRACT**

**Background:** Poor adherence to drug regimens is a major cause of uncontrolled blood pressure (BP) in people with hypertension.

**Aim:** To evaluate the efficacy of adherence therapy (AT) compared to treatment as usual (TAU) in reducing BP in non-adherent hypertensive patients. Additionally, a qualitative study was conducted to understand and explore patient's experience of AT.

**Design:** A single blind parallel group RCT was conducted between August 2009 and January 2010, in outpatient clinics in Jordan. Patients were assessed at baseline and at 11 weeks by blinded assessors. At 11 weeks semi-structured qualitative interviews were also performed.

**Method:** One hundred and thirty six adult patients with a mean baseline BP of 165 mm Hg (sd 10) over 102 mm Hg (sd 7) were randomly assigned to receive either TAU or AT which consisted of seven weekly 20 minutes sessions. The primary outcome was systolic blood pressure (SBP). Semi-structured interviews were conducted with 10 patients who had received AT.

**Results:** AT lowered SBP by-23 mm Hg (95% CI: -26, -20) and diastolic BP (DBP) by -15 mm Hg (95% CI: -18, -13), improved adherence by 37%, and improved their beliefs towards taking medication at 11 weeks compared to TAU. The thematic analysis of the interview transcripts identified five major themes of patient's experience of AT; modifying attitudes and beliefs, positive impact on self efficacy, motivational therapist, positive impact on wellbeing, and a well designed intervention.

**Conclusions:** Adherence therapy changes patients' negative beliefs and attitude toward antihypertensive drugs and this increases their adherence to medication regimes which then leads to a clinically important reduction in BP. This reduction could be predicted to lead to reduced incidence of the adverse consequence of hypertension such as strokes, myocardial infarction, or death.

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**ABBREVIATIONS**

**AA:** Ahmed Alnwafelh

**AC:** Allan Clark

**ACE:** Angiotensin Converting Enzyme

**ANCOVA:** Analysis of Covariance

**AT1:** Angiotensin 1

**BMQ:** Beliefs about Medication Questionnaire

**BP:** Blood Pressure

**CDC:** Centres of Diseases Control and prevention

**CENTRAL:** Cochrane Central Register of Controlled Trials

**CHF:** Congestive Heart Failure

**COMPASS:** Compliance Praxis Survey

**CONSORT:**CONsolidated Standards of Reporting Trials

**COREQ:** Consolidated Criteria for Reporting Qualitative research

**CRTU:** Clinical Research Trials Unit

**CVA:** Cerebrovascular Accident

**CVD:** Cardiovascular Diseases

**DBP:** Diastolic Blood Pressure

**DM:** Deema Mahasneh

**FA:** Fadwa Alhalaiqa

**G-B:** General Benefit

**GDP:** Gross Domestic Product

**G-H:** General Harm

**G-O:** General Overuse

**G-S:** General Sensitivity

**HCPs:** Health Care Professionals

**ICH:** International Conference on Harmonisation

**ID:** Identification

**ISPOR:** The International Society of Pharmacoeconomics and Outcomes Research

**ISRCTN:** International Standard Randomised Trial Number

**JD:** Jordanian Dinar

**KD:** Katherine Deane

**LOCF:** Last Observation Carried Forward

**MEMS:** Medication Event Monitoring System

**MI:** Motivational Interviewing

**MMAS:** Morisky Medication Adherence Scale

**mm Hg:** millimetre of mercury

**MOH:** Ministry Of Health

**MRC:** Medical research council

**N:** number

**NCD:** Non-communicable Diseases

**NESW:** Normative behaviour, Effective structural circumstances, Social support and Wisdom/knowledge

**NICE:** National Institute for health and Clinical Excellence

**NRR:** National Research Register

**ns:** not significant

**PIN:** Personal Identification Number

**RCTs**: Randomised Controlled Trials

**RG:** Richard Gray

**RMS:** Royal Medical Services

**SBP:** Systolic Blood Pressure

**sd:** Standard Deviation

**SL:** Source Language

**SPSS:** Statistical Package for the Social Sciences

**TAU:** Treatment As Usual

**TL:** Target Language

**UEA:** University of East Anglia

**UK:** United Kingdom

**UNRWA:** United Nation Relief and Works Agency

**USA:** United States of America

**vs:** versus

**WHO:** World Health Organisation

**WKNM:** Wisdom/knowledge model

# INTRODUCTION

Hypertension affects almost one billion people globally and this number is expected to increase to 1.56 billion by 2025 (Kearney et al., 2005, WHO, 2003b). It is the major cause of morbidity (particularly cardiovascular and renal disease) and mortality in both developed and developing countries (Kearney et al., 2005, WHO, 2003b).

Although effective treatments (antihypertensive drugs) are available for hypertension, it is often poorly controlled (WHO, 2003a, Nunes et al., 2009). It is estimated that only around 34% of people with hypertension who are prescribed antihypertensive drugs manage to achieve a blood pressure (BP) of less than 140/90 mm Hg (the WHO definition of hypertension) (WHO, 2003b). Poor adherence to medication is one of the major reasons why BP is inadequately controlled (WHO, 2003b, Chobanian et al., 2003). Overall hypertensive patients are estimated to take only 35-70% of the medication prescribed for them (WHO, 2003a, Morisky et al., 2008). This non-adherence has consistently been associated with higher healthcare costs (Wagner et al., 2008, Gaziano, 2005), and negative consequences on health outcomes (WHO, 2003a, Kokubo et al., 2008).

In Jordan, 26% of the adult population suffer from hypertension (Ministry of Health and CDC, 2007). Overall, among Jordanians 13% of male and 21% of female deaths can be directly attributed to hypertension (Ministry of Health, 2009). Almost half of Jordanians with hypertension do not take medication as prescribed (Yousef et al., 2008). There is little evidence in Jordan and the Middle East about which interventions could be used to improve patients medication taking behaviours. Therefore, there is a pressing need to find an effective intervention to enhance patients adherence to prescribed medications. Non-adherence rates in Jordan and the Middle East are very similar to those observed in Western populations. However, a further challenge is to explore whether theories and interventions that have proven effective in Western patients are also effective for Jordanian hypertensive patients and in an Islamic culture. The purpose this thesis is to investigate the efficacy of one such intervention (adherence therapy) in non-compliant Jordanian hypertensive patients.

## OBJECTIVES OF THE STUDY

1. To develop a model of factors affecting adherence to antihypertensive medication in people with hypertension.

2. To identify an effective intervention for improving medication adherence in people with hypertension.

3. To translate the measures of clinical outcomes chosen for this study into the Arabic language.

4. To examine whether the selected intervention has the potential to be effective for non-adherent hypertensive people in Jordan.

5. To explore patient's experience with the selected intervention (adherence therapy).

## STRCUTURE OF THE THESIS

The contents of the following chapters are as follows:

Chapter 2 presents a literature review, which includes an overview of research on hypertension, its definition, causes, signs and symptoms, epidemiology, consequences and treatments. Finally, the Jordanian context which relates to hypertension and Muslim beliefs is discussed.

Chapter 3 presents the literature review about adherence, its definition and related terminology, measures, and epidemiology, followed by a discussion of consequences of the factors that affect adherence behaviour among hypertensive patients. The rationale for identifying factors that affect adherence is to develop a model of themes of adherence for hypertensive patients.

Chapter 4 is a systematic review of clinical trials testing interventions aimed at improving medication adherence in hypertensive patients. The rational for selecting the adherence therapy intervention to be used with Jordanian patients in this study is then specified.

Chapter 5 identifies the un-answered questions from the literature reviews in chapter 2, 3 and 4.

Chapter 6 presents the eight step process used for translating the English instruments used in this study into the Arabic language.

Chapter 7 presents the methodology of our exploratory randomised controlled trial which was designed to compare the efficacy of the adherence therapy intervention identified in chapter 4 compared to treatment as usual in a group of hypertensive patients.

Chapter 8 presents the results of the exploratory randomised controlled trial.

Chapter 9 considers the results of the trial in relation to our experimental hypotheses and compares the outcomes in the context of the results from previous trials. The limitations and strengths of the trial are discussed.

Chapter 10 considers a qualitative sub- study which was designed to explore the patient's experience with our intervention. Results are presented and discussed in relation to previous studies. Limitations and implications of this study are then identified.

Chapter 11 identifies the implication of the trial for clinical practice, future research, and health policy. Future plans are then considered, followed by a summary of the main points arising from the study.

# OVERVIEW OF HYPERTENSION

This literature review provides the necessary background information of hypertension. It also discusses hypertension in Jordan. It then concludes by discussing Muslims beliefs and behaviours.

## WHAT IS HYPERTENSION?

### Definition of hypertension

Hypertension is a common cardiovascular disease (CVD) (WHO, 2003b). It is also considered to be one of the non-communicable diseases (NCD) which has a long duration and slow progression (WHO, 2003b). Hypertension is generally defined as a BP (systolic pressure/diastolic pressure) greater than or equal (≥) to 140/90 mm Hg (Oparil and Weber, 2005, WHO, 2003b).

### Categories and causes

Hypertension is categorised based on its causes as either primary or secondary (Carretero and Oparil, 2000, Mansoor, 2004). Primary (essential) hypertension has no direct cause; it is associated with range of modifiable (e.g. high salt and fat diet, smoking, stress, alcohol consumption and obesity), and non-modifiable (age, hereditary and sex) risk factors (Keith and Maziar, 2002, Lim, 2007, Singh et al., 2000). Secondary hypertension is caused by risk factors that include those related to the heart, kidneys, endocrine system diseases (Carretero and Oparil, 2000, Mansoor, 2004).

### Signs and symptoms

Although, hypertension is usually asymptomatic (Novo et al., 2009, Tu et al., 2008), some patients may complain of headache, vision disorder, confusion, drowsiness, nausea and vomiting (Carretero and Oparil, 2000, Chobanian et al., 2003, Keith and Maziar, 2002, Lim, 2007, Segura and Ruilope, 2007). In secondary hypertension other signs and symptoms may occur depending on the organ affected and the underlying causes. For example, hyperthyroidism can cause tremor, weight loss, abnormalities in heart rate, and increased sweating (Chobanian et al., 2003, Lim, 2007, Keith and Maziar, 2002).

### Epidemiology

Globally in 2000, hypertension affected 26% of the adult population and this number was predicted to increase to about 60% by 2025 (Kearney et al., 2005, WHO, 2002). The estimated total number of adults with hypertension in 2000 was 333 million in developed countries and 639 million in developing countries (Kearney et al., 2005, WHO, 2002). Differences in; diet and alcohol intake, obesity, physical activity, health behaviours, environmental factors, psychological stressors, and genetic susceptibility have been suggested to explain this variation (Brookes, 2008, Motlagh et al., 2009, Oparil and Weber, 2005).

## CONSEQUENCES OF HYPERTENSION

The consequences of hypertension can be categorised into two main sets; health and economic.

### Health consequences

Hypertension leads to an increased rate of mortality and morbidity (Novo et al., 2009, Tu et al., 2008, WHO, 2003b). Annually, it leads to 7.1 million deaths which causes 13% of global fatalities(Kanavos et al., 2007, WHO, 2002, WHO, 2003a). In 2004 the percentage of deaths from CVD was more than 36% in developing countries (Gaziano, 2005). In terms of morbidity, hypertension affects vital body organs including the heart, brain and kidneys (Kanavos et al., 2007, Wong, 2007). It is the cause of around 40% of myocardial infarctions (Giovanni et al., 1996, Tohme et al., 2005, White, 2009) and a similar proportion of strokes (De Schryver, 2003, Giovanni et al., 1996, Tohme et al., 2005). In Jordan around 79% of patients who reported myocardial infarction had a history of hypertensive disease (Nsour et al., 2008). High BP also predisposes individuals to left ventricular hypertrophy, hypertensive retinopathy (Giacchetti et al., 2009), peripheral arterial diseases (Singer and Kite, 2008, Zheng et al., 2008), and loss of kidney function that may lead to irreversible renal impairments (Nwankwo et al., 2006, Ramsay et al., 1999).

### Economic consequences

The economic and human cost of inadequately controlled BP is considerable both in developed and developing countries (Coca, 2008, Gaziano et al., 2009). In developed countries, it was reported that the expenditure associated with healthcare resources used to manage CVD and hypertension represent a significant proportion of healthcare resource use (Balu and Thomas, 2006). The healthcare cost of CVD in the USA was $ 368 billion in 2004 (Gaziano, 2005). The USA also spent approximately $37 billion annually on the medical costs of hypertension (American Heart Association, 2002). Moreover, in the United Kingdom, the estimated cost of CVD is £26 billion per year (British Heart Foundation, 2007).

Indeed, the burden of CVD in developing countries is increased (Kearney et al., 2005, Lloyd-Sherlock, 2010). The economic impact in Jordan of CVD has increased as a result of increased re-hospitalization and lengths of stay (Mawajdeh et al., 1997). Gaziano (2005) reported that a 25% of healthcare expenditure in South Africa is spent on the treatment of CVD. In addition, Wagner et al (2008) estimated the costs to Philippine-Health (the Philippines’ government's department for health) for inpatient care of hypertension and of readmission resulting from its complications including heart failure, renal failure, coronary heart diseases and stroke. From 2002 to 2005 there were 444,628 admissions for hypertension-related diagnoses; 42% were hospitalised with essential and secondary hypertension, and 37% of the hospitalisations were as a result of the complications of untreated high BP. Over 3.5 years, Philippine-Health paid US $56 million for hypertension-related care to hospitals. Of the patients who were admitted to hospital within the first 18 months of the study because of secondary and essential hypertension, 9% were re-hospitalised due to complications.

## THE TREATMENT OF HYPERTENSION

Hypertension can be effectively treated with medication (Keith and Maziar, 2002, Reeder and Hoffman, 2001, Wong, 2007). A small reduction in BP of just 3 mm Hg can decrease the risk of stroke by 34% and of ischemic heart diseases by 21% (Law et al., 2003a). Despite this, globally the control of hypertension is poor (WHO, 2003b). Uncontrolled BP is associated with many factors including poor adherence to medication regimens and patients lifestyle choices (WHO, 2003b, Vrijens et al., 2008). The treatment of hypertension can be divided into pharmacological and non-pharmacological approaches.

### Pharmacological approach:

There are a variety of medications used to treat high BP. These drugs are called antihypertensive agents and are recommended by the WHO to decrease and control BP (WHO, 2003b, Lim, 2007). Hypertensive patients who took their drugs were 71% less likely (OR = 0.29, 95% CI: 0.13–0.53; P < 0.0001) to have myocardial infarction than those who were not taking medication (Nsour et al., 2008). There are different types of antihypertensive medications (Table 1); beta blockers, calcium channel blockers, vasodilators, diuretics, anti-adrenergic agent, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptors blockers (WHO, 2003b, Chobanian et al., 2003). Each of these drug types has advantages and disadvantages, as well as special properties that influence the choice for a particular patient (WHO, 2003b, Chobanian et al., 2003, Lim, 2007, Keith and Maziar, 2002). Physicians often prescribe patients more than one antihypertensive drugs to achieve effective control of BP that complies with WHO and NICE recommendations (NICE, 2006, WHO, 2003b). Choosing a sensible combination therapy with appropriate synergistic effects of the drugs is very important (WHO, 2003b, Keith and Maziar, 2002, Lim, 2007, Wong, 2007).

**Table 1**, Types of Antihypertensive Agents

|  |  |  |
| --- | --- | --- |
| **Name of Anti-hypertensive Agent** | **Effect** | **Main Side Effects** |
| **Diuretics** | Urinary loss of sodium resulting from a blockade of renal tubular re absorption of sodium is integral to the antihypertensive effect; by decreasing the volume of fluid in the bloodstream and the pressure in the arteries. Diuretics are the oldest and most studied antihypertensive agents. | Polyuria, electrolyte disturbances and hypotension |
| **Beta blockers** | Most beta-blockers, with the exception of those with strong intrinsic sympathomimetic activity, reduce cardiac output by virtue of their negative chronotropic and inotropic effects through reducing the force of heart contraction and slow heart rate. | Lethargy, aches in the limbs on exercise, impaired concentration and memory, impotence and bradycardia |
| **Calcium channel blockers** | Selective blocking of L-type calcium channels in vascular smooth muscle cells and thereby inducing vascular relaxation with a fall in vascular resistance and arterial pressure | Peripheral oedema, hypotension and negatively inotropic (decrease heart rate) and negatively chronotropic (decrease the force of the heart's contractions) |
| **Angiotensin converting enzyme inhibitors** | These drugs block the conversion of angiotensin I to angiotensin II by inhibiting ACE. The resulting reduction in levels of angiotensin II leads to vasodilatation and a fall in BP. | Persistent dry cough, allergic reaction |
| **Angiotensin receptors blockers** | These drugs block type I angiotensin II (AT1) receptors leading to vasodilatation and a fall in BP | These do not commonly produce significant side effects. Rarely, they interfere with or worsen kidney function. |
| **Anti adrenergic agent** | Short acting drugs that block the activation of alpha-1 adrenoceptors in the vasculature, leading to vasodilatation | Postural hypotension and headache |
| **Vasodilators** | Direct or centrally acting (affect central nervous system) dilates the arteries and veins in the body, lowering blood pressure | Headache, dizziness, postural hypotension |

There is debate about the best way to treat hypertension pharmacologically (Fine and Cutler, 2006). Some physicians advise that drug therapy should normally begin with a low-dose thiazide-type diuretic (increasing to combination therapy if necessary), aiming for a target BP of less than140/90 mm Hg in patients without diabetes. In patients unable to achieve a target BP, any reduction is beneficial (Chobanian et al., 2003, NICE, 2006, Veronesi et al., 2007). Although drug treatments prove necessary in maintaining adequate BP control, patients face the challenges of adhering to treatment (Mazzaglia et al., 2009, NICE, 2006, WHO, 2003b).

### Non-pharmacological:

Non-pharmacological management has an essential role to play in controlling BP and reducing other risk factors for CVD (Hagberg et al., 2000, Lim, 2007, Sacks et al., 2001). Modification of lifestyle health behaviours (e.g. weight reduction, smoking cessation, dietary modification, exercise, and moderation of alcohol consumption) are the main non-pharmacological strategies for managing hypertension (Chobanian et al., 2003, Keith and Maziar, 2002, Lim, 2007, Wong, 2007). The most important non-pharmacological management is, non-adherence, and is a key modifiable reason for poor BP control (Nunes et al., 2009, WHO, 2003b). Adaptive health behaviours are vital element of hypertension management supporting drug treatment (WHO, 2003b, Lim, 2007).

## HYPERTENSION IN JORDAN

### Jordanian context

Jordan is a Middle Eastern country. It is located in Asia. Jordan has a population of approximately 6 million people, most of them (75%) live in the three main cities (40% in the capital-Amman, 16% in Zarqa and 19% in Irbid) (Ministry of Health and Department of Information and Research, 2008). Islam is the most common religion (92% of population) (Ministry of Health, 2009).

In Jordan there are three main providers of healthcare services; the public, private and military. Each has its own strategy, funding, separate constructs and health insurance schemes to give subsidized healthcare services to its workers only. Approximately 70% of the population have health insurance and the rest pay with their own money for healthcare (WHO, 2003a). The public sector provides low cost medicines, however, the availability of essential medicines (such as antihypertensive drugs) is poor, with limited access (WHO, 2003b), In the private sector medicines are expensive and some treatments are unaffordable for low income groups (WHO, 2003b).

Non-communicable diseases (NCD) such as hypertension have an impact on the health of Jordan’s population directly (CVD) and indirectly (renal and neurological conditions) (Hijazi, 2005, Jordan Human Resources, 2009). About a quarter of the population suffer from hypertension (Ministry of Health and CDC, 2007). However, patient awareness of the disease and how to control it are well below the optimal level (Jaddou et al., 2003, Arbaji, 2002, Jaddou et al., 1996). It is estimated that about 71% of hypertensive patients in Jordan have poor control of their BP (Arbaji, 2002, CDC, 2006). Also, it is estimated that a quarter of hypertensive patients never have their BP checked (Ministry of Health & CDC 2007). Overall, a third of the Jordanian population die from CVD (Ministry of Health, 2009). The main national health system's goal in Jordan is providing good health; in 2003, they spent 9.4% of Jordan’s GDP on health with health expenditure per capita reaching US$177. This compares favourably with other developing countries (Rawabdeh, 2005, WHO, 2007).

### Muslims beliefs and behaviours

Cultural factors derived from religious beliefs and practices affect how health care is perceived and received, affecting health seeking behaviours among Muslims (Soskolne et al., 2007, Yousef et al., 2008). Muslims have faith in God (Tayeb et al., 2010). They consider an illness as a test and a way to atone for their sins and death as a part of a journey to meet God. Therefore they receive and react to illness and death with patience and prayers (Tayeb et al., 2010). In addition, they are strongly encouraged by God to seek medical treatment when required (Tayeb et al., 2010). The Islamic faith teaches Muslims a healthy lifestyle such as general hygiene, healthy diet, prohibiting the consumption of alcohol, and the importance of exercise (Padela, 2007, Sarhill et al., 2001). Furthermore, Islamic faith encourages Muslims to build a safe social relationship on the basis of mutual respect, protection of rights and duties for each member, and consideration of morality and generosity (Ahmed et al., 2006). All these factors play a basic role in safeguarding family and community consolidation, fluency and stability (Daneshpour, 1998). The elderly are members of the family therefore the Qur'an and the Prophetic traditions encourage care of them (Daneshpour, 1998, Rahman, 1998). The elderly in the community are regarded with deep respect and are given priority in all walks of life. Children have a responsibility to look after their parents; neglecting them is considered a serious sin, and care of them is regarded as an avenue to Heaven (Miklancie, 2007). Whether they live together with their children or separately, parents and the elderly are usually consulted in all decision making processes (Miklancie, 2007, Rahman, 1998). In general, there are many reasons for Muslim patients to maintain their health through following healthy lifestyle, care of themselves and others community member.

## SUMMARY

It can be concluded that hypertension is common in both developed and developing countries. Effective drug treatment and modification of health behaviours play an important role in BP control. Islamic culture encourages healthy behaviours such as seeking medical advice for treating diseases. Despite this many patients in Jordan find it difficult to adhere consistently to prescribed treatments for their hypertension.

# OVERVIEW OF ADHERENCE

## INTRODUCTION

Hypertension is a common CVD that has negative economic and health consequences. It can be treated effectively with medication. Patients often have difficulty in taking their medication as prescribed. In this chapter the literature considering the terminology related to adherence is reviewed, and the importance, rates, and measures of adherence. Then factors affecting adherence are considered. Finally, a theoretical model to help us to understand it is presented and the implications for the design of an adherence intervention is considered.

## SEARCH STRATEGY

### Search methods

Electronic databases were searched from their inception to January 2011; CINAHL (EbscoH), Medline, Science Direct (Elsevier) and the Cochrane Database of Systematic Reviews to identify the eligible studies. The database search terms are outlined below (antihypertension, medication for lowering blood pressure or high blood pressure, or hypertensive, or cardiovascular disease (CVD), or blood pressure control, or reduce high blood pressure) and (consequences or complication of non-adherence) and (measures or instruments of adherence or non-adherence) and (barriers, or factors, or determinants) and (adherence, or compliance, or concordance) and (drug and medication). We also searched the reference list of each study for related articles. The identified papers were reviewed against our selection criteria to identify relevant studies.

### Selection criteria

Studies were deemed relevant if they were written in the English language, if the research was conducted with humans, if they were original primary research studies, if they involved patients with hypertension or CVD; if they examined adherence and/or compliance and/or persistence and/or concordance with pharmaceutical interventions (even if the primary objective was not to measure adherence); if they provided a measure of adherence or compliance, if they discussed non-adherence consequences; and if they provided a factor and/or barriers and/or determinants of adherence or compliance with an adequate description of the methodology used. RCTs of clinical efficacy were not included unless they specifically studied adherence.

Studies were excluded from the analysis if they examined non-adherence with medication other than antihypertensive drugs (such as; antiplatelets, aspirin, digoxin, insulin, and non-pharmaceutical therapies), and if they were in a language other than English.

### Data extraction and synthesis

Each full text study was assessed according to the inclusion and exclusion criteria for review. Based on inclusion criteria, studies were included if they reported factors that might have had an impact on patient's adherence to antihypertensive medication. Parameters extracted from the studies included definition and measures of adherence or compliance or persistence or concordance, consequences of non-adherence, and modifying factors or barriers or determinants of adherence for hypertensive patients who take antihypertensive medication. Consequences were divided into health and economic. Factors were classified into themes and these results were merged to formulate the theoretical framework for this study.

## DEFINITION OF RELATED TERMINOLOGY

Medication concordance, persistence, compliance, and adherence are all terms often used interchangeably, to mean are the patients taking the pills as their doctors has prescribed. Concordance relates to the nature of the interaction between patients and healthcare professionals. It is based on the process of shared decision making concerning medicine use (Bell et al., 2007, Marinker and Shaw, 2003, WHO, 2003a, Metcalfe, 2005). In adopting a concordant approach the consultation between patients and prescriber are discussions and a negotiations between equals. Based on the fact that the patient and clinician may differ in their opinions on the value risks and benefits of a particular drug; a patient makes a decision whether or not to take a prescribed drug and the clinician should respect this (Bell et al., 2007, Aronson, 2007). As was discussed above concordance reflects the nature of interaction process between patients and health care professionals but does not reflect a patient’s medication taking behaviours (i.e. if the patient take his/her medication or not) therefore a term which could describe this is needed.

Persistence refers to continued prescription renewal and represents the accumulation of time from initiation to discontinuation of therapy (Cramer et al., 2008, Sluijs et al., 2006). This means continuing to take any amount of drugs is consistent with the definition of persistence definition. This does not reflect the actual patient’s behaviour whether he/she took a partial or full medication dosage.

Another commonly used term is compliance which refers to taking treatment in accordance with factors such as proper dosage and time (Aronson, 2007, Sluijs et al., 2006). In addition, it is defined as the degree to which the patient conforms to medical advice about lifestyle and dietary changes as well as to keeping appointments for follow up and taking treatment as prescribed (Aronson, 2007). This means acting in accordance with a healthcare professionals' advice regardless of the patients' decision whether to agree with it or not. Also, these definitions of compliance betray a paternalistic attitude towards the healthcare professionals (prescribers) on the patients' part. Therefore the term adherence was suggested, which is defined as the extent to which a patient takes medication as prescribed by the health care professionals (Sluijs et al., 2006). The WHO defines adherence in a comprehensive way as "the extent to which a person’s behaviours taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”(WHO, 2003a, p3). Overall, the word “adherence” is preferred by many health care providers as “compliance” suggests that the patient is passively following the doctor’s orders. Compliance suggests that the treatment plan is not based on a therapeutic alliance or contract established between the patients and the clinicians, whereas adherence requires patient decisions and agreements (The American Pharmacists Association, 2004, Wahl et al., 2004, WHO, 2003a). Some authors have argued that compliance and adherence are synonymous, reflecting patient's medicine-taking behaviours (Burrell et al., 2005, Cramer et al., 2008, Dezii, 2000, Metcalfe, 2005, Osterberg and Blaschke, 2005, Tilson, 2004). For example; The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) defined compliance (synonymous with adherence) as "the extent to which a patients acts in accordance with the prescribed interval, dose, and dosing regimen. It is typically expressed as a percentage of the total number of doses taken (if prospectively measured), in relation to the time period of observation during which compliance is measured" (Burrell et al., 2005, p 46). Therefore, in this study the term adherence is used since AT (the intervention which used in this trial) suggests the extent to which patients takes medications as prescribed by their health care providers.

Non-adherence is an opposite term for adherence and it may include inappropriate dosage, frequency and timing, and the irregular use of inappropriate combination (Urquhart, 2002, WHO, 2003a). It can also vary from "irregular taking of medication" (which refers to partial adherence) to "complete cessation" (which refers to non-adherence) (WHO, 2003a, Nunes et al., 2009).

## IMPORTANCE OF ADHERENCE

Any non-adherence to treatment (full or partial non-adherence) negatively influences hypertension outcomes (WHO, 2003b). It leads to an increase in the global burden of disease and from an economic standpoints places unnecessary strain on finite health resources (Al-Mahroos et al., 2000, WHO, 2003b). Non-adherence to antihypertensive drugs leads to worse health outcomes; there is an increased risk of myocardial infarction, stroke (WHO, 2003a) and cognitive impairments (dementia) (Gard, 2010). Also, it is associated with higher hospitalisation rates, consequently increased costs of care (Coca, 2008, William, 2003). By getting optimal adherence, it is possible to reduce SBP by more than 10 mm Hg (Sacks et al., 2001).

## RATES OF NON-ADHERENCE

It is estimated that patients with hypertension only take between 35-70% of the medication prescribed to them (Elzubier et al., 2000, Morisky et al., 2008, Morrison et al., 2000, Vrijens et al., 2008). These rates are within the average in comparison to other long term conditions; the WHO estimated that only 50% of patients with chronic diseases in developed countries follow their prescribed treatment (WHO, 2003a). In developing countries the adherence rate for antihypertensive drugs is similar to the global rate; Tamir et al (2007) found that the Bedouin population adherence range was 27–30%, compared to 40% amongst the Jewish population. Adherence for antihypertensive drugs was 72% in the Jewish population for at least 9 months a year compared with only 45% in the Bedouin population. Another study reported 60% of Sudanese hypertension patients were estimated to be adherent to medication and had controlled BP and a lack of complications (Elzubier et al., 2000).

There are two reasons why the estimation of medication adherence rates in people with hypertension is difficult. First, there is no agreement between researchers about the definition of adherence (see Section 3.2); some studies use adherence/non-adherence as a dichotomous outcome, whereas others use the ordinal scale to measure it. Secondly, there is no gold standard for measuring adherence.

## MEASURING ADHERENCE

Adherence to medication is difficult to measure in a valid way, even though a variety of different ways of measuring it have been developed and tested. Authors differ even on the categorisation of measurements (see Table 2).

Table 2, Categories of adherence measurement

|  |  |  |
| --- | --- | --- |
| Study | Category | Outcomes measured |
| (Chia, 2008) | Subjective | Self reports |
|  | Direct | Blood tests |
|  | Indirect | Pill counting |
| (Vrijens et al., 2008, Kripalani et al., 2007) | Pharmacological | Determination of serum and urinary concentrations of drugs or using biological markers integrated into the tablets |
|  | Clinical | Clinical judgment of the doctor, evaluation of promptness for appointments and the use of questionnaires |
|  | Physical measures | Medication Event Monitoring System (MEMS) |

There are strengths and weakness for each measure of adherence (see Table 3);

Subjective measures, such as self-reported questionnaires, have the risk of personal bias and tend to overestimate adherence (Bosworth et al., 2009, Bosworth et al., 2005). Objective measures also have disadvantages; pill counting assumes that if the tablet was not in the packet it was taken by the patient at the appropriate time (Marquez Contreras et al., 2005, Qureshi et al., 2007, Santschi et al., 2008b). Clinical judgement has the risk of bias by the physician; blood tests can be manipulated by patients who could take their medication just before they take the test (WHO, 2003a). The Medication Event Monitoring System (MEMS) records the time and date of drug taking, and is generally considered to be the most accurate adherence measurement. However, again just because the patients have opened the device does not mean that they have taken the pills. The cost of the device is considered a major barrier to its being used (Ogedegbe et al., 2008, Qureshi et al., 2007, Wetzels et al., 2007, WHO, 2003a). Also, the underlying cause(s) for non-adherence are not captured by electronic systems (Morisky et al., 2008).

The problem of accurately measuring medication-taking behaviour explains inconsistencies in the incidence of non-adherence reported by people with hypertension. For example, Al-Sowielem and Elzubier (1998) found that the adherence rate was 32% when measured using therapeutic outcomes (diastolic blood pressure) and 74% if measured using a self-reported questionnaire. However, Vrijens et al (2008) used MEMS to determine adherence. They observed that 50% of patients stopped taking their antihypertensive medications completely within a one-year period. Furthermore, Birtwhistle (2004) used objective and subjective measures to measure adherence levels. They found that using pill counting was unreliable for measuring adherence levels. They rationalised it with reference to the difficulty in determining exactly how many pills had been taken for some patients who were taking multiple drugs. Therefore they suggested using a self-reported questionnaire as a good measure for adherence. Nevertheless, several self-reported questionnaires for medication adherence were validated using electronic monitoring devices. A majority of them showed moderate to high correlation with medication adherence measured using monitoring devices, and could be used together for more accurate measuring patient adherence in the future (Shi et al., 2010).

Table 3, Criticism of most commonly used adherence measure

|  |  |  |  |
| --- | --- | --- | --- |
| Category | Example | Strengths | Weakness |
| **Subjective** | Self reports (Morisky medication adherence scale (MMAS), Beliefs about medication questionnaire (BMQ), medication adherence rating scale (MARS) | - Easily obtained (using patients interview or questionnaire)  - Inexpensive  - May capture the underlying cause of non-adherence | - Personal bias  - Overestimate adherence. |
| **Objective** | Clinical Judgment (blood test, urine test) | - Confirms patients reporting | - Does not guarantee that patients took medication |
|  | Pharmacy refill monitoring | - Easy, minimal time commitment.  - Effective for large population. | - Patients may use more than one pharmacy. - Does not equate with medication taking. |
|  | Pill counts | - Minimal direct costs  - Could be more accurate if unannounced pill counts done. | - Overestimate of adherence  - Does not prove that patient actually took the medication |
|  | Electronic monitoring (MEMS) | - Claimed to be most accurate measure. | - Expensive  - Requires carrying the container  - Subject to “pocket doses” (removing more than one dose at a time)  - Does not prove that the patient took the medication- The underlying cause of adherence are not captured |

The only adherence measure that has been developed and tested on a population of patients with high BP is the Compliance Praxis Survey (COMPASS) survey instrument (Schoberberger et al., 2002). It consists of four subscales representing the normative behaviour, effective structural circumstances, social support and wisdom/knowledge (NESW) model. Each subscale includes three items which users can rate on a 9-point Likert scale ranging from ‘completely disagree’ to ‘completely agree’. Lower scores represent lower levels of compliance. A minimum overall score of 12 and a maximum overall score of 108 is possible. Patients’ scores were collapsed into groups with low, medium and high compliance scores. Schoberberger and colleagues claimed that the 12-item COMPASS survey instrument was useful for predicting patients’ adherence to antihypertensive medications (Schoberberger et al., 2002) .The authors suggested that there is a correlation between these predictive scores and actual patient behaviour. Patients who were found to be non-compliant at 6 months follow-up had significantly lower baseline physician predictive scores on all four compliance subscales of NESW patients. Therefore, this scale is useful and validated for real behaviours. On the other hand, the study could have been compromised because of increased awareness of compliance by the patients completing the survey. Physicians in the study may have also increased the level of support for the study participants compared to their usual care.

Furthermore, Morisky et al (2008) have examined the psychometric properties and tested the concurrent and predictive validity of the Morisky Medication Adherence Scale (MMAS) in patients with hypertension. The MMAS has a high reliability (internal consistency) and equal concurrent and predictive validity especially for low income, minority patients with essential hypertension attending an outpatient setting (Morisky et al., 2008). Again, it is highly liable to have personal bias as it is a self reported questionnaire.

In general, there is no single validated standard instrument that can be used to measure adherence at the expense of other measures. Therefore, adherence to antihypertensive drugs is a complex and challenging issue. To address non-adherence problems, various factors contributing to medication adherence should be taken into account, as discussed below.

## MEDICATION ADHERENCE MODIFYING FACTORS

Medication adherence is multidimensional and is affected by a range of modifying factors that include patient characteristics, disease condition, type of healthcare provider, type of medication, economic, social, and system-related factors (Osterberg and Blaschke, 2005, Sluijs et al., 2006, Thrall et al., 2004, WHO, 2003a). Touchette and Shapiro’s (2008) theory classified barriers to adherence into behavioural barriers (including social support, cognition, and personal beliefs, attitude and satisfaction), and system barriers (including treatment complexity, system complexity, multiple providers and cost).

In the review of the literature in the area, that there were four main groups of adherence-modifying factors were determined: (a) patient-related; (b) healthcare professional (HCP)-related; (c) medication-related; and (d) condition/disease-related.

### Patient-related factors that affect adherence

This set of factors combines both mutable factors such as patient’s knowledge, beliefs and attitudes and immutable demographic factors such as age and gender, which may act as surrogate markers for beliefs and attitudes.

#### Patient’s knowledge, beliefs and attitudes about hypertension

The relationship between knowledge of hypertension and level of adherence is inconsistent. Some studies have shown that a high level of knowledge of hypertension and how to control it are important in achieving adequate control of BP (Chapman et al., 2005, Morisky et al., 2008, Li and Froelicher, 2007). Others have shown that lack of knowledge is a significant predictor of poor BP control (Al-Yahya et al., 2006, Hadi and Rostami, 2004, Knight et al., 2001, Morisky et al., 2008). This view was supported by Jokisalo et al (2001) who indicated that about 56% of their study participants claimed that they lacked information about hypertension as a disease and reported that this information might be an aid to improving their adherence. On the other hand, several authors have reported that there is no association between adherence and levels of patient knowledge (Hassan et al., 2006, Hunt et al., 2004, Ross et al., 2004).

Patient’s beliefs regarding their level of susceptibility to hypertension (and its consequences), the severity of their disease, its duration, and hence the duration of treatment required, all influence their levels of adherence (Hashmi et al., 2007, Hershey et al., 1980). Those patients who held the belief that they had poor disease and health status were found to have a lower level of medication adherence (Morisky et al., 2008, Chen et al., 2010).

#### Beliefs, attitudes, and experiences of antihypertensive medications

Patients vary in their beliefs about medications, some beliefs are negatively associated with adherence; (e.g. medications are not for them, medications are unsafe and unnatural, they do not wish to get used to the medications) or they are forgetful (Benson and Britten, 2002, Egan et al., 2003, Hashmi et al., 2007, Hsu et al., 2010, Wai et al., 2010). Some beliefs are positively associated with adherence e.g. having a positive attitude towards antihypertensive medications, perceiving benefits from being adherent, and belief in the necessity of the drug (Hadi and Rostami, 2004, Morisky et al., 2008, Touchette and Shapiro, 2008, Ross et al., 2004). Other belief associations with adherence depend on if they are positive or negative. These include beliefs about the importance of the medications, their effectiveness, patients satisfaction with their medications, and patient’s perception of the seriousness of being non-adherent (Benson and Britten, 2002, Dezii, 2000, Hashmi et al., 2007, Wai et al., 2010).

Aspects of self-efficacy affect whether patients believe they can overcome barriers to adherence and their overall control over their health status (Hershey et al., 1980, Morisky et al., 2008). Adherent patients taking antihypertensive drugs, have been shown to have a high level of self efficacy (Bane et al., 2006). Perversely however, other studies have shown that patients with a strong perception of control over their efforts to try to reduce high BP may as a result try to decrease their reliance on drugs and subsequently become non-adherent to their medication regimen (Patel and Taylor, 2002, Wai et al., 2010).

#### Attendance at clinic

There is debate as to whether a patient’s rate of attendance for clinic appointments is associated with adherence. Some studies have found that patients who attend clinics have higher rates of adherence and BP control (Coelho et al., 2005, Hadi and Rostami, 2004). In contrast, Ogedegbe et al (2007) found no relationship between rates of attendance and adherence. The major outcome from continuing to attend clinic appointments may be developing patients’ self-motivation to take their medications (Khosravi et al., 2005). It is possible that the visits themselves and the short intervals between them initiate motivation and remind the patient to take their medication consistently (Hadi and Rostami, 2004).

#### Demographic characteristics and adherence

Several studies have noted correlations between adherence behaviours and patients’ demographic characteristics.

*1- Gender*

There is inconclusive evidence about the impact of a patient's gender on adherence behaviours. In some studies women are more adherent than men (Chapman et al., 2005, Morisky et al., 2008, Ross et al., 2004). Conversely, other studies have found that men are more adherent than women (Knight et al., 2001, Park et al., 2007, Van Wijk et al., 2004). Finally, some studies have found no relationship between gender and the patient's adherence behaviours (Bovet et al., 2002, Hadi and Rostami, 2004, Hsu et al., 2010).

*2- Age*

The relationship between age and adherence is complex. There has been no consistency in the findings about patient's age and adherence to drugs. Age is known to have an effect on patients attitudes, beliefs and satisfaction, and these can impact on adherence (Hadi and Rostami, 2004). Some authors claimed that there was no association between age and adherence (Trivedi et al., 2010). Other researchers report that older patients are more likely to be compliant than younger ones (Hashmi et al., 2007, Park et al., 2007, Ross et al., 2004). They rationalised this referring to the presence of differences in levels of knowledge about the disease and denial of the diagnosis (Hashmi et al., 2007, Park et al., 2007, Ross et al., 2004). Finally, some studies have found that elderly patients tended to have poorer adherence than younger (Chapman et al., 2005, Morisky et al., 2008, WHO, 2003a). They explained this result by the presence of a variety of physical and mental factors (cognitive impairment, reduction in visual acuity, and limitations in hand range of motion) that could affect their ability to open medication bottles. In particular, Chapman et al (2005) observed that patients older than 65 years tended to have a higher rate of co-morbidity and health service use, and therefore more complex medication regimes, which impacts upon adherence (Chapman et al., 2005). Therefore, age has surrogate markers for a complex combination of factors that affect adherence, and may well differ according to the specific population investigated.

*3- Literacy*

There are differing opinions regarding the importance of literacy on adherence. Some researchers reported no relation between patient's taking medication behaviour and literacy, and consequently the level of education (Hsu et al., 2010, Trivedi et al., 2010). In contrast, Al-Sowielem and Elzubier (1998) found that adherence is higher in illiterate patients than in educated ones, though most participants in their study were Saudi female patients, so the generalisability of their findings is limited. Moisan et al (2002) demonstrated the existence of a relationship between non-adherence and the inability to read or understand drug labels (Moisan et al., 2002). Finally other studies reported high levels of education may be associated with increased patient adherence to medications (Hashmi et al., 2007, Kabira et al., 2004). However, levels of education probably influence more than just levels of literacy. It could be argued that these patients are more likely to have read more about their disease and understand more about the complications of hypertension.

*4- Financial status*

Financial security and health insurance is a cornerstone of patients being able to adhere to prescribed medication (Hunt et al., 2008). Financial factors include:

1. The cost of drug(s) and health insurance

2. Level of income

Poor adherence was common among patients with no or low coverage for their medication (Mojtabai and Olfson, 2003). Full coverage for combination drug costs in the USA was shown to improve medication adherence, enhance functional life expectancy and lead to less resource use (Choudhry et al., 2008). A number of authors have suggested that the level of medication adherence is decreased by increasing co-payment level (in which there is a third party participating in paying the drug costs) (Hashmi et al., 2007, Taira et al., 2006).

Adherence to medication is positively correlated with patients level of income (Trivedi et al., 2010). In developing countries, poor adherence was attributable to the lack of money needed to buy the drugs (Elzubier et al., 2000, Kabira et al., 2004). Studies also found that adherence was better among patients with a higher income (Hashmi et al., 2007, Kabira et al., 2004) and with health insurance (Hadi et al., 2004).

*5- Social support*

The presence of social, family and peer support may have an impact on adherence (Johnell et al., 2005, Morisky et al., 2008, Qureshi et al., 2007). A suggested relationship was found between lack of social support, engagement and participation and poor adherence (Johnell et al., 2005, Wai et al., 2010). Positive social support from family member was highly associated with high levels of adherence (Morisky et al., 2008, Wai et al., 2010). A patient’s family members may take full responsibility for the patient's medication routine (Qureshi et al., 2007). For example, among hypertension patients in Pakistan, Hashmi et al (2007) observed that a better social support structure, ensured by the common extended family system, reduced self-reliance and could be the reason for better adherence.

### Healthcare professional theme

The knowledge, skills and approach of healthcare professionals (HCPs), including doctors, nurses, physiotherapists, dieticians and pharmacists, and the organisation of the services they offer may have a profound influence on medication adherence (Osterberg and Blaschke, 2005, Sluijs et al., 2006). If patients have high expectations of healthcare that are not met this can have a negative influence on adherence (WHO, 2003a).

#### HCP skills in communication and development of relationships with patients

Many authors have focused on the importance of patient- professional relationships and communication for affecting adherence behaviours (Bosworth et al., 2009, Qureshi et al., 2007, Schoenthaler et al., 2009, Touchette and Shapiro, 2008). If doctors are perceived as being trustworthy and patients have a positive experience with doctors they are more likely to be adherent (Dezii, 2000, Tabor and Lopez, 2004, Wai et al., 2010). If patient’s have poor experiences, such as not being kept informed, this can have a negative influence on adherence (WHO, 2003a). Training in improving communication skills may improve professional relationship with patients and lead to changes in patient's negative behaviour toward medication (Hunt et al., 2008).

#### Time for development of relationships

There is conflicting evidence regarding relationships between HCPs and patients and adherence. Patients have stated that time to develop a good relationship is necessary to explore their concerns and thoughts about treatment and that may increase their adherence (Qureshi et al., 2007). Medication adherence increased for patients who received continuous and enhanced hypertension care, and whose HCP counselled them more about BP and prescribed more medications to control their disease’s status (Kressin et al., 2007, Park et al., 2007). On the other hand, some authors claimed that providing frequent/adequate counselling time and continuous care did not affect on patient adherence with medication (Al-Sowielem and Elzubier, 1998, Hunt et al., 2008, Schroeder et al., 2005).

#### HCP knowledge and use of guidelines

HCP’s knowledge, skills, and experience of hypertension could influence patients adherence (Bosworth et al., 2005, Touchette and Shapiro, 2008). There is debate about the level of adherence to clinical guidelines for hypertension by HCPs (O' Connor, 2003). Ren et al (2002) reported that patients who had older and non-specialist physicians were less adherent with their medication than patients who had younger physicians and specialist physicians. Special training of general practitioners which focused on standard treatment algorithms for hypertension, substantially increased adherence behaviours among patients (Qureshi et al., 2007). Overall HCPs with more specialist knowledge who adhere to guidelines seem to promote adherence.

#### Organisation of care

Ease of access to pharmacies and drugs had a positive correlation with patients medication-taking behaviour (Hadi and Rostami, 2004). Availability of drugs also had a relationship with adherence (Martin et al., 2010). There is some research examining who should deliver care and if this affects adherence behaviour; Schroeder et al (2005) found that nurse-led interventions had no effect on patient adherence to antihypertensive medication compared to the control group in their randomised control trial involving 245 hypertensive patients with uncontrolled BP. However, involving pharmacists in the delivery of care may enhance patients adherence to antihypertensive drugs (Sookaneknun et al., 2004). Overall, there is insufficient evidence to recommend a specific HCP as being a key for improving adherence in hypertension.

### Medication theme

Adherence to prescribed medication was affected by the side effects, type, combination and complexity, and duration of the hypertension drug. Most authors claim that medications’ side effects are the major barriers to adherence (Al-Yahya et al., 2006, Buabeng et al., 2004, Hsu et al., 2010, Svensson, 2006). Poor adherence because of the side effects from antihypertensive medication was reported by 12% of patients in a study of 360 Nigerian hypertensive patients (Kabira et al., 2004). There is controversy about which type of antihypertensive could increase patient adherence to medication. A number of studies have suggested that poor BP control was associated with calcium channel blocker therapy, which was in turn associated with higher adverse effects (Knight et al., 2001). Other studies found that drug adherence was highest among patients who received Angiotensin type two receptor blockers and ACE inhibitors (69% and 62% respectively) (Veronesi et al., 2007). Patients’ medication-taking behaviours depend on the clinical outcome of the antihypertensive drug, with a greater decrease in BP leading to higher rates of patients persevering with therapy (Veronesi et al., 2007).

Several authors suggested decreasing the drug regime complexity, for example by combining two drugs into a single pill to increase patients adherence to medications (Al-Yahya et al., 2006, Chapman et al., 2005, Fung et al., 2007). However, Hashmi et al (2007) found that patients on mono-therapies had a mean adherence of 79% compared to 90% for those on three drugs or more. Co-morbidity and poly-pharmacies might increase adherence (Chapman et al., 2005) (see Section on disease conditions).

Furthermore, the duration of the use of medication has been linked by some researchers with adherence (Chapman et al., 2005, Cohen, 2001); long-term duration of treatment was associated with non-adherence to medication (Chapman et al., 2005, Cohen, 2001). The pattern of adherence declined sharply in the first six months, followed by a more gradual decline over time. This reflects the importance of early interventions in order to maintain or improve adherence (Chapman et al., 2005, Ogedegbe et al., 2007). Researchers have shown that the longer a patient has been taking medication, the more likely they are to stop (Morisky et al., 2008, Park et al., 2007, Vrijens et al., 2008). Vrijens et al (2008) showed that 50% of patients stopped taking their medication within one year, 48% had missed more than one day of medication per year, and almost 95% of them missed at least a single dose a year, which usually occurred at weekends. In addition, some researchers studied the best day time for adherence; they reported that medication adherence was best if medication was prescribed to be taken in the morning, when patients were in their homes; the second best were evening doses; and the least consistent were midday doses. They explained that patients forget to take drugs at noon because they use all of their energy in the day working, and in the evening they become tired and need rest and sleep (Kabira et al., 2004). Patients are less likely to be adherent to drugs that have unpleasant side effects, have to be used for a long duration, or are part of a complex treatment regimen. Therefore, there is a need to consider these as components for adherence intervention.

### Disease conditions theme

Disease conditions include the presence of:

1. Hypertension complications

2. Other diseases

Several authors found that medication adherence increased when the patient had hypertension complications such as CVD, congestive heart failure (CHF), angina, myocardial infarction, and stroke (Chapman et al., 2005, Hadi and Rostami, 2004, Knight et al., 2001). Most patients reported fearing hypertension complications, controlling their BP and preventing re-hospitalisation as reasons to be more adherent to drugs regimens (Hashmi et al., 2007).

Chapman et al (2005) observed that when hypertensive patients had another disease, often associated with increasing age, this led to increasing the number of other prescribed medications (polypharmacy); consequently, patients adherence decreased. The character of the co-morbidity may influence rates of adherence. One study found that of the co-occurrence of arthritis, decreased adherence to antihypertensive drugs (Hadi and Rostami, 2004). Arthritis may have practical implications on the patient’s ability to open pill bottles or blister packs. Hypertension is relatively asymptomatic in nature (American College of Cardiology Foundation et al., 2010, WHO, 2003b); other diseases may be associated with symptoms such as pain, which reminds patients to take medications, however, hypertensive medications are mainly preventative, and prescribed for long-term issues.

## DEVELOPING A CONCEPTUAL MODEL OF THEMES OF ANTIHYPERTENSIVE MEDICATION ADHERENCE

From the studies (that are discussed above) the results are mixed. They do not readily provide a theory or a direct intervention. The direction of the relationship between these factors and adherence is not clear. Because most of the studies used self-reported measures and interviews, which risk a high level of recall bias, they may have overestimated adherence (Hadi and Rostami, 2004, Hashmi et al., 2007). The studies are also at risk of selection bias as they were conducted in very specific settings, and used non-random sampling techniques (Al-Yahya et al., 2006, Hadi and Rostami, 2004). Some of the characteristics are not capable of change (e.g. age or gender), but probably reflect other underlying issues such as rates of co-morbidity and educational attainment. An intervention to increase adherence would have to consider these complexities.

In general, it seems logical that knowledge about medication and disease conditions might change patients negative attitudes and beliefs, increase patient awareness and satisfaction with medication, and enhance healthy behaviours, but this still needs to be supported by robust evidence (Haynes et al., 2008, Schroeder et al., 2004).

There should be a system-wide evaluation of barriers to adherence, whether that is the ability to pay for medications, accessibility of pharmacies, or practical issues such as simplification of drug regimens or the physical ability to open pill bottles. HCPs should be suitably skilled in communication, knowledgeable about the condition and factors that enhance adherence and have sufficient time to address patients concerns and to encourage adherence specifically.

Adherence behaviours relationship with surrounding factors is a complex phenomenon that may involve other variables that are not fully understood. This review highlights the knowledge base about how these themes influence hypertensive patient medication adherence behaviours. It is apparent from the literature that the model of adherence in hypertension differs to the WHO’s medication with more specification in content. Non-adherence with antihypertensive drugs has multidimensional themes (regarding patients, health care providers, disease and medication) which may affect patients’ medication-taking behaviour. Health care professionals, medication and disease condition themes have two pathways of effect; one directly on adherence and another on shaping and directing the patient-related theme, consequently adherence behaviour (see Figure 1).

Figure 1 Model of Themes of adherence to antihypertensive medications

Effect on patient related theme -

Effect on adherence behaviour

Circle means the four themes have a small effect on each other

Direction of the arrow indicates direction of the effect

## SUMMARY

Adherence to antihypertensive drugs is poor. However, it's estimation is difficult since there is a lack of a presence of agreed definitions and a validated measure for adherence. Non-adherence resulted from multidimensional factors. In designing effective interventions to enhance patient medication taking behaviour, there is a need to identify and explore barriers to adherence. Several interventions were applied to enhance medication adherence, however, it is necessary to identify which one is effective for hypertensive patients.

# INTERVENTION TO IMPROVE ADHERENCE TO ANTIHYPERTENSIVE DRUGS: A SYSTEMATIC REVIEW

## INTRODUCTION

Following the development of a conceptual framework of antihypertensive medications adherence factors in chapter 3, an attempt was made to identify an effective intervention to improve medication adherence in patients with hypertension.

### Background of the interventions type and effect

Although, several reviews have investigated such interventions and strategies to improve patient medication adherence in chronic diseases conditions (Bennett and Glasziou, 2003, Caro et al., 1999, Chrysant, 2008, Dunber-Jacob et al., 1991, Ebrahim, 1998, Hagstrom et al., 2004, Hardy, 2009, Haynes et al., 2008, Kripalani et al., 2007, McDonald et al., 2002, Morrison et al., 2000, Ogedegbe and Schoenthaler, 2006, Roter et al., 1998), none of these has focused on a patient-centred approach, such as modifying attitudes and beliefs. In addition, all of the trials which have been reviewed, have generally taken a pragmatic one size fits all approaches to enhancing adherence (e.g. information, reminders, self monitoring); most of which have been shown to be ineffective. None of these reviews could recommend any single approach that increased adherence to a particular disease condition such as hypertensive medication, thus improving clinical outcomes.

### Reviews that investigated adherence among hypertensive patients

In some reviews an effort made by authors to discuss medication adherence generally without focusing on a particular disease (Haynes et al., 2008, Kripalani et al., 2007, McDonald et al., 2002). Kripalani et al’s (2007) review included short term RCTs in the review but excluded them from analysis to focus more on chronic disease conditions. There were seven studies that discussed adherence to hypertension medication. In addition, McDonald et al (2002) reviewed the published RCTs for medication adherence in medical and psychiatric conditions for which follow up was over 6 months. The commonest condition studied was hypertension (8 studies). Several reviews conducted to investigate the effectiveness of interventions aimed at enhancing adherence in hypertensive patients. However, these reviews have shown some weaknesses that limited the generalisability of their findings; the searches in three of these reviews were limited to studies indexed only in MEDLINE and only included English language publications (Dunber-Jacob et al., 1991, Ebrahim 1998, Morrison et al., 2000), leading to the review search strategies potentially lacking sensitivity and specificity (Higgins and Green, 2009). In addition, such reviews discussed RCTs which focused on specific types of intervention to enhance adherence to antihypertensive drugs, such as computer generated medication reminders or feedback directed to patients or healthcare providers (Bennett and Glasziou, 2003), and home BP monitoring (Ogedegbe et al., 2006). However, these two reviews did not focus on the effect of intervention on clinical outcomes (BP reduction). Other reviews discussed improving adherence among hypertensive patients by including studies with different designs (both RCT and non-RCT) (Chrysant, 2008, Hardy, 2009).

The only review which evaluated RCT evidence for interventions for antihypertensive drugs is Schroeder et al (2004). They did a brief summary for the quality of included studies instead of doing assessment of risk of bias which could facilitate the interpretation of the results (since the Cochrane risk of bias table had not been developed at that time). Schroeder et al Cochrane review (2004) included all studies found up to 2001. For all these reasons, a new review was needed to update Schroeder et al (2004) to assess the effectiveness of multiple interventions, including behavioural interventions, on adherence in hypertensive patients. New studies have been published so an update is warranted. Schroeder et al’s (2004) Cochrane review was updated. The main contents of the review were based on the Cochrane collaboration's systematic review guidelines (Higgins and Green, 2009) and the revised CONSORT statement (Moher et al., 2010).

## QUESTION FOR THE REVIEW

What is the most effective intervention for improving adherence in people with hypertension?

## OBJECTIVE OF THE REVIEW

In this review, the researcher sought to summarize all randomised controlled trials (RCTs) of interventions to enhance adherence with BP lowering medications.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

Published RCTs to increase adherence to BP lowering medication were included in this review.

### Types of participants

Adults with a diagnosis of essential hypertension (as defined by the authors of the included studies) in a primary care, outpatient or other community setting were the participants of RCTs.

Exclusion criteria:

1. Participants suffering from secondary hypertension.

2. Participants in inpatient care settings i.e. hospitalised.

### Types of interventions

Any intervention designed to enhance medication adherence, including the following:

1. Simplification of dosage regimen interventions.

2. Education of caregivers and patients such as face-to-face oral, written educational material or visual aid, mailed instructional materials.

3. Behavioural:

a) Intervention to support behaviour: such as reminders (e.g. vial caps diaries), regular follow up appointments, social/community and professional support, involvement of allied health professionals (e.g. nurses, pharmacists) and home BP monitoring.

b) Interventions to change behaviours such as: self determination, counselling, consultation, and motivational interviewing.

4. Complex/combined interventions: that included two or more of above interventions.

Control groups or treatment as usual (TAU) groups should either have received no intervention or "usual care" and have similar characteristics as the intervention groups. TAU can include “usual” dosage medication regimes.

Exclusion criteria:

1. Interventions not aimed at enhancing adherence to medication

2. Interventions to enhance medication adherence for other chronic diseases.

3. Intervention not directed to patients (e.g. education of healthcare professionals about adherence).

4. Studies that do not report their results in full (e.g. conference abstracts), where further information (sufficient to make a fair appraisal of the quality and results of a study) was not available from the authors.

### Types of outcome measures

1. Adherence to medication (including any definition of adherence and noting how this was defined and measured in each study).

2. BP change in mm Hg or change in BP control according to the criteria used in each individual RCT. A 'net reduction' of BP refers to the 'net' difference between the changes of BP between baseline and follow-up in the intervention and control group.

3. Change in attitudes and beliefs toward medications.

4. Reporting of major clinical events associated with the consequences of hypertension (angina, myocardial infarction, renal impairment, emergency department visits, and hospitalisation).

5. Cost effective analysis of the intervention

6. Adverse events of the intervention

## METHOD

### Review personnel and roles

Fadwa Alhalaiqa (FA) was the primary author of this review, designed the review method, conducted the analysis of the results, and generated the conclusions. Deema Mahasneh (DM) helped in data collection and extraction. Richard Gray (RG) adjudicated on the inclusion of studies and advised on the interpretation of the results. Katherine Deane (KD) advised on the systematic review methodology, advised on the inclusion of studies, aided in the interpretation of results and conclusions.

### Search methods for identification of studies

#### Electronic searches

**In reporting of literature searches STARLITE(Sta**ndards for **R**eporting **Lite**rature searches) which includes sampling strategy, type of study, approaches, range of years, limits, inclusion and exclusions, terms used, electronic sources was **followed** (Booth, 2006). A comprehensive sampling strategy was used because an attempt to retrieve all relevant studies in a topic area in a conventional systematic review manner was made. The Cochrane Central Register of Controlled Trials (CENTRAL) was searched, and the Hypertension Group Specialised Register (The Cochrane Library 2011, Issue 1), MEDLINE (Ovid, 1966 to June 2011), EMBASE (Ovid, 1988 to June 2011), CINAHL (EbscoH, 1981 to June 2011). The WHO International Clinical Trials Registry Platform Search Portal (to June 2011) was also searched, Current Controlled Trials (to June 2011), and the UK National Research Register (NRR) Archive (to June 2011) for ongoing and recently completed trials. There were no restrictions based on language or publication status.

The subject-specific search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (Lefebvre 2008), and the SIGN trial search strategy in EMBASE. Search strategies for all databases and keywords are shown in Appendix (1).

The search strategy was based on the strategy of Schroeder et al (2004) but due to term changes and additions (behavioural and motivational interviewing interventions), the search was re-run without any date limits.

#### Searching other resources

The references of all retrieved articles were screened to identify additional publications. In addition experts in the field were contacted about other relevant trials. In this review 11 authors were contacted about other relevant trials or unpublished material and obtained responses from 9. Also a total of 25 corresponding authors responded to the original review (Schroeder et al., 2004).

### Data collection and analysis

In each step of the following, any disagreement between investigators was resolved by discussion and when necessary, adjudication by a one of the two project supervisors (RG and KD).

#### Selection of studies

Studies were assessed according to the method delineated in the Cochrane Handbook (Higgins and Green, 2009). Two investigators (FA, DM) assessed lists of citations and abstracts independently. Each investigator indicated whether a citation was potentially relevant (i.e. appeared to meet the inclusion criteria), was clearly not relevant, or gave insufficient information to make a judgement. Differences were resolved by discussion and full paper copies of all potentially relevant citations were obtained. Both investigators assessed copies of all potentially relevant articles independently according to the above criteria. Also both, independently, selected and assessed potentially eligible studies.

#### Data extraction and management

Due to the limited evidence in applying quality scores for individual trials, the researcher presented characteristics in a descriptive format, to provide a more accessible and more objective summary. The data extraction was not repeated for previously identified studies. A risk of bias table was completed; however, most of the data had been previously extracted. Two investigators (FA and DM) used a piloted data extraction form to independently collect the data, which were verified by the third reviewer (KD). Both of them extracted details of study design, methods, patient characteristics, interventions, and outcomes.

#### Assessment of risk of bias in included studies

Two investigators (FA and DM) independently assessed, without masking of the source or authorship of trial reports, various aspects of methodological quality of the included studies, using a modified version of the quality assessment tool based on the Cochrane collaboration handbook (risk of bias table) (Higgins and Green, 2009). An impression of the overall risk of bias, based on allocation, concealment, blinding and the potential affect of incomplete outcome data, of the individual studies was also made.

### Data synthesis

Studies were grouped by intervention type into: 1) Simplification of dosage regimen intervention: it is proposed that this enhances adherence through changing dosage schedules to simplify the regimen, and that this encourages patient to be more compliant with the drug regimen that leads to BP change.

2) Patient education interventions: designed to primarily educate patients by instructional means based on the proposed mechanism of action that patients who understand their condition and its treatment will be more informed and more likely to adhere.

3) Behavioural interventions were designed to influence behaviour shaping (changing), reminders (Nunes et al., 2009), reinforcement desired behaviours (rewarding). These interventions have two proposed mechanism of action; one where positive adherence behaviours are assumed, i.e. that the patient wishes to comply with drug regimen, therefore, through enhancing motivation the patient's ability to take medicines as prescribed will be increased which may have a positive effect on BP control (Haynes et al., 2008). The second mechanism of action is one in which the patient’s adherence behaviours are not assumed. The model is that these interventions aim to modify beliefs/attitudes which then change adherence behaviours which lead to changes in BP (Nunes et al., 2009). Therefore, this category was divided into two sub-groups;

a) Interventions to support adherence behaviours

b) Interventions to change adherence behaviour

4) Combined/complex, interventions included two or more of the preceding categories with multiple phases for introducing interventions to participants.

By using these categories, descriptors and examples, each included study was classified. This classification was reviewed by at least one supervisor, and disagreements were resolved by consensus. The interventions tested in factorial trials were reported through choice separately in the respective group and treated these like individual studies.

## RESULTS

### Description of studies

See Appendix (2) Characteristics of included, excluded, and ongoing studies

#### Results of the search

2119 citations were screened; (see Figure 2) 56 new studies were considered in addition to the 46 trials that were included in the first review, as potentially eligible after screening.



**Figure 2** Process of inclusion

#### Included studies

Sixty two studies were included (24 new studies and 38 studies which were included in the previous review) that met all the predefined criteria, involving a total of 27559 patients and testing 86 different interventions. See Appendix 2 for the summary of the characteristics of included studies, which were conducted between 1975 and 2011. Four trials used a cluster design (Amado Guirado et al., 2011b, Pladevall et al., 2010, Blenkinsopp et al., 2000, Santschi et al., 2008a). Four trials also used a cross over design (Asplund et al., 1984, Christensen et al., 2010a, Detry et al., 1995b, Girvin et al., 1999). Overall, eight trials were long term study (i.e. > 1 year duration). Furthermore, twelve of the included studies were factorial trials.

The majority of trials were performed in the USA (n=30) and Canada (n=12) with the remainder located in Europe (n=18), Thailand (n=1) and South Africa (n=1). Study participants fell into a number of different categories that included patients with:

* Newly diagnosed,
* Established hypertension on medication,
* Controlled or uncontrolled hypertension,
* Mild to moderate essential hypertension,
* Patients who were adherent or non-adherent to their medication regimen or patients who were infrequent attendees at clinic.

Adherence was measured in different ways, including self-report, direct questioning, pill counts, pill calendar (daily doses adherence package), reviewing of automated data files, pharmacy refill adherence calculation, and the medication event monitoring system (MEMS). Various criteria for adherence were used in the different studies. All studies examined both men and women in varying proportions, and the duration of follow up ranged from 6 weeks to 60 months. Two studies included only non-adherent patients at baseline (Burrelle, 1986, Nessman et al., 1980).

#### Excluded studies

From the previous review of Schroeder et al (2004) eight studies were excluded for the following reasons (see Appendix 2 characteristics of excluded studies):

1. No adherence outcome (n=3),

2. Conducted in hospital (n=1),

3. No contemporary control group (n=2),

4. Schroeder et al (2004) was unable to interpret the results (n=1),

5. Study design without reporting any results (n=1).

Twenty nine new trials were also excluded for the following reasons (see Appendix 2 characteristics of excluded studies):

1. No adherence outcome (n=9)

2. Interventions were not directed at adherence (n=5)

3. Not RCT design (n=7)

4. Not directed at hypertensive patients (n=4)

5. Not directed at the patients (training of general practitioners in adherence promoting professional behaviours) (n=1)

6. Non-English copy (n=3).

### Risk of bias in included studies

The methodological quality of included studies was generally poor mostly due to inadequate reporting (see Appendix 2 characteristics of included studies (risk of bias tables), Figure 3 and Figure 4).



**Figure 3** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



**Figure 4** Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Details of the method of randomisation, allocation concealment, assessors and analysts blinding, incomplete data outcome, and selective outcome reporting are presented in the risk of bias table for included studies (Appendix 2 Risk of bias tables). Power calculation, loss to follow up, length of follow up, ethical approval, source of funding and similarity between groups at baseline in demographic characteristics are presented in the characteristics of included studies tables (see Appendix 2). A summary of the results and impressions of the likelihood of bias is presented below. Most of the trials (n= 47:78%) reported their source of funding. More than half of included trials (n=37:61%) reported gaining of ethical approval. Eight studies (12%) reported the presence of an imbalance between groups in terms of baseline characteristics (Pladevall et al., 2010, Gabriel et al., 1977, Green et al., 2008b, Hawkins et al., 1979, Rehder et al., 1980, Rudd et al., 2004, Santschi et al., 2008a, Zarnke et al., 1997). A third of studies (n=25:35%) addressed all these issues (gaining ethical approval, source of funding, no significant differences between groups at base line). Around two thirds of trials (n=37:61%) reported a power calculation, and most of the remaining studies (n=26:39%) appeared too small to detect clinically important differences. However, none of the included studies fulfilled all risk of bias quality criteria.

#### Allocation

The method used to generate the allocation sequence was described in sufficient detail in 25 trials (40%) and the allocation sequence was adequately concealed in only (13:17%) studies.

#### Blinding

The outcome assessors were blind to which intervention a participant received in less than third of included trials (n=18:30%). Four studies (6%) described the measures that were used to blind the researcher from knowledge of group allocation received.

#### Incomplete outcome data

The completeness of outcome data for each main outcome was described in (14:12%) trials. Missing data was imputed using a robust and proper method in a minority of trials (n=14:12%). The losses to follow up were well documented in (49:80%) trials. Around one third of trials (n=17:26%) reported the reasons for the losses of follow-up.

#### Selective reporting

The reports of the study were free of the suggestion of selective outcome reporting in only five trials (9%) and were unclear in (59:91%) studies.

#### Other potential sources of bias

In this review we defined other potential sources of bias as; related to particular research design e.g. cross over (mainly carry over, recall and selection biases), cluster randomised (recruitment and selection bias which may result from lack of concealment) (Schulz et al., 2010) and risks of bias related to early stopping of trial. When we applied the risk of bias assessment for the included RCTs, we found that 49 studies (82%) were free from bias related to a particular design. One study reported that the sponsor terminated the trial because the required number of discontinuations had been observed. During the time that participants were still enrolled, they were contacted by telephone to identify any adverse event and estimate their adherence to the drug under investigation (Hamet et al., 2003). In this study the primary effectiveness measure was patient discontinuation from irbesartan drug over 12 months of treatment for their hypertension. The effect of intervention on patient's adherence was measured by comparing the rate and time to discontinuation between the two groups of the study. Time to discontinuation was defined in this study, as a negative patient response to a telephone follow up question which was asked every month (i.e. are you taking your irbesartan every day?).

### Effects of interventions

It was not possible to do meta-analysis for this review due to a combination of factors including the poor quality of the included trials, high levels of variability in populations, intervention aims, content, intensity, duration; variable and unreliable adherence measures, and variation of adherence definition and outcomes. We felt that statistical pooling of the results was inappropriate. Therefore, a descriptive analysis for included studies is provided. An attempt to report mean change or mean difference in change is made, but if the effect size was not reported in any way, the study author's reports of P values and stated them in the text of our review was accepted.

#### Summary of effect of interventions

Please note that in the following section, the total number of interventions is 86 which were conducted in 62 RCTs. This is because some studies reported the results of factorial trials testing two or more different interventions, which have been evaluated separately.

Twenty four interventions reported an improvement in adherence alone (see Table 4 below), of which 16 also reported no significant difference between groups in BP changes. Adherence improvement combined with BP reduction was reported in 15 interventions. Reduction in BP without an increase in adherence reported in 11 interventions. However, BP as an outcome did not report in 17 interventions. All of these RCTs reported differentiation in the BP assessors (patients, nurses, and pharmacists), instruments and setting (patient's home, clinic, and work site). None of the interventions reported a significant change in attitudes and beliefs. Just three trials did cost analysis of their interventions. Three studies examined major consequences of hypertension but no significant differences between groups were found (Pladevall et al., 2010, Bosworth et al., 2009, Schneider et al., 2008). Finally none of the included trials reported any adverse events from the interventions.

**Table 4,** Summary of Findings

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Category** | **Study** | **N** | **Intervention** | **Adherence results**  **Intervention vs control** | **BP results**  **Intervention vs Control** | **Other results**  **Change attitudes/ Cost/ Major consequences/ Adverse events** | **Adherence measure** |
| **1- Dose simplification** | Andrejak 2000 | 162 | Once daily trandolapril 2mg vs twice daily captopril 25mg | Adherence 94% vs 78% (P < 0.0001) | NR | NR | Pill count and electronic monitoring |
| Girvin 1999 | 27 | Enalapril 20mg once daily vs Enalapril 10mg twice daily | Adherence 92% vs 73 % (P < 0.001). | Net reduction 5.3 mm Hg in SBP and 1.0 mm Hg in DBP (P = 0.068 and 0.086 respectively). | NR | Electronic monitoring |
| Mounier-Veh 1998 | 103 | Amlodipine 5mg once daily vs nifedipine 20mg twice daily | Adherence 93%  vs 75%(P < 0.001). | Net reduction in SBP 0.8 mm Hg and 1.1 mm Hg net increase in DBP (ns, no exact P-value reported) | NR | Electronic monitoring |
| Leenen 1997 | 198 | Amlodipine 5mg daily vs diltiazem SR 60mg twice daily | Adherence 90% vs 82% (P < 0.01). | -Net reduction SBP 6 mm Hg (P < 0.01).Reduction in DBP 1 mm Hg (ns, no exact P-value reported) | NR | Medication event monitoring system |
| Boissel 1996 | 7272 | Nicardipine SR 50 mg twice daily vs nicardipine 20 mg thrice daily | Adherence 82% vs 76% (P < 0.001). | Net reduction in BP 0.2 mm Hg (systolic) and 0.3 mm Hg (diastolic) (ns) | NR | Self report |
| Detry 1995 | 320 | Amlodipine 5mg daily vs nifedipine 20mg twice daily | Adherence 94% vs 76% (P < 0.001). | NR | NR | Pill count and electronic monitoring |
| Burris 1991 | 58 | Transdermal clonidine 0.1mg per day with placebo tablets vs verapamil SR 120mg daily plus transdermal placebo | Adherence 96 - 100% of participants wore the active patch vs 100% the placebo patch.  68-88 % had optimal tablet counts in the verapamil SR group compared to 11-37% in the control group (P-values not reported). | Net reduction SBP 5 mm Hg and 1 mm Hg DBP (P < 0.05) | NR | Pill count and visual assessment |
| Baird 1984 | 389 | Metoprolol 200mg once daily vs metroprolol 100mg twice daily | Adherence: 93% vs 82% (P = 0.009) | 1 mm Hg net reduction in SBP and no reduction DBP (ns) | NR | Pill count and urine test |
| Asplund 1984 | 160 | Pindolol 10mg and clopamide 5mg once daily in one combination tablet versus two tablets | Adherence 41% vs 69% (ns, but no exact P value reported) | Net increases of 2.8 mm Hg systolic and 3.0 mm Hg diastolic (ns, no exact P value reported). | NR | Pills count and self report questionnaire of adherence |
| **2- Patient education** | Amado Guirado 2011 | 996 | Personalised information by trained nurse and written leaflets (information about disease, medication, healthy lifestyle habits). | Adherence measured by Morisky-Green test increased by 10% (95%CI: 5.5-13.6%) in the IG vs 9% (95% CI: 4.9-12.6%) in the CG (P < 0.05).  No significant differences in the adherence measured with other test (pill count and Haynes -Sacket) | - No significant difference in BP | NR | Haynes -Sacket questionnaire of adherence, pills count and MMAS |
| Hunt 2004 | 312 | Providing educational hypertension packets through mail | -There was no significant difference in patient-reported medication compliance (0.35 intervention vs 0.35 control; *P* = ns) | - No significant differences was found in mean BP between two groups (135/77 mmHg vs 137/77 mmHg; *P* = .229). | NR | Self report |
| Marquez-Contr. 1998 | 110 | Group sessions with  information about BP management and postal education (with information on BP and the importance of compliance, sent at months one, three and five) | Adherence 93% vs 69% (P< 0.002) | NR | NR | Pill count |
| Kerr 1985 | 235 | Education sessions | Adherence 81% vs 100% in control group (ns) | - BP increased by 5 mm Hg (ns) | NR | Self report |
| Pierce 1984 | 115 | Education | Good adherers 28%in intervention group vs 24% in the control (ns) | Reduction in BP 83% vs 67% (P< 0.05, effect size unclear) | NR | Pill count and self report |
| Webb 1980 | 123 | Education sessions | Differences in adherence score -0.2 (P >0.10) | Net reduction in BP 3.3 mm Hg (P > 0.1) | NR | Pill count |
| Kirscht 1977 | 400 | Written educational material | Percentage of maximum adherence score 91% vs 90% (ns) | NR | NR | Self report |
| Sackett 1975 | 230 | Educational programme | Adherence 50% vs 56% in control (ns) | BP reduction ns | NR | Pill count |
| **3- a Intervention to support behaviour**  **1- Reminders** | Christensen 2010 | 398 | Electronic monitoring of drug adherence | Adherence rate increase 91% vs 85%. Improved self reported compliance by 6% | Differences between groups was not significant in BP. | NR | Self report |
|  | Santschi 2008 | 68 | Electronic monitoring of drug adherence | Median taking adherence of 96%(range ; 79-100%) (P <0.05). | -SBP reduced by 3.9 mm Hg (P < 0.05)  -DBP differences between groups was not significant. The difference decreased with time. | NR | MEMS |
| Schneider 2008 | 85 | Pill calendar | Adherence 80% vs 66% (P = 0.01) | -DBP was 2.6 mm Hg lower at 6 months and 5.7 mm Hg lower at 12 months (ns)  - No significant difference in any of long term concequences measures (angina, MI, renal impairment, emergency department visit, hospitalisation) | Clinical outcomes differences (ns) | Medication refill |
| Barrios 2007 | 1523 | Lercandipine providing through electronic monitoring (MEMS) | Adherence 92% vs 91% (ns) | BP net reduction ns | NR | MEMS and pill count |
| Wetzels 2007 | 258 | Using MEMS | Adherers 81 patients vs 77 patients (ns) | BP decreased in 17% vs 11% of patients (ns) | NR | MEMS and drug refill |
| Da Costa 2005 | 71 | Provided a card reminder: alarm card set up to peep every day at the same time for a period of 84 days. | In the intervention group the adherence rate remained consistent through the study duration 97%. In control group adherence dropped from 95% at the beginning of the study to 87% at the end (P = 0.01). | BP reduction ns | NR | Pill count |
| Skaer 1993 | 304 | Postal reminder | Increased medication possession ratio by 8% (P < 0.05) | NR | NR | Prescription record |
| Skaer 1993 | 304 | Special unit (provided  unit-of-use packaging with each prescription refill request) | Increased medication possession ratio by 11% (P < 0.05) | NR | NR | Prescription record |
| McKenney 1992 | 70 | Electronic medication aid cap with recording card | Adherence 95% vs 78% (P = 0.0002) | Net SBP reduction 4.8mm Hg (P = 0.0006) and DBP 8.6 mm Hg (P = 0.001) | NR | Pill count |
| Becker 1986 | 180 | Special unit dose reminder packaging | Adherence 84% vs 75% (ns) | Net BP reduction 0.2 mm Hg (ns) | NR | Pill count and self report |
| Rehder 1980 | 150 | Special medication container | Adherence 94% vs 88% (ns) | NR | NR | Pill count |
| Gabriel 1977 | 79 | Daily drug reminder chart with pharmacist supervision | Adherence 82% vs 70% (P = 0.002). | They reported significant correlation between positives attitudes toward the chart and higher compliance but no P value reported. | NR | Pill count and self report |
| Eshelman 1976 | 100 | Compliance dispenser versus usual medication bottle | Adherence 63% vs 61% (ns) | NR | NR | Pills count and self report questionnaire of adherence |
| **2- Change follow up period** | Birtwhistle 2004 | 609 | Follow up every 3 months versus 6 months | Adherence to treatment was equivalent between groups (ns) | BP measurement was equivalent between groups and the difference (ns) | NR | Pills count and self report questionnaire of adherence |
| **3- Monitoring of BP** | Bosworth 2009 | 636 | Home BP monitoring vs TAU | Adherence ns | BP control increased 8% (CI95%: 2%- 20%) and SBP reduced by -0.6 mm Hg (CI: -3.6-2.3 mm Hg) (P = 0.010) | Cost of intervention ($90). No significant differences between groups in major consequences.  NR adverse events | Self report |
| Marquez-Contreras 2006 | 250 | Home BP monitoring vs TAU | Adherence 92% vs 74% (P = 0.0001) | - Fall in DBP 12.8-/+9.9 mm Hg (P < .05).  - SBP ns | NR | MEMS |
| Zarnke 1997 | 31 | Home blood pressure monitoring vs TAU | 0.3 doses missed /subject /week vs 0.4 in the control (ns) | Net BP reduction 2.9 mm Hg (P = 0.039) | NR | Self reported |
| Kerr 1985 | 235 | Self monitoring of BP vs TAU | Adherence 84% vs 100% in control group (ns) | - BP increased by 1 mm Hg (ns) | NR | Self reported |
| Pierce 1984 | 115 | Self monitoring of BP vs TAU | Adherers 30% vs 24% (ns) | 74% had BP reduction vs 78% (ns) | NR | Pill count and self reported |
| Johnson 1978 | 204 | Self monitoring of BP vs TAU | Adherence increased 12% vs 1% (ns) | DBP reduction 2 mm Hg (ns) | NR | Pill count and interview |
| Kirscht 1977 | 400 | Self monitoring of BP vs TAU | Adherence 94% vs 94% (ns) | NR | NR | Self report questionnaire |
| **4- Providing support** | Marquez- Contreras 2005 | 636 | Telephone intervention group done by nurses; to reinforce compliance and remind the subjects of the scheduled visits vs TAU. | Compliers 96% (P = 0.0001) | BP controlled subjects 63.3% (P = < 0.05).BP reduction: SBP(30-+10 mm Hg) and DBP , 18-+46.7mm Hg (P = 0.0001) | NR | Pill count |
| Morisky 1985 | 193 | Family member support vs TAU. | Adherent 53% vs 40% (P < 0.05) | BP control 75% vs 50% (P < 0.05) | NR | Self report |
| Morisky 1985 | 193 | Small group training to reinforcement of medication taking behaviour vs TAU. | Adherence 40% vs 40% (ns) | BP control 46% vs 50% (ns) | NR | Self report |
| Johnson 1978 | 204 | Monthly home visit vs TAU. | Adherence increased by 10% vs 1% (ns) | DBP net reduction 2mm Hg (ns) | NR | Interview and pills count |
| Kirscht 1977 | 400 | Nurse phone call vs TAU. | Adherence 96% vs 91% (ns) | NR | NR | Self report questionnaire of adherence |
| Kirscht 1977 | 400 | Social support vs TAU. | Adherence improved 98% vs 93% P < 0.05 | NR | NR | Self report |
| **3.b. Interventions to change behaviour**  **1- Motivational interviewing** | Alhalaiqa 2010 | 136 | Adherence therapy (motivational interviewing and cognitive therapy) vs TAU. | Adherence was improved in the AT group by 37% at 11 weeks (97% vs 70%) | Reduction in SBP by -23 mm Hg (95% CI: -25.9, -20.4) and DBP by -15.2 mm Hg (95% CI: -17.6, -12.8) compared to TAU. | The BMQ scores showed that beliefs and attitudes about medications in the AT group moved away from believing that medications are intrinsically harmful (G-H -5.7) and towards beliefs in the benefits of the medications (G-B 2.7) with little or no change in attitudes in control group over the study period.  -cost of delivery of intervention£130.  No adverse events  NR major consequences | Pill count and BMQ |
| Ogedegbe 2008 | 190 | Motivational interviewing techniques vs TAU. | Steady maintenance of medication adherence over 12 months 57%, compared to a significant decline noted in UC group 43%, P = 0.027). | SBP and DBP the difference between group was -6.1 mm Hg (P = 0.065) and -1.4 mm Hg (P = 0.464) (ns) | NR | MEMS |
| **2- Counselling/ consultation** | Schroeder 2005 | 245 | Nurses consultation vs TAU. | Compliance was high (91+\_16%) (95+\_8%) (ns).Intervention had not had effect on timing compliance at follow up. | There was no difference at follow up in SBP (-2.7 mm Hg; 95%CI-7.2 to 1.8) and DBP (0.2mm Hg; 95% CI-1.9 to 2.3). | Cost of the primary care /consultation£6.60 vs £5.08 for usual care | MEMS |
| Rudd 2004 | 150 | Counselling vs TAU. | Adherence rate 81% vs 69% (P = 0.03). | SBP fell by 14.2 mm Hg (P < .01). DBP fell by 6.5 mm Hg ( P < .05) | NR | Electronic drug event monitoring |
| Friedman 1996 | 267 | Telephone linked computer counselling vs TAU. | Adherence 18% vs 12% (P = 0.03). | Net reduction SBP 4.7 mm Hg (P = 0.85) and DBP 4.4 mm Hg (P = 0.09)(ns) | NR | Pill count |
| Park 1996 | 64 | Counselling vs TAU. | Adherence 87% vs 89% in the control group (ns) | NR | NR | Pills count |
| Morisky 1985 | 193 | Counselling vs TAU. | Adherence 36% vs 41% (ns) | BP control 54% vs 50% (ns) | NR | Self report |
| Rehder 1980 | 150 | Counselling vs TAU. | Adherence 90% vs 88% (ns) | NR | NR | Pill count |
| Webb 1980 | 123 | Nurse counselling vs TAU. | Differences in adherence score plus 0.2 (P > 0.10) (ns) | Net reduction in BP (ns) 2.3 mm Hg (P > 0.1) | NR | Pill count |
| **3- Self determination** | Bosworth 2009 | 636 | Behavioural self management included perceived risk for hypertension, memory, literacy, social support, and patient’s relationships with their health care providers, and side effect of anti-hypertension medication and modifying lifestyle vs TAU.. | Adherence ns | Differences in SBP - 0.6 mm Hg (CI: 95% : -3.6- to 2.3 mm Hg) | Cost of intervention ($345). NR adverse event, they reported ns difference between groups in major consequences of hypertension over 24 months, | Self report |
| Nessman 1980 | 52 | Nurse and psychologist teaching self-determination vs TAU. | Compliant for 5 out of seven weeks vs 3weeks (P < 0.001). | Reduction in SBP 6 mm Hg (P < 0.05). | NR | Pill count |
| **4- Complex/ combined intervention** | Morgado 2011 | 197 | Counselling and education vs TAU. | Adherence higher in IG 75% vs 58% (P= 0.012). | BP control was higher in IG (P = 0.005).SBP lowered by -6.8 (P = 0.006) and DBP -2.9 mm Hg (P = 0.02). | NR | MEMS |
| Pladevall 2010 | 935 | Motivational interviewing and educational information vs TAU. | Intervention group more likely to be adherent (odd ratio 1.91 (95% CI: 1.19-3.05) than CG at 6 months (P < 0.05). | - IG were less likely to have uncontrolled SBP (odd ratio 0.62 (95% CI 0.50-0.78) (P < 0.05). | NR of attitudes change and cost of intervention.  -After 5 years of follow up. 153 patients had at least 1 of the composite cardiovascular events: 67 (16%) in the IG and 86 (19%) in the CG (ns). | MEMS |
| Bosworth 2009 | 636 | Home BP measurement and behavioural self management vs TAU. | Adherence ns | SBP lowered by -3.9 (P = 0.010) and DBP -2.2 mm Hg (P = 0.009) | Major consequences of hypertension ns differences.  Cost of combined intervention ($416) | Self report |
|
| Rinfret 2009 | 223 | Educational booklet, digital home BP monitor, log book and telephone linked IT management support program vs TAU. | Adherence improved 95% compare to 91% (P = 0.07). | BP control in intervention group greater than control for both SBP (-11.9 versus -7.1 mmHg P <0.001), DBP (-6.6 versus -4.5 mm Hg P =0.007). | NR | MEMS and pharmacy refill |
| Green 2008 | 778 | Home BP monitoring and secure patient Web site training plus pharmacist care management delivered through Web communications vs TAU. | Adherence 67% vs 69% (P = 0.77) (ns) | Reduction SBP (-13.2 mm Hg P = .001) and DBP (-4.6 mm Hg P = .001) | NR | Reviewing of automated data base files |
| Green 2008 | 778 | Home BP monitoring and secure patient Web site training vs TAU. | Adherence ns | BP reduction ns | NR | Reviewing of automated data base files |
| Hunt 2008 | 233 | Participation of pharmacy practitioners in the hypertension management vs TAU. | Adherence 67% vs 69% (ns) | SBP decreased by 6 mm Hg (P = 0.007) and DBP by 3 mm Hg (P= 0.002)  -62% achieved target vs 44% (P = 0.003). | NR | Self report |
| Bosworth 2005 | 588 | Tailored intervention (nurses answer the patients questions related to their hypertension which focus on; perceived risk of hypertension, memory, literacy, social support, patient's relation with health care providers, drug's side effects, pill refill, missed appointment and health behaviours) bimonthly for 2 years vs TAU.. | Adherence 46% vs 34% were adherent at follow up (P = 0*.*08). | NR | NR | Self report |
| Marquez- Contreras 2005 | 636 | Mail intervention group (MIG): (health education about hypertension included information about hypertension; definition, diagnosis, signs and symptoms, reminding patients with taking drugs...etc) vs TAU. | -Compliers 91% vs 69% (P = 0.0001) | - BP controlled subjects 61.3% P < 0.05  - Reduction in SBP and DBP ns | NR | Pill count |
| Sookaneknun 2004 | 235 | Pharmacists involvement in patient's care vs TAU. | Better adherence (P = 0.014) 70 patients in treatment group and 60 patients in control considered adherent. | Reduction in both SBP and DBP than CG (P = 0.037, 0.027, respectively) | NR | Pill count and interview |
| Hamet 2003 | 4864 | Reminders, counselling, education vs TAU. | - Adherence rate was 75% in both groups- No significant differences in the duration of irbesartan compliance between the treatment groups (23% vs 24% ) | NR | NR | Self report |
| Vivan 2002 | 56 | Pharmacists managed care intervention vs TAU. | Adherence (ns) differences | Mean changes in SBP from baseline for the intervention and control groups were -18.4 (95%CI-26.3,-10.5) and -3.98 (95%CI-11.83.79) respectively (P = 0.01). the mean change in DBP -12.38 (95%CI -16.49,-8.28) and 2.54 (95%CI, -149, 6.57) respectively with P = 0.001) | NR | Self report and drug refill |
| Blenkinsopp 2000 | 180 | Structured brief questioning protocol on medication problems, including advice, information and referral to general practitioner by pharmacists three times at two-month intervals vs TAU.. | Adherence: 62% vs 50% (P < 0.05) | BP controlled 36% vs 17% (P < 0.05) | NR | self report |
| Mehos 2000 | 41 | Home BP measurement, diary, instruction to measure blood pressure, information on hypertension and risk factor with subsequent evaluation vs TAU. | Adherence 82% vs 89% in the control group (P = 0.29). | BP net reduction 10.1 mm Hg systolic (P = 0.069) and 6.7 mm Hg diastolic (P = 0.02) | NR | Prescription refill data |
| Marquez-Contr. 1998 | 110 | Group sessions with information about blood pressure management and postal education vs TAU. | Adherence 93% vs 69% P < 0.002 | NR | NR | Pill count |
| Solomon 1998 | 133 | Patient centred pharmaceutical care vs TAU. | Better compliance score 0.23 vs 0.61 (P < 0.05) | Net SBP reduction 6.9 mm Hg ( P < 0.05)  -DBP -0.6 mm Hg (ns) | NR | Pill count and self report |
| Hamilton 1993 | 34 | Postcard reminder, nurse-led educational appointment and follow-up phone call vs TAU. | Adherence score 28 vs 25 ( P = 0.12) | Net reduction SPB 17.3 mm Hg (P = 0.03), DBP 4.7 mm Hg (P = 0.22) | NR | Self report |
| Skaer 1993 | 304 | Special unit with postal reminder vs TAU. | Increased medication possession ratio 23% (P < 0.05) | NR | NR | Prescription record |
| Saunders 1991 | 224 | Written reminders, patient-held records, home visits vs TAU. | Adherence 68% vs 37% (P = 0.009). | Reduction DBP 7 mmHg (ns, no exact P-value reported) | NR | Pill count |
| Scalr 1991 | 344 | Prescription refill pack containing drugs and educational material vs TAU. | Adherence 34% of newly diagnosed and 41% of established hypertensive patients had higher medication possession ratio (P < 0.05) | NR | NR | Pill count |
| Burrelle 1986 | 16 | Home visits, education, special dosing devices vs TAU. | Adherence 92% vs 71% (P < 0.0001). | Net reduction in SBP 7 mm Hg and net increase of 7 mm Hg in DBP(P > 0.05). | NR | Pill count and self report |
| Kerr 1985 | 235 | Education and self-monitoring vs TAU. | Adherence 100% vs 100% in control (ns) | BP zero reduction (ns) | NR | Self report questionnaire of adherence |
| Pierce 1984 | 115 | Education and self monitoring vs TAU. | Adherence 26% vs 24% (ns) | 74% had BP reduction vs 78% (ns) | NR | Pill count and self report |
| Logan 1983 | 194 | Nurse led care vs TAU. | Adherence 55% vs 56% in the control group (ns). | Net reduction in DBP 3 mm Hg (ns). | Cost for intervention was $53.67 vs $32.65 for control group | Pill count |
| Rehder 1980 | 150 | Counselling and special medication container vs TAU. | Adherence 99% vs 88% (ns) | NR | NR | Pill count |
| Hawkins 1979 | 1148 | Post-diagnostic management of patients with hypertension and diabetes by clinical pharmacist vs TAU | Adherence 61% vs 53% (P < 0.7), diuretic plus methyldopa: 85% adherent in intervention group vs 65% among controls (P = 0.2). | Net reduction in BP 4 mm Hg systolic(P <0.001)and zero reduction in diastolic BP (ns) | NR | Reviewing of  prescription record |
| Logan 1979 | 457 | Nurse-led work-site care vs TAU | Adherence 67% vs 49% (P < 0.005). | Reduction in DBP 4 mm Hg (P < 0.001) | NR | Pill count |
| Johnson 1978 | 204 | Monthly home visits and self BP monitoring vs TAU | Adherence increased 10% vs 1% (ns) | DBP net reduction 1 mm Hg (ns) | NR | Interview and pills count |
| Haynes 1976 | 39 | Self-measurement of blood pressure, medication and blood pressure charting, tailoring to daily routines, fortnightly review and rewards (financial and praise) vs TAU | Adherence 66% vs 43% (P < 0.025). | Net reduction in DBP 4 mm Hg (P = 0.12) | NR | Pill count |
| Sackett 1975 | 230 | Doctor led work site care with educational programme vs TAU | Adherence 54% vs 51% (ns) | Net Reduction in BP ns | NR | Pill count |

Abbreviations: N: Number of participants, vs: versus, BP: Blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, NR: not reported, ns: not significant, TAU: Treatment as usual

The shadowed cell has significant results

Major consequences (of hypertension) e.g. angina, myocardial infarction, renal impairment, emergency department visits and hospitalisation

N: Number of participants. vs: versus

**1) Simplification of dosing regimens (nine interventions)**

a) Description

No new studies were found for this updated review. However, the previous reviews had identified nine studies (see Table 4). All these trials were assessed to be poor quality (see Figure 3 and Figure 4). Interventions evaluated in this category included once daily versus twice daily preparations of metoprolol, amlodipine, or enalapril, however, all these drugs were in differing classes of antihypertensive drugs (Keith and Maziar, 2002, Lim, 2007, Wong, 2007). One study tested transdermal clonidine plus placebo tablets versus verapamil and a transdermal placebo (Burris et al., 1991). Asplund and colleagues (1984) compared pindolol and clopamide combined in one tablet versus both drugs in separate tablets. Five studies used objective outcome measurement (MEMS) (Andrejak et al., 2000, Girvin et al., 1999, Mounier-Vehier et al., 1998, Leenen et al., 1997a, Detry et al., 1995b), and five trials used pill counting (Andrejak et al., 2000, Asplund et al., 1984, Detry et al., 1995a, Burris et al., 1991, Baird et al., 1984).

b) Effect of intervention

Simplifying dosing regimens improved adherence in eight trials (see Table 4); seven studies improved adherence alone (ranging from 8% to 20% improvement) (Mounier-Vehier et al., 1998, Andrejak et al., 2000, Baird et al., 1984, Boissel et al., 1996, Detry et al., 1995b, Girvin et al., 1999, Leenen et al., 1997b).One study showed an increase in adherence (90% vs 82%, P < 0.01) together with a reduction in SBP of 6 mm Hg (P < 0.01) (Leenen et al., 1997). The changes in DBP in this study were not significant. Seven trials also reported BP changes with one study showing significant BP reduction (SBP 5 mm Hg and 1 mm Hg DBP (P < 0.05) with no effect on adherence (Burris et al., 1991). One study showed no effect either on adherence or BP (Asplund et al., 1984). Finally, none of these nine trials reported changes in attitudes toward medication, cost analysis, major consequences of hypertension and adverse events.

**2) Patient education (eight interventions)**

a) Description

All these studies were assessed as being poor quality trials (two new studies and six trials that had previously been found by Schroeder et al (2004)) (see Figure 3 and Figure 4). Educational interventions in the included studies consisted of: an educational programme via slides, audiotape and booklet (Sackett et al., 1975), group education (Marquez-Contreras et al., 1998, Pierce et al., 1984, Webb, 1980), written educational material (Kirscht et al., 1977), and education via visual aids, lecture, discussion and knowledge test (Kerr, 1985), providing educational hypertension packets through the mail about hypertension, lifestyle modification, drug adherence and BP control (Hunt et al., 2004), providing personalised information delivered by a trained nurse and written leaflets (covering information about disease, medication, healthy lifestyle habits) (Amado Guirado et al., 2011a). Adherence measures were; self report (n=6) (Amado Guirado et al., 2011a, Hunt et al., 2004, Kerr, 1985, Pierce et al., 1984, Webb, 1980, Kirscht et al., 1977), and pill count (n=5) (Amado Guirado et al., 2011a, Sackett et al., 1975, Webb, 1980, Pierce et al., 1984, Marquez Contreras et al., 1998) (see Table 4).

b) Effect of intervention

Only two interventions showed significant improved adherence but with no associated effect on BP; adherence improved 93% vs 69%, P < 0.002 when measured by pill count, in the intervention group compared to the control group (Marquez Contreras et al., 1998), and increased by 10% vs 9% when measured by MMAS (Amado Guirado et al., 2011a). Six interventions did not have a significant effect on adherence. Six interventions also had no significant effect on BP, and one intervention did not report BP as an outcome (see Table 4). None of these interventions reported changes in attitudes toward medication, cost analysis, major consequences of hypertension or adverse events.

**3) Behavioural intervention:**

This type of interventions is classified into A and B categories as follows:

A) Interventions supporting adherence behaviours

The different types of interventions that aimed to support adherence behaviour included reminders, reduced time between clinic appointments, community/social/professional support, and self monitoring of BP at home

a) Description

1. Reminders (13 interventions):

Six new studies were found in addition to the six trials that were previously included in Schroeder’s review (2004). These 12 trials were assessed to be poor quality due to the inadequate reporting resulting in an unknown level of bias (see Figure 3 and Figure 4). Reminder interventions included; special compliance dispensers (Christensen et al., 2010b, Barrios et al., 2007a, Becker et al., 1986, Eshelman and Fitzloff, 1976, McKenney et al., 1992, Rehder et al., 1980, Santschi et al., 2008a, Skaer et al., 1993, Wetzels et al., 2007); drug reminder charts (Gabriel et al., 1977), card reminders (Da Costa et al., 2005) pill calendar (Schneider et al., 2008), and postal reminders (Skaer et al., 1993). Adherence measured by; pill counting (n=7) (Barrios et al., 2007b, Da Costa et al., 2005, McKenney et al., 1992, Rehder et al., 1980, Gabriel et al., 1977, Eshelman and Fitzloff, 1976), self report(n=4) (Eshelman and Fitzloff, 1976, Gabriel et al., 1977, Becker et al., 1986, Christensen et al., 2010b), MEMS (n=3) (Barrios et al., 2007a, Santschi et al., 2008b, Wetzels et al., 2007), and medication refill (n=3) (Wetzels et al., 2007, Skaer et al., 1993, Schneider et al., 2008) (see Table 4).

2. Reducing follow up period between clinic appointments (one intervention): One new study was found and assessed as being of poor quality (Birtwhistle et al., 2004) (see Figure 3 and Figure 4). It reduced the period between clinic appointments from 6 to 3 months and measured adherence by self report and pill counting.

3. Community/social/professional support (six interventions): Four studies were found and assessed to be poor quality (one new trial and three studies from the previous review) (see Figure 3 and Figure 4). This type of intervention included; monthly home visits (Johnson et al., 1978), nurse phone calls (Kirscht et al., 1977, Marquez Contreras et al., 2005), social support (Morisky et al., 1985, Kirscht et al., 1977), and small group training of patients (Morisky et al., 1985).

Adherence measured by; pill counting (n=2) (Marquez Contreras et al., 2005, Johnson et al., 1978), and self report (n=3) (Morisky et al., 1985, Johnson et al., 1978, Kirscht et al., 1977).

4. Self monitoring of BP at home (seven interventions): Seven trials were found and assessed for being poor quality reporting (two new trials and five studies from old review) (see Figure 3 and Figure 4) (Bosworth et al., 2009, Marquez-Contreras et al., 2006, Zarnke et al., 1997, Kerr, 1985, Kirscht et al., 1977, Johnson et al., 1978, Pierce et al., 1984). Adherence measured by self reports (n=6) (Kerr, 1985, Zarnke et al., 1997, Bosworth et al., 2009, Johnson et al., 1978, Pierce et al., 1984, Kirscht et al., 1977), pill counts (n=2) (Johnson et al., 1978, Pierce et al., 1984), and MEMS (n=1) (Márquez-Contreras et al., 2006).

b) Effect of interventions that aimed to support adherence behaviour

1) Reminders: Eight interventions had significant effects (see Table 4); six of them significantly improved adherence alone (range 80-87 % compared to 66-87 % in TAU groups) (Skaer et al., 1993, Schneider et al., 2008, Da Costa et al., 2005, Gabriel et al., 1977, Christensen et al., 2010b), and two improved adherence (96- 95% compared to 67% - 78% ) with an associated significant BP reduction (SBP 3.9- 4.8 mm Hg/ DBP 8.6 mm Hg) (Santschi et al., 2008a, McKenney et al., 1992). Five interventions had no effect on adherence (see Table 4) (Barrios, et al., 2007, Becker, et al., 1986, Eshelman and Fitzloff, 1976, Rehder et al., 1980, Wetzels et al., 2007); seven interventions had no effect on BP and four did not measure BP as an outcome. None of these eight interventions measured change in attitude, cost analysis, major consequences of hypertension and adverse events (see Table 4).

2) Reducing the follow up period between clinic appointments: this intervention showed no effect on adherence and BP (Birtwhistle et al., 2004). Also it did not report change in attitudes, cost effective analysis, major consequences of hypertension or adverse events (see Table 4).

3) Community/social/professional support: Three interventions showed significant effects (see Table 4); one intervention significantly improved adherence alone (98% compared to 93%) (Kirscht et al., 1977), two interventions improved adherence (53%-96.2% compared to 0-40%) with associated significant BP reduction (SBP 30+\_10/18\_+46.7 mm Hg) or BP control ( mean BP < 140/90 mm Hg) (Morisky et al., 1985, Marquez Contreras et al., 2005). One study did not measure BP as an outcome (Kirscht et al., 1977). Three interventions had no significant effect either on adherence or BP. Finally, none of these interventions measured change in attitude, cost effective analysis, major consequences of hypertension or adverse events of the intervention (see Table 4).

4) Self monitoring of BP at home: six interventions failed to have any effect on adherence (see Table 4) (Bosworth et al., 2009; Pierce et al,. 1984, Johnson et al., 1978, Kerr, 1985, Kirscht et al., 1977, Zarnke et al., 1997). One intervention significantly improved adherence (92% compared to 74% in control group. P = 0.0001, with an associated significant fall in DBP, however, the observed fall in SBP was not significant (Marquez-Contreras et al., 2006). Two interventions significantly reduced BP (net reduction 2.9 mm Hg) with no significant effect on adherence (Bosworth et al., 2009, Zarnke et al., 1997). Just one intervention did not measure BP as an outcome (Kirscht et al., 1977), and the reminded interventions had no significant effect on adherence and BP. One intervention did cost analysis of the intervention and reported no significant difference between groups in major consequences of hypertension over 24 months (Bosworth et al., 2009).The remaining six interventions did not measure costs or consequences and none of these interventions reported adverse events (see Table 4).

In general, interventions that supported adherence behaviours increased adherence level in 12 of 27 interventions. Five of them improved adherence with an associated BP reduction. One study estimated the cost of the home BP monitoring intervention to be ($90) and the consequences of hypertension over 24 months did not differ significantly (Bosworth et al., 2009). None of the interventions measured adverse events.

B) Interventions that aim to change/modify adherence behaviours (ten interventions)

The different types of interventions that aimed to change adherence behaviour included motivational interviewing, counselling or consultation, and self determination:

a) Description

We found ten trials (four new studies and six trials from the previous review). Eight trials were assessed as being poor quality (see Figure 3 and Figure 4). Two trials were assessed as being good quality, however, they did not report sufficient details about blinding of the outcome assessors and analyst (Bosworth et al., 2009, Ogedegbe et al., 2008) (see Figure 3 and Figure 4). In this category, we included interventions such as teaching on self-determination (Bosworth et al., 2009, Nessman et al., 1980), counselling (Morisky et al., 1985, Park et al., 1996, Rehder et al., 1980, Rudd et al., 2004, Webb, 1980), telephone-linked computer counselling (an interactive computer based telecommunications system that converses with patients in their homes between office visits to their physicians) (Friedman et al., 1996), nursing consultation / counselling (Schroeder et al., 2005), and motivational interviewing intervention (Ogedegbe et al., 2008). Adherence was measured by; self report (n=2) (Bosworth et al., 2009, Morisky et al., 1985), MEMS (n=3) (Ogedegbe et al., 2008, Rudd et al., 2004, Schroeder et al., 2005), and pill count (n=5) (see Table 4).

b) Effect of interventions that aimed to change adherence behaviour

Four interventions had a significant effect (see Table 4); two interventions improved adherence with no significant effect on BP; Friedman et al (1996) increased absolute adherence by 18% compared to 12% in TAU (Friedman et al., 1996), whilst in Ogedegbe et al (2008) trial the intervention group maintained adherence at 57% over 12 months compared to the control group whose adherence declined by 14% over the same period. Two other interventions improved adherence level (range from 57% to 81% compared to 43% to 67% in TAU) with an associated reduction in BP (range SBP 6-14 mm Hg / DBP 1-6 mm Hg) (Nessman et al., 1980, Rudd et al., 2004). Six interventions showed no effect on adherence; four of them had also shown no significant reduction in BP and two of them did not measure BP as an outcome. Cost analysis was done for two interventions (Schroeder et al., 2005, Bosworth et al., 2009) (see Table 4).Bosworth et al (2009) estimated the cost of behavioural intervention to be $345. Whilst Schroeder et al (2005) estimated the cost of each consultation to be £6.60 compared to £5.08 for TAU. None of these ten interventions measured changes in attitudes, major consequences of hypertension or adverse events.

**4. Complex/combined interventions (30 interventions)**

a) Description

Nineteen studies were identified in the previous review and 12 additional trials were found for this update; three of them were assessed as being good quality studies, however, two of them did not report sufficient information about the process of maintaining binding of outcome assessors and analyst (Green et al., 2008a, Bosworth et al., 2009), and one did not provide adequate information about allocation concealment (Rinfret et al., 2009) The remaining 19 trials were assessed also as being poor quality (see Figure 3 and Figure 4).

The interventions in this category consisted of complex combined interventions or structured hypertension management regimens (see Appendix 2 table of included studies for further details). There were different types of complex/combined interventions (see Table 4). Adherence was measured by MEMS (n=3) (Rinfret et al., 2009, Pladevall et al., 2010, Morgado et al., 2011), reviewing database and drug refill (n=5) (Hawkins et al., 1979, Skaer et al., 1993, Mehos et al., 2000, Vivian, 2002, Green et al., 2008a), self report (n=11) and pill count (n=13) (see Table 4).

b) Effect of the interventions

Thirteen interventions showed significant increase adherence; seven interventions improved adherence (ranging 66% - 93% vs 34% - 71%) (Haynes et al., 1976, Burrelle, 1986, Saunders et al., 1991, Sclar et al., 1991, Skaer et al., 1993, Marquez Contreras et al., 2005, Marquez-Contreras et al., 1998), Six interventions improved adherence (ranging from 62% - 74.5% adherence in the intervention groups vs 49% - 57.5% in the control groups) along with an associated significant reduction in BP ((reductions in BP in the intervention group ranging from SBP 4-7 mm Hg, DBP 3 -4 mm Hg greater than the control group). The complex interventions that demonstrated these improvements were varied in character and duration. Four of the interventions involved pharmacists providing care and education; Morgado et al (2011) provided a pharmacist counselling to solve patients practical problems and educational materials over 9 months follow up, the Sookaneknun et al (2004) study provided pharmacist involvement in patient hypertension management for six months, in Blenkinsopp (2000) the pharmacists' explored issues related to medication taking, provided advice, information, and referral to general practitioner, and Solomon et al (1998) provided a pharmaceutical care model led by a pharmacist over a six month follow up period. The other two interventions involved nurses or family support; Logan et al (1979), provided nurse led work site intervention for six months (through monitoring, advising, and referral). Pladevall et al (2010) provided family member support, motivational interviewing and educational information, over 39 months. Eighteen interventions failed to improve adherence. Eight interventions reported a significant BP reduction change in BP in the intervention group (ranging from 4-13 mm Hg for SBP and 2-7 mm Hg for DBP more than the control group) without any significant effect on adherence (see Table 4); six interventions did not measure BP as an outcome. None of these 30 interventions measured changes in attitudes toward medication; two of them reported major consequences of hypertension but no significant differences between the groups were found at 24 and 39 months (Pladevall et al., 2010, Bosworth et al., 2009). Just two studies did the cost analysis of the intervention (Logan et al., 1983a, Bosworth et al., 2009); Bosworth et al (2009) estimated the cost of combined intervention (behavioural and BP monitoring) to be $416 but the cost of TAU was not reported. Whilst Logan et al (1983a) reported the cost of occupations health nurse intervention to be $229.09 compared to $148.91 cost of TAU (see Table 4).

## DISCUSSION

### Summary of main results

In this updated systematic review we found RCTs that evaluated a number of strategies to improve adherence to BP lowering medication, including simplification of dosing regimens, patient education, behavioural interventions as well as complex/combined interventions.

The previous review identified nine interventions of dose simplification in a total 8689 of patients. It was not possible to add any more studies to this subset. Most (8/9) interventions improved adherence (ranging from 8-20% improvement) but with no associated significant effect on BP. It is unclear why the improvements in adherence were not matched by reductions in BP. It may be that there is a minimal adherence threshold that must be exceeded before clinical effects are demonstrated. Just one study showed a combined effect on both adherence (8% improvement) and BP (Leenen et al., 1997a). The SBP reduction in this study was clinically significant (6 mm Hg). None of the studies examined were of good quality so the positive results should be regarded with caution as poor quality studies at risk of bias tend to over-estimate effect sizes (Juni et al., 2001, Moher et al., 2010).

We identified eight educational interventions in a total 2511 patients. Two interventions (n=2,1106 patients) reported improvement in adherence (10-24%) with no others significant effects (Amado Guirado et al., 2011, Marquez-Contreras et al., 1998). It is possible the effects of Marquez-Contreras, et al (1998) intervention may have resulted from reminding patients to take medication since; the postal education was provided frequently at one, three, and five months rather than just the specific educational content of postal package (Marquez-Contreras et al., 1998).Also none of the studies examined were of good quality so the positive results should be regarded with caution.

Twenty eight interventions were found that aimed to support behaviours in a total of 3590 patients. Around half of the interventions (n=12:2858 patients) improved adherence (ranging from 53% to 96%). Only five of these interventions that aimed to support adherence behaviours (28%) reported reductions in BP (range from SBP 4-20 mm Hg, DBP 1-12 mm Hg). These changes in BP were clinically significant However, all of these trials examined were of poor quality; therefore the results should be interpreted with cautions.

Ten interventions that aimed to change adherence behaviours were identified in a total of 2170 patients. Less than half of interventions (n=4:659 patients) reported adherence improvement (range of 57% to 81%); Two of them (20%) showed an associated BP reduction (range from SBP 6-14 mm Hg, DBP 1-6 mm Hg), which was clinically significant. Two trials had good quality (Bosworth et al., 2009, Ogedegbe et al., 2008); just one study showed a significant effect only on adherence (Ogedegbe et al., 2008). However, the reporting of blinding of outcome assessors and analysts was inadequate. For this reason the positive results should be interpreted with caution.

Finally 30 interventions of complex/combined interventions were identified in a total 14317 patients. Adherence improved in 13 out of 30 interventions (n=3810 patients) (ranging from 5 up to 41% improvement in comparison to the TAU group). As associated reduction in BP was shown in six studies (n=2814 patients) of 4-7 mm Hg SBP, and 3-4 mm Hg DBP which is clinically significant. The quality of the trials which examined these types of intervention was varied. Overall only three studies were good quality (Green et al., 2008a, Bosworth et al., 2009, Rinfret et al., 2009), however, those trials showed significant effects on BP reduction only, whilst the remaining trials (n=26) were poor quality. The significant effects on adherence and BP reduction were demonstrated by poor quality trials; therefore, these results should be regarded with caution.

While an effect on both adherence and BP was only observed for a minority of interventions (15/86), not all studies (12/62) reported BP as an outcome. So not only may there be a threshold level of adherence that must be reached before changes in BP can be demonstrated, due to lack of this clinical outcome in 20% of studies it is not possible to be sure of the level of this threshold. Just three trials reported major clinical consequences of hypertension over 6, 24, and 39 months with no significant differences found between the groups. However it is likely that the period of follow-up was too short for any significant differences to be shown in such long term outcomes. Three trials reported the costs of their interventions; two reported cost of intervention and TAU (Logan et al., 1983, Schroeder et al., 2005), one study reported only the cost of interventions but did not estimate the cost of TAU ((Bosworth et al., 2009). Therefore, it was not possible to do cost comparison between them. They also were varying in type of interventions used, currency, setting, and cost equation factors. Finally none of the studies included in this review measured change in attitude toward medication or adverse events of interventions. Thus it is no clearer whether changes in beliefs change behaviours, which is concerning as this is the proposed mechanism of action of many of the interventions. Additionally as records of adverse events are lacking it is not possible to understand the risk profile of this kind of intervention.

It was noticed that some authors applied the same interventions (i.e. the use of special medications dispenser), and used the same adherence measures (i.e. pills count and MEMS) but with a different sample size (Eshelman and Fitzloff, 1976, Rehder et al., 1980, Becker et al., 1986, McKenney et al., 1992, Barrios et al., 2007a, Santschi et al., 2008a, Wetzels et al., 2007). However, their results were varied (the significant results did not correlate with large or small sample size). It is believed that many of the variations in the interventions' size of effects in other studies resulted from the differing character of the interventions (even within the same group of interventions), differing periods of intervention and follow-up, and from using different types of adherence outcome measures. Additionally, the inconsistent results were probably partly due to unknown biases in the studies examined which are all the harder to define with the overall poor quality of reporting (see Figure 3 and Figure 4).

### Overall completeness and applicability of evidence

The search was performed across an extensive list of electronic databases and clinical registers and developed with the aim of locating all possible relevant trials. Efforts to identify unpublished and published trials in English through Internet searches and by contacting experts in the field were made.

The 62 included trials did not allow a comprehensive review of the relative effectiveness of interventions that enhance adherence to BP lowering medication. For all included studies, the evidence is not robust due to; first, the heterogeneity of the included studies in terms of participants, interventions, adherence measures and definition and outcomes. Second, due to the unknown effect of biases mainly as a result of inadequate reporting, where issues that could cause bias were reported individual RCTs demonstrated variable and often poor methodological quality, particularly with regard to randomisation, blinding of outcome assessors and analysts, incomplete reporting of outcomes, losses to follow-up, and selective reporting of results.

There are also some difficulties in interpreting the results of this systematic review. Adherence was measured with many different instruments (e.g. self-report, pill counts, direct questioning, electronic monitoring, drug blood levels) all of which are relatively unreliable measures (WHO, 2003a). There were disparities in findings for reviewed RCTs, though some of them used the same interventions and measures of adherence (Eshelman and Fitzloff, 1976, Rehder et al, 1980, Becker, 1986, McKenney et al, 1992, Barrios et al, 2007, Wetzels et al, 2007, Santschi et al, 2008), and diversity between these studies in their sample size reflected the complexity of measuring the actual change in adherence behaviours. Therefore we cannot recommend any specific intervention as being superior to others. However, we recommend using a reliable clinical outcome measure (short term such as BP reduction, long term such as myocardial infarction and stroke) in addition to adherence measurement. Also adherence was calculated in many different ways (e.g. using arbitrary cut-off points to define adherence such as 80%), and in addition it was often measured by assessors who were not blinded to allocation status, which made the comparison of RCTs difficult. Levels of adherence in the control groups of the trials studied ranged from 12% to 94%, which is indicative of the heterogeneity in both criteria for defining adherence and in the participants selected for the studies.

While it was clear that all interventions were applied to enhance adherence, most of the trials did not measure adherence at baseline and just two of these RCTs were selected for just non-adherent participants at the baseline (Burrelle, 1986, Nessman et al., 1980). This hampers interpretation of the applicability of the evidence. The categorization and grouping of trials was subjective, because such intervention (e.g. BP measurement, regular follow-up) may be viewed as a reminder of intervention. Also the group allocation of some trials could be challenged by others. In addition, it is possible that the interventions studied in the factorial trials were dependent on each other. Particularly in the case of complex interventions evaluated in factorial trial designs, interactions are expected and so the exact causal mechanism of the effects is harder to determine.

Indeed, the findings of this review are likely to overestimate the benefits of the interventions tested to date because only published studies were considered in the review (Butler, 2009). Some authors provided adequate description for the intervention's content but did not adequately describe other parts of their intervention (e.g. the person or method of administering the intervention). Furthermore, seventeen trials (27%) only reported that the patients in the control group received "standard medical care" or "usual care", but they did not provide a description of the exact nature of the standard medical care. If the standard medical care considered adherence factors and took them into account, it might have worked very well. Therefore, the result might be affected and led to no significant difference between the intervention and control group, because both (intervention and control) worked and had effect. For that reason, the generalization about the effectiveness of interventions here is problematic.

### Quality of the evidence

Full critical appraisal for RCTs cannot be done when the design, conduct and analysis of the trials are not thoroughly described in the report (Adetugbo and Williams, 2000, Moher et al., 2010). Overall, in this review the available evidence for effectiveness of adherence interventions was of poor quality. The CONSORT statement was first published in 1996 and was developed to improve the quality of reporting of RCTs, it was updated in 2001 and 2010 (Moher et al., 2010). Although several trials concerning interventions to improve adherence with medications were conducted, only a few relatively rigorous trials of adherence interventions for hypertensive patients existed. These provide little evidence that patient adherence to BP lowering medication can be improved consistently; 25 trials (39%) appeared too small to detect clinically important significant data and none of the included studies fulfilled all the quality criteria. Most of the reviewed studies did not adhere to the CONSORT statement 2010 in many aspects. Most of the trials did not use; validated instruments to measure adherence outcomes, define completely the primary and secondary outcomes, report the source of funding and the gaining of ethical approval. In addition, the sample size for trial should be planned carefully for ethical and scientific reasons, thus determining of sample size based on power calculation is recommended to detect the statistically significant differences between groups (Moher et al., 2010, Charles et al., 2009). However, only 37 trials (61%) of reviewed trials reported a sample size calculation.

Bias, has been shown to mainly exaggerate treatment effects. Bias is generated by poorly designed and inadequate quality RCTs which affect the internal and external validity of the trials (Juni et al., 2001, Moher et al., 2010). A good quality randomisation method and allocation concealment are considered an important aspect of RCTs in order to achieve statistical equivalence of the experimental and control group prior to, during, and after the intervention is implemented (Guyatt et al., 2008) and to avoid selection and unconfounded factors bias (Moher et al., 2010). However, only 40% of our reviewed trials (25 trials) reported their method of randomisation and only 17% (13trials) maintained allocation concealment. Also, some authors suggested that keeping observers/raters "blind" with respect to knowledge of an assigned group is essential to maintain the internal validity of RCTs (Guyatt et al., 2008, Moher et al., 2010). The outcomes assessors for reviewed trials were blind in 30% (18 trials) of trials and 6% (4 trials) of studies maintained the blinding of the analysts. Furthermore, most of the reviewed RCTs were liable to have reporting bias since just 14 (12%) studies described the completeness of outcome data and only six (9%) studies were free from selective reporting. Overall, the findings of all 62 RCTs should be interpreted with caution, and be viewed at this stage as requiring confirmation with studies of good methodological quality and adequate power.

### Potential biases in the review process



This review was conducted according to the criteria and methods set out in the Cochrane handbook 2009. Overt effort was made to minimise the publication bias during the review process; this was achieved through a comprehensive search strategy which has been maintained properly and regularly updated by the contact of the project supervisors (KD, RG). It has included the search for ongoing and recently completed trials. However, it cannot be guaranteed that some studies have not been missed. Thirty six authors provided further details that helped in understanding unclear issues related to their studies.

### Agreements and disagreements with other studies or reviews



This review is similar to the previously published review but used a more comprehensive search strategy and reported the results from individual arms of factorial trials separately. Compared to the latest review on adherence enhancing strategies (Schroeder, et al., 2004), we found an additional 24 studies suitable for inclusion, which brought the total number of studies evaluated to 62. The review by Schroeder et al (2004), extracted data about adherence and BP outcomes and did not assess change in attitudes and beliefs outcomes. We added this outcome because as we noted from chapter 3 when we developed a conceptual framework we identified the importance of beliefs and attitudes in guiding patients medication taking behaviours. We added the longer-term health consequences of hypertension. These outcomes can be hard to measure over the relatively short period of the trials, however they are important as BP is merely a surrogate measure of the risk of these health outcomes, which are the true cost of having hypertension. The cost of the intervention is added, because we know the importance of economic analysis in adoption of new interventions by health policymakers. Finally, adverse events were added as it is critical that any assessment of an intervention has a full picture of both the risks and benefits that it can deliver. This review is different in that we have reported results whose interpretation is informed by the risk of bias assessment of the RCTs rather than just summarising main points of bias.

Schroeder et al's (2004) and Chrysant's (2008) reviews showed that dose simplification interventions improved adherence (Chrysant, 2008, Schroeder et al., 2004), however, the effect on the key short term clinical outcome (BP reduction) was very weak. In this updated review any more trials that tested dose simplification were not found. It may be that this method to improve adherence is redundant in the light of new recommendations for the treatment of high BP that requires the prescription of two or more antihypertensive medications to improve BP control (Ho et al., 2008, National Institute for Health and Clinical Excellence, 2006, WHO, 2003b).

Dunber-Jacob et al's review reported the benefits of educational interventions in improving adherence (Dunber-Jacob et al., 1991). Also, Devine's review showed that education interventions had a positive effect on adherence for medication in hypertensive patients (Devine and Reifschneider, 1995). Devine’s review was not restricted to RCT level evidence so the threats to validity of included studies limited their conclusion’s generalisability. Conversely, in this review it was found that the six interventions showed that providing education for patients about their hypertensive disease, medications and the adverse effects of treatment did not affect their adherence. This is consistent with Haynes et al’s (2008) and old review of Schroeder et al’s (2004) in their conclusion about educational interventions, when even assuming the largest effect of these interventions was “true”, this did not lead to large improvement in adherence.

Although, it is difficult to say that the behaviourally targeted interventions are effective, the reported differences in improvement in adherence between intervention and control groups for this review were greatest in the trials that tested these interventions (42%). That is consistent with Ogedegbe and Schoenthaler’s (2006) review that found that over half of the reviewed studies (57%) reported a significant improvement in medication adherence in behaviourally targeted interventions (i.e. home BP monitoring, patient counselling, patient reminders, and the use of nurse case managers). However, in this review home BP monitoring alone seems ineffective for improving adherence since just one study of Marquez- Contreras et al (2006) showed enhanced adherence with only significant reduction in DBP (Marquez-Contreras et al., 2006).

Haynes et al (2008) review reported that the interventions which improved adherence have better treatment outcomes for a variety of diseases. In contrast, Van Wijk et al (2005) review reported that interventions which significantly improved patient adherence to medication for chronic conditions did not have any significant effects on clinical outcome. In this review around 14 (22%) of the interventions (behaviourally targeted and complex/combined interventions) reported improved adherence combined with improved clinical outcome (BP reduction). The findings showed that the trials which tested behaviourally targeted interventions had greater association with improved adherence and clinical outcome (BP reduction 24%). However, clinical outcomes and BP measurements were not measured for most of the included studies. Moreover, none of the included trials measured changes in attitude and beliefs toward medication which highlight the need for evidence to support the importance of exploring patient's attitudes/beliefs toward diseases and medication for enhancing adherence behaviour (Banning, 2009, Nunes et al., 2009).

In addition, this review showed that complex/combined interventions seem promising for use in enhancing adherence among hypertensive patients, this is consistent with the review of Kripalani et al (2007) and Haynes et al (2008) who found that the use of combined interventions increased patients’ adherence with medication (Haynes et al., 2008, Kripalani et al., 2007). The review by McDonald et al found that in complex interventions it is often difficult to estimate the independent effects of the individual components of the interventions was in line with the findings of this study (McDonald et al., 2002). It also remains difficult to disentangle specific adherence effects as opposed to the non-specific effects of increased attention. The findings from this review confirm that even the most effective interventions do not appear to lead to large improvements in adherence and BP reductions.

The use of cost effective intervention for improving a BP outcome is recommended (Nunes et al., 2009, WHO, 2003a). However, only three studies had measured costs for the interventions; two studies that estimated the costs of interventions and TAU showed that interventions (nurse-led work-site care and nursing-led) were not cost-effective; with an incremental cost-effectiveness ratio almost double that of usual care (Logan et al., 1983, Schroeder et al., 2005), in contrast to Bosworth et al (2009), who just estimated the cost of interventions. Future research should focus on this area to facilitate transferring of effective evidence based intervention into clinical settings.

## IMPLICATION OF THE REVIEW

### Implications for practice

This review's findings suggest that introducing behaviourally targeted interventions can be effective in improving adherence, with an important effect on subsequent BP reduction. Although, there is some evidence from a single study that suggested that exploring patients negative attitudes and beliefs toward medication improved patients adherence, however this improvement in adherence did not have a significant effect on BP reduction (Ogedegbe et al., 2008); The effectiveness of this proposed mechanism of action on adherence and BP reduction needs to be retested. The effects of more complex/combined interventions on BP reduction are promising as well. However, there is insufficient evidence to suggest a single approach.

It is important that physicians are aware of the various reasons for poor adherence and aim to collaborate with other health care providers to improve the environment in which adherence behaviours can be changed. It is important to recognise that different health professionals were involved in delivering the interventions in the studies included in this review. In many countries, the role of allied health professionals such as nurses or physician assistants is expanding, which may lead to new management opportunities for tackling adherence-related problems in patients with high BP. Currently there is very limited evidence for any of the interventions regarding their long-term effects (i.e. what happens after 6 months). It is suspected that there is likely to be a decrease in the size of effect over time. There is no evidence that low adherence can be “cured” once and for all. Thus at present efforts to improve adherence should be assessed regularly and must be maintained for as long as the treatment is needed.

## Implications for research

The results of this review highlight a number of problem areas in adherence related research. One of the key problems in this area is that all measures of adherence have low levels of accuracy. Even MEMS is only estimated to be 50% sensitive (De Bleser et al., 2010). We therefore recognise that although theoretically adherence should be the primary outcome for these intervention studies, due to the poor accuracy of measurement the more reliable clinical measurement of BP is the most useful primary outcome; because BP reduction does not need a long duration to happen and can be directly measured immediately in order to observe patients adherence to medication. Therefore, all adherence studies should include the measuring of BP outcomes. However, we noticed that all dose simplification interventions had improved adherence with one only reducing SBP which suggested that there is a minimal adherence threshold that needs to be exceeded before the clinical effects (BP reduction) are observed. Future research should examine this proposition.

It is very important for long term adherence studies to measure the major clinical outcomes (e.g., myocardial infarction and stroke) to determine the rates of the actual consequences of hypertension (rather than just the BP which is a surrogate measure). It is also useful to examine the proposed mechanism of action; exploring patients’ beliefs and attitudes towards medication improves adherence. Finally we need to observe the adverse events of the interventions to facilitate its acceptance and applicability (Haynes et al., 2008). We feel this is particularly important in the context of high prevalence of non-communicable diseases and an increasing elderly population of people who often take multiple medications. It is quite feasible that increased adherence would increase the rates of adverse events and even increase the incidence of potentially hazardous interactions between the various medications an individual is prescribed

Hypertensive patients may fail to take their medication due to several reasons these include; the long duration of the therapy, the relatively symptomless nature of the condition, the side effects of the medication, complicated drug regimens, lack of understanding about hypertension management, lack of motivation and the challenge to individual patients' health beliefs (Nunes et al., 2009). It would seem logical that future studies should try and adopt a 'tailored' approach aimed at individual patient's behaviour and addressing the above mentioned barriers to adherence (Haynes et al., 2008, Nunes et al., 2009). Combinations of strategies that modify patient's attitudes/ beliefs, behaviourally targeted and that involve other health professionals in a patient-centred approach should be further investigated. In addition, patients' views should be taken into account when piloting interventions (Hardy, 2009, Nunes et al., 2009, WHO, 2003a). Also the interventions themselves should be based on shared decision-making in a partnership between patient and practitioner (Hardy, 2009, Nunes et al., 2009, WHO, 2003a). It is paramount that every study that evaluates an intervention to increase adherence to BP lowering medication should also measure BP as a short term clinical outcome to help examine the relationship between adherence and BP control.

Adherence to BP lowering medication must persist long-term to show a clinically relevant benefit. Many studies included in this review had a follow-up period of less than six months (see Table of Characteristics of Studies).We therefore suggest that interventions in future studies should be tested over a period of at least six months. Our findings emphasize the need for further RCTs with sufficient power and of rigorous methodology to determine the effectiveness of interventions aimed at changes to medication adherence behaviour. We suggest that the recommendations of the CONSORT statement should be introduced in the context of the design and reporting further RCTs (Moher et al., 2010). Future trials also should use standard/validated outcome measures. At that point, the innovation should be tested in more substantial trials to determine the effects on adherence behaviour, clinically important outcomes (including adverse effects, modification of attitudes and BP reduction), and feasibility and durability in the usual practice settings. Because the results could be widely applicable, effective ways to help people follow medical advice could have far larger effects on health than any treatment itself. As the context in which an adherence behaviour and intervention occurs is important and vital that there is consultation with interested parties in the development of the intervention so that it is tailored to the needs of the patients and the culture in which they live and the healthcare provision that is available. Finally, it is important that future studies include economic analyses because adherence interventions will generally have cost implications.

## SUMMARY

Due to poor methodological quality and heterogeneity of the trials reviewed, a definitive conclusion cannot be established and the results of this review should be interpreted with caution; some intervention may have been effective, but the key clinical outcomes (BP reduction) was not always well measured. Behaviourally targeted and complex/combined strategies appear to be the most promising interventions to increasing adherence to BP lowering medication. Our findings emphasize the need for further RCTs in medication adherence behaviour, with sufficient power and with rigorous methodology to determine the effectiveness of intervention which should be based on a patient-centred approach such as exploring attitudes and beliefs toward medication.

# UNANSWERED QUESTIONS

## INTRODUCTION

Chapter 2 and 3 presented an overview of hypertension and adherence. Then a conceptual model for medication adherence factors among hypertensive patients was developed. It was clear from this model that the patient theme is at the core of adherence relative to other factors, supporting the need to adopt a patient-centred approach when designing an intervention to enhance medication adherence. Also, it highlighted the importance of exploring attitudes and beliefs in adherence behaviours. In chapter 4 a review for RCTs testing interventions aimed at enhancing medication adherence among hypertensive patients was done to identify the potentially most effective intervention to be used with Jordanian hypertensive patients.

It was clear from literature reviews that while the prevalence of hypertension and poor adherence rates in Jordan are high, no research focusing on these topics was found. In addition, no randomised controlled trials evaluating these interventions had been performed in the Middle East and Arabic regions.

## UNANSWERED QUESTIONS

The key research question for this study is:

What are the effects of adherence therapy on the systolic blood pressure of non-compliant hypertensive patients in Jordan?

The secondary research questions are:

What are the effects of AT on:

* The diastolic blood pressure
* Adherence level
* Attitudes and beliefs

of non-compliant hypertensive patients in Jordan?

There are also a number of questions that I have identified as unanswered through chapter 2, 3 and 4:

1. Is there a definite relationship between a patient's drug taking behaviours and their positive or negative attitudes and beliefs toward medications?

2. Is there a definite relationship between a patient's drug taking behaviours and their attitudes and beliefs about their disease and its impact on their wellbeing and/or risk of death?

3. What is the character of an intervention that combines a patient-centred approach with exploring and challenging attitudes and beliefs?

4. How can a patient-centred approach be achieved in a clinical setting?

5. What are the appropriate outcome measures to be used for research in this area?

6. What is the most robust process for translating the measures into Arabic language?

7. What is the most appropriate outcome to reflect the effectiveness of an adherence intervention?

8. Are there positive consequences from exploring patient's attitudes and beliefs regarding medications and disease on adherence behaviours and do positive changes in these lead to changes in clinical outcomes (e.g. BP reduction)?

9. Is there a cost effective simple intervention for enhancing patients’ medication adherence?

10. Is the application of a robust RCT methodology based on the principles of CONSORT difficult to achieve in practice in a clinical setting?

11. Does the adherence therapy intervention which has been developed and proven effective in Western countries and cultures have the same positive results when applied in a Middle Eastern country and culture?

12. How could patients’ experiences explain their behaviours toward medications?

# TRANSLATIONS OF THE MEASURES:

## INTRODUCTION

In chapter 5 important unanswered questions were listed. To address some of these questions we have to use a culturally appropriate intervention and outcome measures. We need an appropriate method for translating the intervention and the outcome measures into Arabic. The adherence therapy (AT) treatment protocol, Morisky medication adherence scale (MMAS) and beliefs about medication questionnaire scale (BMQ) all required translation. None of these had been previously translated into the Arabic language. Therefore, we undertook a translation process for AT, MMAS, and BMQ. Other authors have complained that translation procedures are often insufficiently described in the literature (Maneesriwongul and Dixon, 2004, Ozolins, 2009, Su and Parham, 2002). This chapter presents our standard translation procedures, the modified, eight-step translation process employed for this study. Our translation model is a hybrid of those described by literature review, WHO (2011) and Brislin et al (1970, 1973, 1986), we have sought to take the best elements of each which could be practically applicable.

## TRANSLATION PROCESSES IN THE LITERATURE

Processing research instruments from one cultural group to another is a procedure that is vulnerable to translation problems (Ozolins, 2009). Translating research instruments into the language of the culture being studied is a first crucial step in cross-cultural research. Such translation is not easy, however, because a scale proven valid and reliable in one culture may not have the same characteristics in another culture (Su and Parham, 2002).

Several methods of translation have been suggested. Most researchers used a back translation method which help in maintaining quality control, putting the translator in a position of having a voice vis-à-vis the clients through establishing an ongoing dialogue between a translator and client for mutual benefit (Ozolins, 2009). Two similar models are commonly used WHO (2011) and Brislin et al (1970, 1973, 1986). WHO (2011) proposes a process of translation and adaptation of research instruments. This process aims to achieve translated versions of English instruments that are conceptually equivalent in each of the target cultures. Also it focuses on a cross cultural and conceptual, rather than linguistic equivalence through forward and backward translation. WHO approves the translation when the following steps are adhered to:

1- Forward translation.

2- Expert panel back-translation.

3- Pre-testing and cognitive interviewing.

4- Final version.

Brislin et al (1970, 1986, 1973) has proposed an alternative translation model which requires:

1- Preparing the measure and identifying the translators.

2- Forward and backward translation.

3- Comparing the original and back-translated versions.

4- Pre-testing the translated versions on a group of target language speaking participants.

5- Testing the translated versions with bilingual participants.

6- Comparing the results of step 4 and 5.

7- Pre-testing the translated version.

The WHO and Brislin models provide a full description for the translation process that the researchers must adhere to in order to create cross-culturally acceptable tests of scales (Su and Parham, 2002, Costa et al., 2007). Some of the steps might not be applicable and realistic. For example, "revising the original version" cannot be done simply unless the translators are the originators of a given scale, who are the only ones with the right to modify their own instrument (Su and Parham, 2002, Costa et al., 2007). Also, a major weakness of the Brislin model is a failure to stipulate the number of independent bilingual translators that are needed to get content equivalence between the original and the translated versions (Cha et al., 2007).

In fact, most translation processes reported in the literature do not strictly follow the models of the WHO (2011) and Brislin et al (1970, 1973, 1986). Maneesriwongul and Dixon (2004) after reviewing 47 studies found that most studies inadequately described the process and steps of translation. Some studies modified the standard methods according to their individual circumstances. Although these translation methods vary in quality, we can place them in six categories (Table 5)

Table 5, Instrument Translation in the Literature (Adapted from Maneesriwongul and Dixon 2004).

|  |  |
| --- | --- |
| **Forward-only Translation**  One translator translates the instrument from the source language (SL) to the target language (TL) | **Category**  **1** |
| **Forward Translation with Testing**  Forward-only translation + the pre-test of the TL version | **Category**  **2** |
| **Back Translation**  Forward-only translation + the translation from the TL version back to the SL version by another translator; the back translated version is then compared with the SL version. | **Category**  **3** |
| **Back Translation and Monolingual Test**  Back translation + the test of the TL version with monolingual participants | **Category**  **4** |
| **Back Translation and Bilingual Test**  Back translation + the test of both the SL and TL versions with bilingual participants | **Category**  **5** |
| **Back Translation and Bilingual and Monolingual Test**  Back translation + the test of the TL version with monolingual participants + the test of both the SL and TL versions with bilingual participants | **Category**  **6** |

SL: Source Language. TL: Target Language.

As we have seen in the literature, the methods of translation vary widely in quality and do not always adhere to the aforementioned models. Intensive methods such as that described in category 6, have been applied in only four studies. The "back translation and monolingual test" (category 4) was the most commonly used method. Indeed, there are strengths and limitations for each method. For example, the method of category 1 is time and cost-efficient. However, proving the similarity of conceptual meaning between the source language (SL) and the target language (TL) is problematic and questionable (Brislin et al., 1973). The strengths of the category 6 method are that discrepancies between SL and the TL are detectable, the equivalence in meaning of individual words from the SL and TL can be verified, and there is the possibility of conducting reliability and validity tests (Ozolins, 2009, Su and Parham, 2002). Category 6 is not applicable for this study because most Jordanian people cannot understand English well.

To maintain the content equivalences between the original and translated instruments in international research a combined process is an appropriate method. Researchers suggested several possible combination techniques. Differentiation of research questions and research environment (e.g. accessibility and availability of bilingual people) has lead to the absence of an ideal process for translation techniques (Cha et al., 2007).

## STEPS OF TRANSLATION PROCESS FOR RESEARCH MEASURES

Based on the literature discussed above, I decided that the most practical choice of method for this study would be a modified version of category 4 (Back Translation and Monolingual Test) combined with some of methods recommended by (WHO, 2011) and Brislin et al (1970, 1973, 1986). The following eight step translation process was formulated (see Table 6).

**Table 6**, Steps of translation process

|  |
| --- |
| 1 Obtaining permission from the original authors to conduct the translation |
| 2 Forward translation from English into Arabic (by two translators) |
| 3 Back translation from Arabic into English (by two further translators) |
| 4 Expert evaluation for the equivalence of conceptual meaning |
| 5 Preliminary check by the original authors on the back translated documents |
| 6 Altering the new English version in comparison with the Arabic version. |
| 7 Final check by the original authors |
| 8 Testing for clarity, comprehensiveness, appropriateness, and/or cultural relevance |

The equivalence of conceptual meanings between SL and TL versions can be verified by using these steps. We can also test the reliability and validity of the TL version (Maneesriwongul and Dixon, 2004, Ozolins, 2009).

### Obtaining permission from the original authors

The principle authors of measures were contacted, the purpose being to explain the aims of the study and to ask for permission to translate the instruments. The authors or co-authors kindly provided their written permission (see Appendix 3).

### Forward translation

Both the WHO (WHO, 2011) and Brislin et al (1970, 1973, 1986) recommend that the forward translation be conducted by one translator and the back translation by a second, independent translator. In this study, the task was done by four independent translators (forward by two translators and back translation by other two translators).

I contacted two bilingual persons for their cooperation in translating the instruments from SL (the English language) to the TL (Arabic language). One translator was a cardiologist and the other a nursing lecturer at Al-Hashmiah University. Both of the translators’ mother tongues were Arabic. They independently translated the original English measures into Arabic. I then combined the translations from these two people to create a single Arabic version.

### Back translation

Two other bilingual persons were contacted to back translate. One translator was an English Masters student and the other one was a registered nurse with a Masters degree. Both translators were Jordanian, whose mother tongue was Arabic. I combined the two back-translated versions to create a single back-translated version.

### Expert evaluation for the equivalence of conceptual meaning

Two linguistic translators (English language lecturers having Arabic as their mother tongue) independently checked the back-translated Arabic versions against the original English version. The conceptual meanings of particular terms (not necessarily their literal meanings) were then compared. A final English version of each measure was then obtained.

### Preliminary check by the original authors

The English versions were next sent to the original authors. All of whom kindly compared their originals against the new version and offered recommendations. There were no changes made to the back-translated version.

### Altering the new English version in comparison with the Arabic version

Some Arabic terms have more than one meaning, and I found it necessary to change such terms in consultation with linguistic translators.

### Final check by the original authors

A final check of the modified version was done by the original authors of the instruments. This process confirmed the final versions as comparable and acceptable in term of conceptual meaning. All the authors were satisfied with the final English versions.

### Testing for clarity, comprehensiveness, appropriateness, and/or cultural relevance

This step was essential to ensure that the instruments were readable and understandable by all participants (Maneesriwongul and Dixon, 2004, Su and Parham, 2002). Therefore, the instruments were tested on five Jordanian people with hypertension who were visiting outpatient clinics in Princess Rayah hospital in Irbid.

The test instruments were carefully worded to be understandable to most people regardless of education level; people who had a low level of education were included in this pilot phase. All participants were interviewed and encouraged to give comments on the measures. After that the participants were interviewed based on the WHO's (2011) recommendations:

1. What they thought the question was asking

2. How they repeated the question in their own words

3. What came to mind when they read a particular phrase or term

4. How they chose their answers

5. Which words were unclear, unacceptable, or offensive

6. What substitute words from their native language would be better

Minor revisions were made to the Arabic versions of instruments based on the results of interviews, without any change to the conceptual meanings.

## DISCUSSION

There are some differences between the two languages that made translation and back translation difficult. The general structure of the English sentence is subject + verb + object and it differs from the Arabic verb + subject + object. For example, in English the phrase "medicines help many people to live longer" in Arabic would be structured "help medicine many people to live longer" (Al-Muhtaseb and Mellish, 2008).

In addition, conjugation in Arabic is different compared to English. All verbs stem from a root verb (usually the past form of that verb) and are conjugated depending on number and gender. The root verbs conjugate to express different time and meanings as well, if you know the root word; you can almost always guess what the conjugated verb means so the back translation for this conjunction was not easy to conduct (Al-Muhtaseb and Mellish, 2008). For example, "Most medicines are poisons" in Arabic that means “most medicines and poisons” which is not the same meaning at all. Furthermore, for some phrases like "cut back, sticking, and pills" the literal translation could not be used because it resulted in an awkward meaning (Al-Muhtaseb and Mellish, 2008). In addition, in English an adjective is placed in front of a noun whereas in Arabic it is the reverse. For instance, in Arabic, one writes "reactions stronger" instead of "stronger reactions". Interestingly, the translators could correctly back translate these sentences into English. Perhaps, the translators were familiar with English structure and had a tendency to use it interchangeably with the Arabic structure. This phenomenon appears to be common in translations (Al-Muhtaseb and Mellish, 2008).

All the participants in the pilot phase came from northern Jordan (Irbid) and thus used the northern dialect. The test measures used the official Arabic language which slightly differs from the northern dialect. However, northern dialect was used to talk with participants in the research during the interviews, so as to more easily cultivate rapport. In general, the participants could understand all the items very well, as they had learned the official Arabic language in school.

## LIMITATIONS

Several limitations were noticed. First, Arabic contains hundreds of different dialects depending on which city, country, or town the speaker comes from in the Middle East. However most dialects are commonly understood amongst all Arabs, with the exception of the Franco-Arabic dialect of Tunisia, Algeria, and Morocco, Therefore, this translation is not valid for speakers of the Franco-Arabic dialect. It is important to note, however, that equivalence of meaning between a source and target version of an instrument does not ensure that performance of the populations for whom these versions are intended will be equivalent. This means that, although there may be confidence that there is a valid instrument for translation, it cannot be assumed that normative data gathered with the source version are applicable to the population for whom the translation is intended. Second, the backward translation process was conducted by bilingual translators whose mother tongue was Arabic; it was not possible to find bilingual translators whose mother tongue was English. Finally, as the patients did not know English, testing of both the English and Arabic versions of instruments with bilingual participants was not possible.

## SUMMARY

For any cross-cultural study, the accurate translation of test instruments from the source language to the target language is essential. The rigorous translation procedures used to produce Arabic versions of AT, BMQ, MMAS should minimise the influence of errors in translation when using these instruments in Jordan. A proper translation process ensures that the measures are valid to be used in cross cultural research. The "back translation and monolingual test" is considered the minimum standard by Ozolins (2009). Equivalence in conceptual meanings was maintained and ensured by adding more steps to the translation process than those recommended as the minimum required. A translation process for study instruments was developed and faithfully implemented. The Arabic version of AT, MMAS, BMQ are available to be used in the trial.

# METHODOLOGY

## INTRODUCTION

The review in chapter 4 showed the need to test the effectiveness of behaviourally targeted interventions through carefully designed RCTs. Chapter 5 raised some questions about the characteristics of the interventions which could be used in this study. The researcher decided to use Adherence Therapy (AT) as an intervention that had the potential to answer most of these questions and have a desired effect of improving clinical outcomes in noncompliant hypertensive patients in Jordan. There is evidence of AT’s effectiveness in the field of psychiatry (schizophrenia). Additionally, AT has never been practised in Jordan. Therefore we need to prove it is effectiveness in hypertensive patients in Jordan. This chapter provides a description and justification for the design of our research. I will discuss: the use of a randomised controlled trial (RCT) methodology; the intervention (AT) and control arms; the researcher’s background; the methods of data collection; analysis and handling; and the ethical issues.

## RATIONALISATION OF RANDOMISED CONTROLLED TRIAL

RCT design is a quantitative methodology (Guyatt et al., 2008, Moher et al., 2010). It is considered the strongest research design for the evaluation of the efficacy or effectiveness of health care interventions and services (Moher et al., 2010).

There are many advantages of the RCT method. It increases internal validity (which refers to the extent to which it can be accurately stated that the independent variable produced the observed effect (Rothwell, 2005, Zwarenstein et al., 2008). Increased internal validity could be confirmed through enhancing the quality of the study and decreasing the risk of bias (e.g. selection bias and placebo effect) (Higgins and Green, 2009, The Cochrane Collaboration, 2006). Internal validity could also be increased by identifying and dealing with known and unknown confounders (Moher et al., 2010). This is achieved by the random allocation of eligible participants into experimental and control groups under investigation (Guyatt et al., 2008, Moher et al., 2010). In addition, the RCT maintains external validity (which reflects whether the results can be reasonably applied to all patients in different clinical settings in routine practices or not) (Moher et al., 2010, Zwarenstein et al., 2008). Moreover, the RCT provides a realistic compromise between observational studies (which have good external validity at the expense of internal validity) and other traditional experimental designs such as independent group design (which has good internal validity at the expense of external validity) (Hotopf, 2002). The results of RCTs can also be pooled in systematic reviews which can establish whether or not there is conclusive evidence about a specific treatment (Moher et al., 2010).

A number of articles and textbooks provide researchers of clinical trials with a list of criteria with which to assess their validity (Hopewell et al., 2010, Stolberg et al., 2004, Zwarenstein et al., 2008). This study adheres to the Consolidated Statement of Reporting Trials (CONSORT) (2010), which aims to enhance the reporting of RCTs. Consequently researchers can assess validity based on standard criteria for participants, experimental and control group, randomisation, blinding, intervention, methods, results, and reporting (Moher et al., 2010). The CONSORT statement focuses on aspects that minimise the risk of bias (internal validity) and enhance applicability (external validity) (Zwarenstein et al., 2008).

In chapter 3 it was shown that adherence is a complex behaviour, affected by several factors and the complexity of the causal chains linking outcomes with intervention which were observed. Also, in chapter 3 the need to have a complex intervention was highlighted (Hawe et al., 2004, Rifkin, 2007). AT could be considered a complex intervention (see below) because it has several interacting components (e.g. problem solving, exploring ambivalence and attitudes/beliefs), and addresses problems associated with non-adherence (e.g. drug adverse events, forgetting to take medication, patients attitudes and beliefs, and patient-physician relationships) (Hawe et al., 2004, Rifkin, 2007). The Medical Research Council (MRC) framework for the development and evaluation of complex interventions recommends the use of RCT design when at the stage of evaluating the efficacy of a complex intervention (Craig et al., 2008). For this reason, an RCT design is necessary to test whether the intervention is feasible to deliver and is acceptable for both therapists and patients.

## Overview of adherence therapy (AT)

From chapters 2, 3 and 4; it was recognised that there were some unanswered questions (chapter 5) that highlighted the need to have an intervention which used a patient-centred approach to exploring and challenging attitudes and beliefs and so enhancing adherence behaviours. The NICE and the WHO encourage the use of an individualised consultation style and involving patients in treatment decisions to enhance adherence. They recommended that researchers also focus on exploring beliefs and attitudes toward disease and treatment when designing adherence interventions (Nunes et al., 2009, WHO 2003a). In addition the Haynes systematic review (2008) encouraged the researchers to use an applicable strategy with minimal adverse events to get benefit from any intervention target enhancing medication adherence. Therefore, the intervention under investigation in this trial was AT which captures all of the elements of the adherence guidelines developed in the UK by NICE (2009). AT is a brief pragmatic intervention based on cognitive behavioural and motivational interviewing (Kemp et al., 1998). It is rooted in the observation that a patient’s beliefs impact on their treatment adherence (Morrison et al., 2000). For example, if patients do not believe that their health depends on medicines, are worried about having to take medicine, or are concerned about the side effects of medicine, they are less likely to adhere to treatment than patients with more positive treatment attitudes; for example, “my medicines protect me from becoming more sick” (Horne et al., 1999). AT is a patient-centred approach which is normally delivered by trained therapists over a series of a 20 minutes/week over seven week of consultations each with a different theme. Building on a structured adherence assessment key therapy techniques include generating discrepancy; medication problem-solving; exchanging information; exploring ambivalence; and checking beliefs (see Figure 5). Theoretically these techniques amplify the personally relevant benefits of treatment, modify illness and treatment beliefs and resolve ambivalence towards taking medication (Gray et al., 2006). Two of the AT techniques will be described, “generating discrepancy” and “checking beliefs”, in more detail. Through generating discrepancy between what the patients say is important to them (e.g. being able to work, not visiting hospital so frequently, and not worrying family), the therapist can intensify the personally relevant benefits about medication. The therapist might respond to a patient who says that their medication is important but repeatedly misses doses by saying; “I’m a bit confused, because you say that you need to keep your BP under control so that you are able to work and yet you keep missing doses of medication, can you help me understand that a bit better?”.

Beliefs identified from the assessment that may negatively affect adherence are explored using a three step process. Step 1, the patient is asked to rate the conviction (as a percentage) with which they hold a belief (e.g. the patient says they are 60% sure most medication is addictive). Step 2, they are then asked to generate evidence that supports and refutes the belief. Step 3, the therapist rechecks the conviction with which the belief is held. This process provides patients an opportunity to “test out” their beliefs. Direct confrontation or challenge of the belief is avoided since one of the most important skills which the therapist should utilise during all AT steps, is to reduce resistance and keep patient engage in a dialogue.

Each consultation follows a standard structure (review of previous meeting and homework, set agenda, complete task (e.g. exploring ambivalence), feedback and setting homework). The mechanism of action that is being proposed here and will be tested in this trial is that AT will modify patient’s unhelpful beliefs about taking their medication, which will in turn improve compliance, which will ultimately result in a reduction in patients’ BP.

The adherence therapy manual describes in detailed the multistep phased approach to promoting adherence in patients with schizophrenia by enhancing an awareness in the patient of the importance of antipsychotic medication and increasing patient’s confidence in taking medication (Gray et al., 2003) (see Appendix 4 for English version of manual).

Foundation skills

Interpersonal skills

Process skills

Figure 5 Adherence Therapy Model

Adherence assessment

Five key skills:

Problem solving

Looking back

Exploring ambivalence

Talking about beliefs

Looking forward

lo

Reduce resistance

Exchange information

Adherence assessment

## Therapist background and AT training

**EXCHANGE**

**INFORMAT**

**ION**

I served as the therapist for the study. I was trained in adult nursing as a part of a Bachelor’s degree in Jordan. Between the Jordanian and British curriculum there are some important differences. The most important one is that nursing students in the UK focus on a specialised branch of nursing (such as adult or mental health) before qualifying as a nurse. In Jordan, nursing students are trained in all branches, as they need the ability to work in any field of nursing, because of the shortage of healthcare professionals. If they want to specialise in a particular area, they can pursue specific training or obtain a higher degree such as a Masters degree.

After graduating, I spent 6 years working on the critical care unit in public governmental hospitals. That provided me with an opportunity to identify the most common problems for chronic diseases patients such as hypertension. I then got a Masters degree in adult nursing that helped me to acquire the skills and competencies to increase my awareness of their health problems. I was then awarded a scholarship to pursue a doctoral degree in adult nursing.

As part of my doctoral studies, I received adherence therapy training. I was trained in AT by Professor Richard Gray who developed and has conducted a considerable body of research, teaching and clinical experience with intervention, I attended seven, one hour weekly training sessions. The manual was amended to be easily used among hypertension patients and was focussed on four key skills (use of medication timelines, medication problem solving, exploration of ambivalence, discussion of patient's beliefs and concerns about medication). Role playing at the end of each session was done to get feedback from the trainer.

## OBJECTIVES AND HYPOTHESIS

### Primary objective

The overall primary objective of this trial is to assess the efficacy of AT compared to treatment as usual (TAU) in reducing SBP in non-adherent people with hypertension in Jordan at seven weeks after baseline.

### Secondary objectives

The secondary objectives are to evaluate the efficacy of AT at seven weeks compared TAU to effect:

1. Reducing DBP

2. Enhancing adherence (measured by pill counting) to antihypertension medication

3. Modifying beliefs and attitudes toward medication

### Research hypothesis

Compared to TAU, AT at study endpoint (11 weeks) will:

1. Reduce SBP.

2. Reduce DBP

3. Enhance adherence to antihypertensive medication.

4. Modify patients’ attitudes and beliefs in a favourable direction towards taking their medication

## METHOD

### Summary of trial design

This study was a single-blind parallel group randomised controlled trial of adherence therapy.

### Setting

This study was conducted in out-patients clinics of public hospitals from the three main Jordanian cities (Amman, Irbid and Zarqa). Names of the hospitals are shown below in Table 7. Those cities provide treatment to more than 85% of the hypertension patients in Jordan and cover more than 75% of all of the Jordanian population (Jordan Human Resources, 2009, Jordanian Department of Statistics, 2007).

Table 7, Statistical information about the three governmental hospitals

|  |  |  |  |
| --- | --- | --- | --- |
| **City Name** | Amman | Alzarqa | Irbid |
| **Population number** | 2265100 | 1041300 | 871600 |
| **Hospital name** | Albashire | Alzarqa | Princess Basmah |
| **Number of beds** | 921 | 300 | 202 |
| **Number of admission** | 73467 | 28607 | 18028 |
| **Number of CVD patient's visiting for outpatient clinic** | 17982 | 61364 | 77431 |

### Participants

#### Inclusion criteria

All hypertensive patients that met our selection criteria who attended the outpatient clinics in three government run hospitals were invited to participate. The trial was conducted between August 2009 and January 2010. Eligible patients were:

1. Adult aged ≥ 18 years.

2. With a diagnosis of hypertension (Rogers et al., 2001).

3. Currently hypertensive (BP ≥140/90 mm Hg (WHO, 2003a)).

4. On monthly follow up schedules at the participating clinics.

5. Non-adherent according to the Morisky Medication Adherence Scale (see screening below for details).

6. Not participating in another research project.

#### Exclusion criteria:

The intention was to give AT the best chance of success; therefore patients were excluded if they had:

1. Complications of hypertension, had diabetes, congestive heart failure, renal impairment. These patients were excluded because their treatment regime was more likely to be complex, introducing more potential confounders that might not be adequately dealt with by randomisation.

2. Mental illness or any other long term health conditions e.g. asthma, Parkinson’s disease, epilepsy, cancer, and chronic obstructive pulmonary disease. These patients were excluded because these co-morbid conditions may also introduce confounding factors that might limit the effectiveness of the therapy

3. Pregnant patients were excluded as the aetiology and duration of their hypertension would likely differ from essential hypertension.

4. Participating in another research project.

### Recruitment procedure

#### Screening

Participants were recruited by reviewing patient’s health records to determine if they met the primary inclusion criteria. Records were selected for assessment on the basis that the patients had been seen recently in the clinics. Records were assessed in reverse date order of the last clinic appointment, and assessment of potential participants was stopped when sufficient numbers had been recruited to the study. Further screening for non-adherent patients was conducted using the Morisky Medication Adherence Scale (MMAS). MMAS was used to assess patient’s notes to determine medication adherence prior to the trial. The nurse who had already worked in an outpatient clinic was asked to administer the MMAS to 190 eligible potential participants to complete it. MMAS was fully completed and returned by 181 patients (5 questionnaire had not been returned and 4 had not been fully completed). Patients completed the MMAS within an average of three minutes. I calculated the MMAS score for each patients; fifteen patients were excluded because they had a medium adherence rating according to MMAS. The remaining 166 patients were predicted by the MMAS to be non-adherent and met all inclusion criteria. Those patients who were eligible were written to by their treating physician from the outpatient clinic to invite them to participate in the trial (Appendix 5). Also, they received a written information sheet describing the study so they could decide whether to participate or not in the trial (Appendix 6). Care was taken in the wording of both (invitation letter and information sheet) so that it was understandable to participants. At the end of the information sheet there was a reply slip. Patients who were interested in the trial were asked to complete a reply slip and send it back in the freepost envelope provided.

#### Informed consent

Those patients who returned the reply slip back and expressed an interest in participating in the study were contacted by phone. A meeting was scheduled with the patients for a further explanation about the trial. This meeting provided an opportunity to explain the randomised allocation element of the trial and to ensure that it was clear that the patient was free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The patients were allowed as much time as they wished to consider the information and ask questions. Thirty patients refused to participate and 136 agreed to be included in the study. All participants gave written informed consent by means of a participant dated signature and dated signature consent form which was countersigned by the author (Appendix 7).

### Study outcomes

#### Primary outcome

An adherence rate in this study was not used as a primary outcome due to poor validity and reliability of different types of measurement (WHO, 2003a). Therefore, the more reliable clinical measurement is BP. Some researchers argued that SBP is a more important measure of hypertension than DBP. SBP tends to increase with age whilst DBP tends to decrease (Panda, 2006, WHO, 2003a). For that reasons the primary outcome in this trial was SBP:

#### Secondary outcomes

The secondary outcomes were DBP, adherence rate, attitudes and beliefs with medication (BMQ) and a note was made of the amount of time taken to deliver the AT, so that an estimate of the costs of delivery could be made.

### Measures

How data are collected can affect internal validity. This might result from the observer, or recorder error or bias, ceiling and floor effects (Moher et al., 2010). Variations in the procedures for gathering data and the instrument lead to measurement bias (McMillan, 2007). A valid and reliable measure should be used by researchers to protect from such bias and maintain internal validity. The following measures and procedures for assessment of study outcomes were used:

#### Baseline non-adherence

The MMAS was used to determine patients who were non-adherent to their medication before conducting the trial. Many researchers have used MMAS in adherence studies (Krapek et al., 2004, Krousel-Wood et al., 2004). MMAS has a higher reliability (internal consistency) and equal concurrent and predictive validity especially for low income, minority patients with essential hypertension attending an outpatient setting (Morisky et al., 2008). It is a self report measure; consisting of 8 items which focus on factors that affect patient adherence to drug regimens such as “do you sometimes have problems remembering to take your medication”, “do you sometimes forget to take your medication,” and complexity of the medical regimens problem such as, “do you ever feel hassled about sticking to your treatment plan”. Morisky et al claimed that the questions are phrased to avoid respondents giving the same answer. They guaranteed this by reversing the wording of the questions about the way patients might experience failure in following their medication regimen to avoid the “yes-saying” bias, since there is a tendency for patients to give their physicians or other health care providers positive answers. Response categories are yes/no for each item with a dichotomous response (first seven items) and a 5-point Likert response for the last item. I followed the Morisky's recommendation for coding MMAS. The code responses for items 5 and 8 were revised to be in a positive direction. Also for item 8 it was divided by 4 for calculating a summated score. The total scale has a range of 0 to 8. Morisky categorised adherence level into low adherence (0-5), medium Adherence (6-7), and high Adherence (8) (Morisky et al., 2008).

#### Blood pressure (BP)

Blood pressure can be measured by invasive or non-invasive procedures. The non-invasive measurements are simpler, safer, and less painful for patients than invasive (e.g. sphygmomanometer and oscillometric method (digital/automated) BP monitoring). Therefore, it is more commonly used for routine BP examinations and monitoring (Pickering et al., 2005, Chobanian et al., 2003). The sphygmomanometer includes two types; mercury (which is referred to liquid element) and aneroid (indicate the lack of any liquid) (Pickering et al., 2005). The mercury sphygmomanometer is considered the gold standard method because it measures the height of a mercury column and there is limited requirement for re-calibration unlike other methods, as it is not subject to error or drift (Pickering et al. 2005, p.146, Chobanian et al., 2003). However, the mercury sphygmomanometer has some problems for example; knowledge of previous reading, digit preference, threshold avoidance, potential breakage and leakage, all of which have the potential to affect the accuracy of the BP’s reading recorded (Pannarale et al., 1993, Bruce et al., 1988). Also, Mion and Pierin (1998) found that most manual mercury and aneroid sphygmomanometers showed inaccuracy (21% vs 58%) and unreliability (64% vs 70%) (Mion and Pierin, 1998). In this study the calibration of the sphygmomanometers was checked prior to their use in the research (Perloff et al., 1993). Although, the accuracy of oscillometric method (e.g. digital or automated) BP monitoring would be affected by patients characteristics (age, sex blood pressure, pulse pressure) (Appel et al., 1990, Pannarale et al., 1993), some researchers prefer to use automated BP monitoring (Wilton et al., 2006, Pickering et al., 2005). Automated BP measurement requires less skill than the mercury sphygmomanometer technique. Therefore, it is suitable for use by untrained staff and for automated patient home monitoring. In this study I have used the mercury sphygmomanometer because it is more commonly used in outpatient clinic in Jordan and it is the recommended method to be used for measuring BP in clinical trials (Perloff et al., 1993, Pickering et al., 2005, p147).

A training session about BP measurement procedures was provided for the staff nurses who were assigned to do this measurement. The American Heart Association’s recommendations for BP measurement were used and a brochure that contained the detailed procedure steps was provided (Pickering et al., 2005). BP was measured using a stethoscope with a mercury sphygmomanometer (mm Hg) twice from the right upper arm of a seated person who had been resting for more than 10 minutes, and the average of the two measurements used. Patients were asked to not smoke or drink coffee during the examination and it was recorded if they had had any alcohol, coffee, or cigarettes in the thirty minutes before the examination (Lin et al., 2007, Michigan Department of Community Health, 2003, Pickering et al., 2005).

#### Adherence rate

Adherence in this study was defined as a percentage of prescribed doses taken during the research interval. This was measured by pill counting for one month from week 7 to 11 (i.e. after the end of AT sessions for those allocated to two groups (AT and TAU)) for each participant according to their prescribed doses.

#### Beliefs about medication questionnaire (BMQ)

The BMQ was used to measure patients’ attitudes and beliefs toward medication in general (Horne et al., 1999). The BMQ has robust internal consistency and validity (Horne and Weinman, 1999). Attitudes and beliefs to medication may be influenced not only by beliefs about their intrinsic properties and how they are used by doctors but also by perceptions of the self in relation to medicines. Beliefs about personal sensitivity to the effects of medication are likely to be particularly salient. Therefore, we used the General BMQ. The patients were on a variety of antihypertensive medications, therefore the Specific BMQ which relates to attitudes to a specific medication was not appropriate for this population. The BMQ measures both positive (benefit) and negative attitudes (harm, over use and sensitivity). However, it is important to note that this does not necessarily mean that all people see medicines in this way. People can disagree with each statement in the scale and so express a view of medication as essentially safe and appropriately used (Horne and Weinman, 1999, Horne et al., 1999).

Each question is rated on a five point Likert scale, with a score of 5 indicating “strongly agree”. The questionnaire has four sections which evaluate attitudes about:

1. General Harm (G-H) i.e. the intrinsically harmful properties of medications (4 questions such as "most medicines are addictive").

2. General Overuse (G-O) of medications by healthcare professionals (4 questions such as "Doctors use too many medicines").

3. General Sensitivity (G-S) to adverse events from medications (5 questions such as "my body is very sensitive to medicines").

4. General Benefit (G-B) i.e. the intrinsically beneficial properties of medications (4 questions such as "in the most cases the benefit of medicines outweigh the risks").

Scores are taken from the sum of answers to all relevant questions. High scores signify agreement with the idea that medicines are harmful, overused, give little benefit and agreement with the idea that these patients have sensitivity to medication's adverse effects (Horne et al., 1999).

#### Additional patient information

Based on the literature review regarding factors that could influence adherence (Chapter 3) and BP, the following demographic information and patients clinical characteristics at the baseline assessment was recorded (see Appendix 8); age, gender, living arrangements, marital status, employment status, level of education, presence of medical insurance, and income, number of antihypertensive medication and number of other medications currently being taken, smoking status, self reported level of physical activity and adherence to a low salt and low fat diet.

### Randomisation

Trial participants were randomised to the two groups in order to achieve statistical equivalence of the experimental and control groups prior to, during, and after the implementation of intervention. Randomisation is used also to minimize confounding factors by allocating the characteristics of patients randomly between groups, and consequently to reduce selection bias (Guyatt et al., 2008, Stolberg et al., 2004).

#### Sequences generation

Patient eligibility and consent was checked against a checklist. I allocated a personal 6-digit 'PIN' identifier which allowed access to the online independent randomisation service at the Clinical Research Trials Unit (CRTU) at the University of East Anglia (UEA). On entry of a valid PIN, the system generated a unique Study Code and randomly allocated the patients to either the AT or TAU arm of the trial. The Study Code and allocation was sent in an email to the author and the trial database manager and stored in the trial database on the secure CRTU server at UEA.

A computer generated randomisation list allocated patients in a 1:1 ratio to AT or TAU. To ensure a reasonably even distribution of patients in the 2 arms throughout the course of the trial, patients were allocated in randomly permuted blocks of 4 and 6.

#### Allocation concealment

The author was the only member of the research team who had contact with the clinical trial unit. The author recruited and gained written informed consent for small groups of patients at any time (e.g. 5-10 patients). Once this list of participants was obtained CRTU was contacted for their allocation. This was done strictly in the same order as they were consented. Emails of the assignments were sent to FA. Each participant was allocated their patient ID number at this point.

#### Implementation

The author printed the stored assignment copy then it was handed to AA who assigned a patient ID to their name with each treatment group following the sequence. Then a list of the names of the patients in the experimental group was provided, after the therapy sessions were commenced. At this time, there were not yet enough patients available. As the patients could not all be enrolled at once, it was decided to start the treatments anyway, concurrent with the enrolment and assignment of new participants.

### Interventions

Placebo interventions are recommended for use in pharmaceutical studies (Benson and Friedman, 1996, Chambless and Hollon, 1998). Creating placebos that can be mistaken for active treatments in clinical practice setting is difficult (Benson and Friedman, 1996, Chambless and Hollon, 1998). In this trial placebo intervention were not used because proof of whether AT worked or not was required. Future research which includes a placebo group is needed.

#### Control group

To conduct a robust RCT there is a need to have a group that matched with the intervention group in all respects except the intervention under investigation, this group is called the "control group". The control group functions by controlling the influences of other unknown factors in the experimental setting the researcher may not know about (Moher et al., 2001, Stanley, 2007). A control group is a critical part of the RCTs method because it ensures that any changes observed in an intervention group are due only to experimental intervention and not to any other factors (Moher et al., 2010). However, this may lead to difficulties in interpretation of results because the findings will only tell the researcher whether the intervention had specific impact or not, it will not imply that the treatment intervention is different or better than existing alternatives (Stanley, 2007, Moher et al., 2010). Some researchers prefer to use the term "Treatment as Usual" as the control condition when conducting community-based effectiveness trials because experimental and control groups may receive care from different sets of healthcare providers, and the care the control participants receive may not be under the power or control of the researcher to influence (Charles et al., 2001).

In this study the control group patients received treatment as usual (TAU), which consisted of medication prescription, BP measurements, laboratory investigation and other care depending on individual needs. Guidelines about what constituted usual care was not provided. TAU was provided by the patients usual clinical care team. This consisted of a clinician-led team of medical and nursing staff based in the outpatient clinic. The clinical health team who dealt and provided care for control group were asked not to discuss any issue regarding patients adherence with medication and to avoid any intervention focused on this topic over the study period.

#### Intervention group

In addition to TAU, patients in the experimental group received seven one-to-one sessions of AT lasting 20 minutes over a seven week period. AT sessions were delivered in the hospital outpatient clinic (~25% of all sessions) or at the patient’s home (~75% of all sessions) depending on patient preference. Cultural considerations were taken into account when providing AT to Jordanian people with hypertension (i.e. with the prior permission of the participant the researcher introduced herself to the participant's partner who was informed about patient's engagement in the trial). I delivered the AT; however, this may have led to unintentional experimenter effects which may violate the internal validity of the study. Experimenter bias could occur when the participants may want to please the researcher, have been paid more attention to (Hawthorne effect), and when the researchers have a vested interest in the study there is motivation to find results that will enhance their position (McMillan, 2007, Moher et al., 2000, Moher et al., 2010). Therefore, such issues were taken in consideration to control over these potential sources biases by using techniques such as the assessment of treatment fidelity, and blinding of outcomes assessors (see potential bias section below). In the current trial all AT sessions were done as planned without any need to repeat any one. No adverse events occurred that stopped an AT session.

In Jordan, supervision was provided by (AA) who lived there, by the AT trainer and supervisor (RG) and the secondary supervisor (KD) via telephone and electronic communication. Whenever a practical problem during field work was encountered, advice was obtained from one of my supervisors (RG, KD, and AA).

### Data collection procedure and Follow up

Blood pressure (BP) and BMQ were measured at baseline, and 7 weeks. Patients took an average of 10 minutes to complete the BMQ. Drug doses for a further month were distributed to each participant at the end of 7 weeks. At 11 weeks adherence was measured. This short follow up period was decided upon because of the aim to prove the concept that adherence therapy works. Also, pragmatically this research was conducted for the purpose of obtaining a PhD degree by full time student who had a limited study time duration.

### Analysis

#### Determination of sample size

A statistical power calculation was performed based on the following assumptions:

1. The difference in SBP between the two groups at follow-up was expected to be 3 mm Hg (Capewell et al., 2010, Prospective Studies Collaboration, 2002).

2. Assuming a standard deviation of 5.7 mm Hg (Goldstein et al., 2005, Schroeder et al., 2005).

3. The level of significance for detecting the effect of the intervention was set at 5% (2-tailed test), and the power was set at 80% power.

Therefore, 60 patients in each arm of the trial were required, i.e. a sample size of 120.

4. We estimated the drop-out rate from previous studies with hypertension to be around 13% (i.e. 16) of patients.

Based on the above assumptions, the power analysis indicated that 136 participants would be required to have an 80% chance of rejecting the null hypothesis at the 0.05 level (two-tailed). That agreed with the Haynes review's recommendation for studies with single intervention and control group about the need to include at least 60 participants per group if they have at least 80% power to detect a 25% difference in the proportion of adherence. Noting however, that in this study SBP and not the adherence was the primary outcome (Haynes et al., 2008).

#### Data analysis

The SPSS statistical package for windows version 16 was used to analyze data; an independent blinded analyst (AC) did the analysis. The baseline comparability of the groups using descriptive analysis were investigated; categorical data (gender, education, employment status, living arrangement, marital status, currently smoker, self reported level of physical activity, self reported adherence to a low salt and low fat diet, and insurance status) are expressed as numbers and percentages. Continuous data (age, SBP, DBP, number of daily antihypertensive, number of daily other drugs and BMQ (general harm, general overuse, general benefits and sensitivity to adverse events) as mean (standard deviation). For the continuous covariates, two sample t tests were applied since the two sample size of were equal. For categorical variables a chi square test was used for association (Pallant, 2003). The Kappa statistic was used to confirm that the blindness of outcome assessors has been maintained (Uebersax, 1987). The Kappa statistic measures the percentage of data values in the main diagonal of the table then adjusts these values for the amount of the agreement that could be expected due to chance alone it is range between zero and one; zero indicates the agreement is no better than that expected by chance.

All analyses were conducted on an intention to treat basis with multiple imputation (Rubin, 1987) for missing data. In multiple imputation analysis each missing value is replaced with a set of *m* plausible values (*m*>1, where *m* is typically small (e.g. 3-10)) that represent the uncertainty about the value that would have been observed. Then the analyses of these multiply imputed data sets are done by using standard procedures as they would be for a complete data set. Finally, the results are combined to produce estimates and confidence intervals that incorporate uncertainly due to both sampling variation and missing data (Rubin, 1987). In this study the multiple imputation was done using iterative chained equations, the equations represent regression models for each variable in the data set and includes all available outcome measures and their baseline values, and treatment arm as covariates in the regression models. Five imputed datasets were created which were then analysed and combined using Rubin’s equations (Rubin, 1987).

Based on our examiner’s advice we also analysed our data using the Last Observation Carried Forward (LOCF) method and also by analysing the data without any imputation for missing values (per protocol). LOCF is one of the methods which use to handle missing data by imputation values based on existing data (National Research Council, 2010). We could not analyse the percentage of adherence at 11 weeks and medication changes over 11 weeks by using LOCF, since we did not measure these outcomes at the baseline of the study.

The differences in change of BP and BMQ were assessed using an unadjusted analysis and after adjusting for possible prognostic factors (gender, education, economic status, and medical insurance status) using an analysis of covariance (ANCOVA). ANCOVA used to compare multiple means while controlling for the effect of covariates to reduce the within-group error variance and eliminate possible confounders (Borm et al., 2007, Pallant, 2003).

Adherence and medication change was similarly analysed using logistic regression with only treatment arm as a covariate as an unadjusted analysis and an adjusted analysis was based on included prognostic factors. Logistic regression is used for prediction of the probability of occurrence of an event (Pallant, 2003, Hosmer and Stanley, 2000).

Subgroup analyses of change in adherence by the use of two or more antihypertensive drugs or not at baseline, was based on testing for an interaction effect in a regression model.

### Potential bias

In order to compensate for any possible "researcher bias" the following elements have been included in the research design:

#### Treatment fidelity

Treatment fidelity was checked to determine whether the actual intervention was being implemented in a way or manner consistent with the study protocol or not (Bellg et al., 2004). It is essential to enhance internal and external validity of behavioural intervention (Moher et al., 2010). Treatment fidelity could be done through interviews or self-reports of subjects, observations, and third party reports about what occurred. In this study, random samples of AT sessions were audio-taped with patient permission to verify that the interventions are properly administered. AA checked the treatment fidelity of these sessions based on an AT fidelity checklist (see Appendix 9).

#### Blinding

The author was not masked to the patient assignments as she served as the therapist. Likewise, masking of patients was not possible because of the nature of study which required active participation of patients (Moher et al., 2010, Rothwell, 2005). It was also clear to subjects that a specific outcome was desired (they had read the information sheet which listed the goal of the study was to demonstrate that the intervention was effective in improving adherence) (Guyatt et al., 2008). This is therefore a single blinded trial since the outcomes assessors were blinded to group assignment in order to maintain the internal validity of trial (Guyatt et al., 2008, McMillan 2007, Moher et al., 2010). Specifically the BP measurement, pill counting and handling BMQ for patients to complete, were done by trained nurses who were masked to group allocation and time of intervention. Masking was ensured in three ways; the nurses were at no time informed of the group allocation of the patients they were visiting to assess, patients were asked to avoid talking about their group assignment with the assessors, the assessors were also instructed, not to discuss any aspects of the trial with patients. The physician who provided the hypertensive care for patients at clinic was asked to randomly request two outcomes assessors if they could guess to which group this patient might belong, then the physician provided the author with the patients health record's ID and assessors' answers. Additionally the data analysis was conducted by a statistician blinded to the allocation of the groups. To ensure this the statistician was provided with a data set with patients allocated to group 0 or 1. The blind was broken after analysis was complete.

## ETHICS

### The International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice

It was ensured that this study was conducted to fully conform with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996 (ICH, 1996)

### Translation and Approval

The translation to Arabic language for AT, MMAS, BMQ and research related papers (consent form, information sheet, invitation letter, and research protocol) was performed (see chapter 5). After submission of all these papers, appropriate permissions and ethical approvals were given by the Ministry of Health in Jordan (MOH), and the University of East Anglia’s ethics committee (see appendix 10).

### Treatment fidelity

Treatment fidelity was confirmed by the process described above after taking permission from patients for the audio recording of their therapy sessions.

### Participant confidentiality

Patient confidentiality and privacy was maintained. The participants were identified only by participant ID number on any electronic database. All collected data documents and computerised files have been kept securely and were only accessible by trial staff and authorized personnel. The study complied with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

### International Standard Randomised Controlled Trial Number (ISRCTN)

ISRCTN was obtained from current controlled trials limited, and the protocol for the RCT registered under ISRCTN 99494659.

### Data handling and record keeping

All staff involved with this study complied with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and maintained the Act’s core principles (ICO, 1998). The participants were identified by a study specific participant number and/or code in any database. The name and any other identifying details were not included in any study data electronic file. Anonymised study data were entered on a password protected secure computer. To ensure validity and quality of collected data double entry to computer software was done by FA.

### Access to source documents/data

All documents were stored safely in confidential conditions and will be kept locked in secure storage for 20 years by the research team. On all study-specific documents, other than the signed consent form, the participants were referred to by participant number/code alone.

## Summary

The methodology described was strictly adhered to. Our findings are described in the next chapter.

# RESULTS

## PARTICIPANTS FLOW

Figure (6) shows the sequences of events in the trial. Two hundred and twenty four of the 360 patients who passed the initial screening where excluded from the trial because they did not meet with the inclusion criteria; one hundred and seventy of them did not meet with primary inclusion criteria (137 patients were diabetic, 10 had congestive heart failure, 7 had kidney impairment, 9 were pregnant women, 3 were mentally ill, 4 had severe disease condition (CVA)). MMAS was done for 190 patients. Five questionnaires were not returned and four had not been fully completed. Fifteen patients were excluded because they had medium adherence and 30 patients refused to participate. This resulted in the final sample of 136 non-adherent patients with hypertension that were randomised equally to the AT and TAU groups. Six patients (3 in each group) died before the end of the study (due to reasons unrelated to their hypertension), three withdrew from the AT intervention (without giving a reason) and one patient in the AT group was lost to follow-up.

Figure 6 CONSORT diagram showing the participant flow in the trial

6028 Patient records available at clinics

1230 Patients records available for those who had recently attended clinics

360 Patient records assessed for eligibility in reverse date order of attending clinics. Recruitment stopped when sufficient numbers of participants recruited

224 Excluded; 30 refused to participate 194 did not meet inclusion criteria i.e. 137 diabetic, 10 congestive heart failure, 7 kidney impairment, 3 mentally ill, 4 cerebrovascular accident, 9 pregnant,5 didn't return and 4 didn't fully completed MMAS, 15 medium-adherent

136 Randomised

68 started TAU

68 started AT

3 discontinued AT

1 lost to follow up

3 died

3 died

65 completed follow-up

61 completed follow up

68 analysed\*

68 analysed\*

\* All analyses conducted on an intention to treat basis with multiple imputation of missing data.

## BASELINE DATA

### Demographic characteristics

Demographic characteristics of patients by group at baseline are presented in Table 8. The baseline outcomes were imbalanced between the two groups in terms of gender, education, economic status and medical insurance. There were numerically important differences (but not statistical) between the two groups that could be rated as potential confounders. The average of age was 53.6 years. The majority of participants in both groups were educated, lived with someone else, and were married. However, more than half of the AT group’s patients were female, not working, and medically uninsured.

Table 8, Demographic characteristic of patients by groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ***Characteristics*** | **AT Group n=68**  **n (%), unless \* then mean (SD)** | **TAU Group n=68**  **n (%), unless \* then mean (SD)** | **p- value** | **BRFSS STEPwise Survey Jordan 2007** |
| *Age \** | 53.4 (10.7) | 53.9 (11.7) | 0.78 | 64.5% of the population range between age 15-64,Or/ 85% for age group 45-64yrs |
| *Female* | 43 (63%) | 30 (44%) | 0.05 | 50% |
| *Not educated* | 2 (3%) | 10 (15%) | 0.05 | 7.9% |
| *Educated* | 66 (97%) | 58 (84%) | 0.05 | 92.1% |
| *Living alone* | 4 (6%) | 9 (13%) | 0.15 | Not reported |
| *Marital status: Married* | 56 (82%) | 47 (69%) | 0.19 | 71.7% |
| *Marital status: Single / widower* | 12 (18%) | 21 (31%) | 0.19 | 28.3% |
| *Working* | 33 (49%) | 42 (62%) | 0.29 | 48.9% |
| *Not working* | 35 (51%) | 26 (38%) | 0.29 | 51.1% |
| *Medically insured* | 29 (43%) | 36 (53%) | 0.14 | 41.6% |
| *Medically uninsured* | 39 (57%) | 32 (47%) | 0.14 | 58.4% |

BRESS STEPwise Survey Jordan 2007 will be discussed in section 9.2 of chapter 9

### Clinical characteristics

There were no significant differences between groups in any of clinical variables at the baseline (see Table 9). Patients in both groups had had uncontrolled BP, with the same attitudes and beliefs toward antihypertensive medications. Members of both groups had a similar numbers of prescription drugs whether antihypertensive or other types of medication; the patients were taking an average of 2.6 antihypertensive medications and a further 0.7 other medications daily. Most patients in both groups did not smoke and did not follow regular exercise and the hypertension diet regimen (low fat, low salt).

Table 9, Clinical characteristics of participants by groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | **AT Group n=68**  **n (%), unless \* then mean (SD)** | **TAU Group n=68**  **n (%), unless \* then mean (SD)** | **p- value** | **BRFSS STEPwise Survey Jordan 2007** |
| SBP \* | 165.6 (10.1) | 163.4 (9.7) | 0.2 | Not reported |
| DBP \* | 103.2 (7.0) | 101.3 (6.9) | 0.13 | Not reported |
| Number of anti-hypertensive prescribed daily | 2.72 (0.75) | 2.41 (0.63) | 0.5 | Not reported |
| Number of other medications prescribed daily | 0.88 (1.00) | 0.48 (0.76) | 0.5 | Not reported |
| BMQ: General Harm \* | 13.5 (2.4) | 12.4 (3.0) | 0.056 | Not reported |
| BMQ: General Overuse\* | 15.4 (2.3) | 14.9 (2.0) | 0.14 | Not reported |
| BMQ: Sensitivity to drugs \* | 14.9 (2.7) | 15.0 (2.1) | 0.89 | Not reported |
| BMQ: General Benefit \* | 13.6 (2.4) | 14.3 (2.3) | 0.09 | Not reported |
| Current smoker | 19 (28%) | 25 (37%) | 0.5 | 29% |
| Currently exercising + | 22 (32%) | 20 (29%) | 0.7 | 33.4% |
| Keeping restricted diet ++ | 30 (44%) | 23 (34%) | 0.22 | Not reported |

+ Minimum exercise of walking 30 minutes/day (the exercise definition is the same for general population), ++ Adhering to low salt, low fat diet.

### Baseline characteristics for participants who lost of follow up

The demographical and clinical characteristics for those participants who lost follow up are presented in Table 10 and 11. There were no significant differences in demographical characteristics between whole participant population and those who dropped-out from the study (see Table 10). In regarding to clinical characteristics the only difference was in patient’s views on their sensitivity to drugs (as measured in the BMQ), which was higher in whole population (p = 0.007) as compared to those who dropped-out (see Table 11).

**Table 10,** Demographical characteristics for dropped-out participants

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Whole participants** | **Drop-out participants** | **p- value** |
| *Age \** | 53.4 (11.1) | 57 (11.1) | 0.32 |
| *Female* | 59 (47%) | 4 (45%) | 0.9 |
| *Not educated* | 11 (9%) | 1 (11%) | 0.79 |
| *Educated* | 116 (91%) | 8 (89%) | 0.79 |
| *Living alone* | 12 (9%) | 1 (11%) | 0.87 |
| *Marital status: Married* | 97 (76%) | 6(68%) | 0.79 |
| *Marital status: Single / widower* | 30 (24%) | 3 (32%) | 0.79 |
| *Working* | 70 (55%) | 5 (56%) | 0.6 |
| *Not working* | 57 (45%) | 4 (44%) | 0.6 |
| *Medically insured* | 61 (48%) | 4 (45%) | 0.69 |
| *Medically uninsured* | 66 (52%) | 5 (55%) | 0.69 |

Table 11, Clinical characteristics of participants who dropped-out

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Whole participants** | **Drop-out participants** | **p- value** |
| SBP \* | 164.7 (10) | 161.7 (11) | 0.38 |
| DBP \* | 102.4 (7.0) | 100.7 (5) | 0.46 |
| Number of anti-hypertensive prescribed daily | 2.72 (0.75) | 2.41 (0.63) | 0.5 |
| Number of other medications prescribed daily | 0.88 (1.00) | 0.48 (0.76) | 0.68 |
| BMQ: General Harm \* | 12.9 (2.8) | 14 (1.9) | 0.16 |
| BMQ: General Overuse\* | 15 (2) | 15.9 (2.5) | 0.29 |
| BMQ: Sensitivity to drugs \* | 15 (2.4) | 12.9 (1.8) | 0.007 |
| BMQ: General Benefit \* | 13.9 (2.4) | 14.3 (2.9) | 0.58 |
| Current smoker | 19 (28%) | 25 (37%) | 0.16 |
| Currently exercising+ | 22 (32%) | 20 (29%) | 0.36 |
| Keeping restricted diet ++ | 30 (44%) | 23 (34%) | 0.29 |

## TREATMENT OF MISSING DATA

Missing data are common, even with well-designed RCTs (Altman, 2009). In this study missing data occurred because participants had died, were lost to follow up, or withdrew before completing the intervention. The characteristics of individuals who dropped-out were similar for whole population, except their sensitivity to the drug was significantly lower (p = 0.007). There is no perfect method for treating missing data, and there is no gold standard for how much missing data can be tolerated (Altman, 2009, Moher et al., 2010). Generally, a few missing data points (less than 10%) will not be a cause for concern (Moher et al., 2010, Wood et al., 2004). In this study, the proportion of missing data was 7.4% of participants. Surprisingly, there were no missing data due to incomplete datasets (e.g. questions not answered, BP not taken), therefore 100% of data points for participants that did complete the study was achieved.

The estimated dropout rate before conducting this trial was very useful in reducing the effect of missing data on results and detecting of treatment effects (Elobeid et al., 2009). The Last observation carried forward (LOCF) is considered to be a conservative method to deal with missing data (Altman, 2009, Wood et al., 2004). Multiple imputation of missing data was used being based on iterative chain equation modelling including all available outcome measures and their baseline values, and treatment arm. Five imputed datasets were created which were then analysed and combined using Rubin’s equations (Rubin, 1987). Both of these analysis were carried out on with an intention to treat basis with missing data estimated using LOCF or multiple imputation; therefore, the number of participants included in each analysis was 68 per group. Per protocol analysis, which did not impute missing data was also conducted, here the numbers of participants analysed varied according to the data points available.

## Blinding of outcome assessors (Kappa statistics)

We found Kappa to be = 0.156 (p = 0.2) which reflected a low level of agreement between the outcomes assessors. This led to acceptance that the agreement between outcome assessors was by chance. This result confirms that the blindness of outcomes assessors was maintained.

## Patient adherence to BP measurement advice:

In this trial most of the patients reported that they adhered to our advice (not to smoke or drink coffee during the examination). Just 10 patients had drunk coffee and smoked cigarettes, these patients kindly agreed to wait 30 minutes before their BP was measured.

## PRIMARY AND SECONDARY OUTCOMES

The results of Levene’s test for equal variance are given in Table 12. These show that the standard deviation in the change from baseline is significantly different in each group and that the two sample t-test with unequal variances should be used.

**Table 12**, Results of Levene’s test for equal variances for outcome measures

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Group 0** | **Group 1** |  |  |
| Outcome | SD | SD | F | p-value |
| SBP | 9.8 | 5.3 | 19.3 | <0.0001 |
| DBP | 8.7 | 3.7 | 31. | <0.0001 |
| G\_H | 2.5 | 1.0 | 42.8 | <0.0001 |
| G\_O | 1.8 | 1.3 | 10.4 | 0.0016 |
| G\_B | 2.4 | 1.6 | 16.5 | <0.0001 |
| S\_S | 1.6 | 1.1 | 12.2 | 0.0006 |

### Change in Blood Pressure

Tables 13, 14, and 15 summarize the change from baseline in each of the treatment groups. With multiple imputation analysis, the results show that systolic blood pressure (SBP) was reduced in the AT group by 23 mm Hg (95% CI: 20.7, 26.2) more than in the TAU group and similarly diastolic blood pressure (DBP) was reduced in the AT group by 15.6 mm Hg (95% CI: 13.2, 17.9) more than in the TAU group (see Table 13). Analysing by LOCF and per protocol (without ITT) methods led to the same results (see Table 14 and 15). Due to the imbalance between treatment groups in terms of gender, education and medical insurance at baseline, an analysis was conducted adjusting for these factors and the baseline value of the outcome. The adjusted and unadjusted analyses also produced very similar results (Table 13, 14, 15).

Table 13, Analysis of outcome measures (change from baseline) with multiple imputation technique

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **AT** | | **TAU** | | **Unadjusted** | | **Adjusted** | |
| **Outcome** | **N** | **Mean (SD)** | **N** | **Mean (SD)** | **Mean difference (95% CI)** | **p-value** | **Mean difference (95% CI)** | **p-value** |
| SBP | 68 | -22.1 (9.7) | 68 | 1.0 (5.5) | -23.1 (-25.9, -20.4) | <0.01 | -21.6 (-24.4, -18.8) | <0.01 |
| DBP | 68 | -14.7 (8.6) | 68 | 0.5 (3.9) | -15.2 (-17.6, -12.8) | <0.01 | -12.8 (-15.0, -10.6) | <0.01 |
| G-H | 68 | -5.8 (2.4%) | 68 | -0.1 (1.1) | -5.67 (-6.3, -5.0) | <0.01 | -5.0 (-5.6, -4.4) | <0.01 |
| G-O | 68 | -1.2 (1.9) | 68 | 0.1 (1.3) | -1.3 (-1.9, -0.8) | <0.01 | -1.4 (-2.1, -0.8) | <0.01 |
| G-S | 68 | -1.8 (1.6) | 68 | 0.02 (1.32) | -1.8 (-2.3, -1.3) | <0.01 | -1.9 (-2.4, -1.4) | <0.01 |
| G-B | 68 | 2.6 (2.4) | 68 | 0.37 (1.59) | 2.3 (1.5, 3.0) | <0.01 | 1.8 (1.2, 2.5) | <0.01 |
| Percentage adherence at 11 weeks | 68 | 97.2% (4.0) | 68 | 70.6% (10.7) | 26.7% (23.9, 29.4) | <0.01 | 26.4% (23.4, 29.4) | <0.01 |
| Medication changes over 11 weeks | 68 | 8.2 (12.1%) | 68 | 16.8 (24.7%) | OR (95% CI) 0.4 (0.2, 0.6) | 0.08 | OR (95% CI) 0.6 (0.2, 1.7) | = 0.30 |

Unadjusted analysis based on a two-sample t-test and adjusted analysis based on an analysis of covariance model. OR – odds ratio

Table 14, Analysis of outcome measures (change from baseline) with using of LOCF

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **TAU** | **AT** | **Unadjusted** | | **Adjusted** | |
| **Outcome** | **Mean (SD)** | **Mean (SD)** | **Mean difference(95% CI)** | **p-value** | **Mean difference(95% CI)** | **p-value** |
| SBP | -20.32 (11.28) | 1.1 (5.17) | -21.43 (-24.4,-18.45) | <0.001 | -19.75 (-22.68,-16.81) | <0.001 |
| DBP | -13.68 (9.33) | 0.53 (3.58) | -14.21 (-16.6,-11.81) | <0.001 | -11.68 (-13.79,-9.57) | <0.001 |
| G-H | -5.19 (2.89) | -0.01 (0.97) | -5.18 (-5.91,-4.45) | <0.001 | -4.44 (-5.17,-3.71) | <0.001 |
| G-O | -1.09 (1.79) | 0.12 (1.26) | -1.21 (-1.73,-0.68) | <0.001 | -1.31 (-1.91,-0.7) | <0.001 |
| G-S | 2.49 (2.38) | 0.35 (1.56) | 2.13 (1.45,2.81) | <0.001 | 1.7 (1.09,2.31) | <0.001 |
| G-B | -1.63 (1.6) | 0 (1.04) | -1.63 (-2.09,-1.17) | <0.001 | -1.73 (-2.21,-1.26) | <0.001 |

Table 15, Analysis of outcome measures (change from baseline) with per protocol analysis (without using ITT)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **TAU** | **AT** | **Unadjusted** | | **Adjusted** | |
| **Outcome** | **Mean (SD)** | **Mean (SD)** | **Mean difference(95% CI)** | **p-value** | **Mean difference(95% CI)** | **p-value** |
| SBP | -22.29 (9.76) | 1.15 (5.28) | -23.44 (-26.18,-20.71) | <0.001 | -21.65 (-24.32,-18.97) | <0.001 |
| DBP | -15 (8.68) | 0.55 (3.66) | -15.55 (-17.88,-13.23) | <0.001 | -12.86 (-14.93,-10.8) | <0.001 |
| G-H | -5.69 (2.5) | -0.02 (0.99) | -5.68 (-6.34,-5.02) | <0.001 | -4.92 (-5.54,-4.3) | <0.001 |
| G-O | -1.19 (1.85) | 0.12 (1.29) | -1.32 (-1.87,-0.76) | <0.001 | -1.41 (-2.05,-0.78) | <0.001 |
| G-S | 2.73 (2.36) | 0.37 (1.6) | 1.87 (1.25,2.49) | <0.001 | 2.36 (1.65,3.06) | <0.001 |
| G-B | -1.79 (1.59) | 0 (1.06) | -1.79 (-2.26,-1.32) | <0.001 | -1.86 (-2.36,-1.37) | <0.001 |
| Percentage adherence at 11 weeks | 97.49 (3.58) | 70.45 (10.80) | 27.04 (24.16,29.91) | <0.001 | 26.53 (23.41,29.65) | <0.001 |
| Medication changes over 11 weeks | 46/65 (47.57%) | 54/61 (52.43%) | 2.52 (0.96,6.64) | 0.062 | 1.88 (0.66,5.37) | = 0.238 |

### 8.6.2 Change in Beliefs about Medications Questionnaire (BMQ)

The BMQ scores show that beliefs and attitudes about medications in the AT group move away from believing that medications are intrinsically harmful (G-H-5.1 using LOCF, see Table 14; G-H -5.7 using multiple imputation and per protocol analysis, see Table 13 and 15), and towards beliefs in the benefits of the medications (G-B 2.7 using multiple imputations see Table 13; G-B 1.9 using LOCF and with per protocol analysis, see Table 14 and 15) with little or no change in attitudes over the period of the study in the TAU group.

### Adherence rate

Patients in the AT group took substantially more of their medications (97%) compared to those in the TAU group (71%) (The results were similar with both multiple imputation and per protocol analysis (see, Table 13 and 15).

## ADDITIONAL OUTCOMES

### Correlation BMQ, adherence and blood pressure

The proposed mechanism of action is that AT will positively influence attitudes and beliefs about medications, which will improve adherence, and which will, in turn, reduce blood pressure. The BMQ scores indicating negative beliefs about medication were all negatively correlated with adherence (GH: -0.73, p < 0.001, G-O: -0.31, p < 0.001 and G-S: -0.46, p < 0.001) and the BMQ General Benefit score was positively correlated with adherence (0.44, p < 0.001), i.e. a reduction in negative beliefs and an increase in positive beliefs about medication improved adherence. The adherence scores were negatively correlated with BP (SBP: -0.71, p < 0.001, DBP: -0.63, p < 0.001) i.e. an improvement in adherence reduced BP. Finally the results also identified that the BMQ scores indicating negative beliefs were positively correlated with SBP (G-H: 0.75, p < 0.001; G-O: 0.20, p = 0.028; G-S: 0.53, p < 0.001) and the BMQ General Benefit score was negatively correlated with SBP (-0.45, p <0.001) i.e. negative beliefs about medication are associated with higher SBP, and positive beliefs about medication are associated with lower SBP.

### Size of the effect

The size of effect of the AT on adherence (37% increase) and BP (SBP -23.1 mm Hg (95% CI: -25.85, -20.36), DBP -15.2 mm Hg (95% CI: -17.55, -12.80)) were all clinically relevant. The results of LOCF and per protocol analyses were nearly identical (see Table 14 and 15).

### Subgroup analysis

There was no significant difference in the average adherence rate between individuals on mono-therapy compared to those prescribed two or more antihypertensive medications in either the AT or TAU groups.

### Medication change

Table 13; reports that 12% patients in the AT group changed their hypertensive medications compared to 25% in the TAU group when analysed using the multiple imputation technique. However, this was not statistically significant. Analysis using per protocol techniques also showed there was no statistically significant difference in the numbers of patients who changed their hypertensive medications between TAU and AT groups (48%, 52% respectively) (see, Table 15). (LOCF was not possible as the measures were only conducted once at the end of the study).

### Cost Estimation

The estimated cost of the delivery of the intervention was 7 AT sessions x 20 min i.e. 2 hours 20 minutes of a mid-grade nurse (mid-Band 6 in the UK, including all employers’ costs) plus the hire of a suitable room in an outpatient clinic for the same duration. From this we calculated that the price of a course of AT would be approximately US$ 130 per person. In Jordan this is equivalent to 100 JD per person.

### Negative events during trial

There were no serious adverse events reported in either group. Three patients in each group died as the results of accidents unrelated to the adherence intervention and their hypertensive care. No other serious events were reported.

## THE RESULTS WHICH USED IN DISCUSSION

We analysed our results by ITT (LOCF and multiple imputations) and without ITT (per protocol), however, the findings were same for all outcomes. Use of the LOCF analysis may sometimes lead to loss of power in detecting treatment effects since it may exaggerate the available sample size, lead to low standard deviation and low p value (Shao and Zhong, 2003). The National Academy of Science advised that "single imputation methods like last observation carried forward and baseline observation carried forward should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified" (National Research Council 2010, p110-112). Also they recommended the use of multiple imputation methods, because they are more robust, reliable and can work with variety of conditions compared to single-imputation methods (e.g. LOCF) (National Research Council, 2010). Also, Elobeid et al’s (2009) review claimed that the multiple imputations is better than other methods for handling missing data in RCTs because it reduces the risk of underestimating the variance of the treatment effect. For all these reasons, consequently, we believed of multiple imputation is a conservative and appropriate technique for this trial so our discussion will be based on the results of the multiple imputation analyses.

## SUMMARY

This trial demonstrated that AT had clinically relevant effects on the BP, level of adherence and attitudes and beliefs of medication non-compliant patients with hypertension in Jordan. A discussion of these findings compared to those from previous trials, as well as the limitation of this trial, is presented in the following chapter.

# DISCUSSION

## INTRODUCTION

A parallel group single blind RCT was conducted to assess the efficacy of AT in hypertension. The primary hypothesis was that AT would lead to a significant reduction in SBP in Jordanian people with hypertension at 11 weeks, as compared to TAU. The secondary hypotheses were that AT compared to TAU would lead to a reduction in DBP, enhance adherence rates to antihypertensive medication, modifying attitudes and beliefs towards taking medications at 11weeks. The correlations between main outcome variables were identified. Other potential outcomes included changes in medication in AT compared to TAU, differences in adherence rates between patients on mono-therapy, compared to those prescribed two or more antihypertensive drugs in either the AT or TAU group, and cost estimation.

One hundred and thirty six non-complaint Jordanian people diagnosed with hypertension from three general hospitals outpatient clinic were randomly assigned to an experimental group (AT) and a control group (TAU). Patients in the AT group received one session of 20 minutes per week over seven weeks of AT from a trained therapist, whereas patients in the control group received treatment as usual from their usual health care team (physicians and nurses). Baseline, one and 11 weeks assessment were carried out by three nurses who masked to the interventions group assignment. The primary outcome measure was SBP measured using a stethoscope and a manual mercury sphygmomanometer. The secondary outcomes measures were in addition to DBP, pill count, and beliefs about medications (BMQ).

The results revealed that the patients in the AT group, compared with those in the TAU group showed significant reduction in SBP at 11 weeks. The study also demonstrated a reduction in DBP, an improvement in adherence rates, and modified patient attitudes and beliefs in a favourable direction in the AT group at 11 weeks. Twelve percent of AT patients changed their hypertensive medications compared to 25% in receiving TAU during the 11 week study period with no significant differences between groups. There were also no significant difference in the average adherence rate and number of antihypertensive drugs which had been taken by the patient. The negative beliefs of BMQ scores were associated with non-adherence and BMQ general benefit score was associated with adherence. Non-adherence also was associated with higher BP. BMQ General Benefit scores were associated with SBP reduction. In summary, the trial results demonstrated that the AT was effective among non-compliant Jordanian hypertensive patients and can be administered effectively by a nurse.

This chapter considers the findings of the trial in the context of available evidence. Following an exploration of the representativeness of the sample, the outcomes of the hypotheses tested are discussed and the limitations of the trial are reviewed.

## REPRESENTATIVENESS OF THE SAMPLE

The participants in this trial were representative of people with hypertension in Jordan. There is a national report of demographic and clinical characteristics of Jordanian people with hypertension available to compare with those in the current trial (see Table 8 and 9, chapter 8).

The characteristics of patients in this trial are similar to those in the national Jordanian report 2007. In the current study more than half of participants were female, educated, married, and with no medical insurance. Also less than half of them did not take the minimum recommended amount of exercise (30 minutes walking per day) and most of them were non-smokers.

### The lower proportion of living alone

Similar to other Mediterranean Muslims, only around 10% of patients were living alone. This is because most Jordanian people live in extended families generally consisting of more than one generation living together, which allows family members to take care of each other. The Jordanian culture and beliefs are based mainly on Islamic principles (Dhami and Sheikh, 2000, Miklancie, 2007). Muslims are not only encouraged but rather ordered by Allah to establish good relations with and prevent harm to their family members, particularly elderly ones (Dhami and Sheikh, 2000, Yousef et al., 2008). Muslims also take care of parents and the elderly whether they live together or separately (Dhami and Sheikh, 2000, Miklancie, 2007, Rahman, 1998).

### The higher reading of blood pressure

In this trial the mean baseline SBP reading was 164.5 mm Hg, DBP was 102.2 mm Hg. This level of hypertension is higher than what has been reported in other studies of hypertensive patients in Jordan (Jaddou et al., 2003, Kahasawneh et al., 2005, Yasein et al., 2010) and the Gulf area (Al-Mahroos et al., 2000, Al-Mehza et al., 2004, Al-Sowielem and Elzubier, 1998, Al-Yahya et al., 2006). All of these studies targeted hypertensive patients regardless of their level of compliance at baseline. However, all of the participants who were recruited to our study at baseline were non-compliant hypertensives as determined using the Morisky Medication Adherence Scale (MMAS) as a predictor of adherence. It would be logical to suggest that poor compliance would be associated with a higher BP, thus explaining our higher level of BP compared to studies that had mixed populations of adherent and non-adherent hypertensive patients.

## PRE-SPECIFIED OUTCOMES

Current clinical guidelines on strategies for enhancing adherence are based largely on observational data that has yet to be rigorously tested in robust RCTs (Nunes et al., 2009, WHO, 2003a). AT uses cognitive and motivational interviewing techniques to modify beliefs and amplify the personally relevant benefits of medication with the aim of improving adherence. Throughout the AT's sessions the patient’s desire to comply was not assumed and personal construction of meaning and responsibility were emphasized (Gray, 2003, Hardy, 2009). AT incorporates all of the key elements of the NICE and WHO guidelines (Nunes et al., 2009, WHO, 2003a) and this study represents a rigorous test of them. Since there are few studies that have used motivational interviewing for enhancing hypertensive patients adherence, in this section, the results of current trial are discussed in comparison with previous trials (particularly trials that evaluated behavioural interventions aimed at changing behaviours for enhancing patients adherence to a hypertensive drug regimen) (see Chapter 4).

### Change in BP compared to previous pharmacological studies

Analysis of covariance showed that AT lowered SBP by -23.11 mm Hg (95% CI: -25.85,

-20.36) and DBP by -15.18 mm Hg (95% CI: -17.55, -12.80), compared with TAU. This difference between groups is statistically significant.

Law’s review (Law et al., 2003b) of 354 RCTs of BP lowering drugs showed that the average BP of trial participants was 154/97 mm Hg (90% range: SBP 139-170, DBP 97-106), making the current trial patient’s baseline average BP (164/102 mm Hg) towards the top of the range that is usually recruited into hypertension trials. They determined that patients placed on two drugs had an average reduction of 14.6 mm Hg for SBP, and 8.6 mm Hg for DBP. Our patients were prescribed 2-3 antihypertensive drugs on average, which may in part account for the larger reductions in BP observed (SBP 23.1 mm Hg, DBP 15.2 mm Hg). It may also be that patients recruited to pharmaceutical trials tend to be selected for adherent behaviours; consequently there may be less potential room for improvement (the ceiling effect). The patients in this study were specifically selected for their non-adherence to their medication at baseline, and as compliance levels improved so dramatically in the AT group, I may be observing close to the maximum change capable of being achieved by these antihypertensive drugs.

Another possible explanation for the observed effect AT might be changes in patient lifestyle behaviours. Some researchers discussed the effect of modification of the patient's lifestyle on BP control and improvement; a Cochrane review conducted for 20 RCTs in individuals with elevated BP showed that the modest reduction in salt intake for four weeks duration or more had a significant main reduction in SBP (-5. 06 mm Hg ( 95% CI: -5.81 to -4.31 ) and -2.70 mm Hg (95% CI: -3.16 to – 2.24) ) for DBP for individuals with elevated BP (He and MacGregor, 2004). In addition, smoking cessation has been shown to lower BP; however, the mechanism is not fully understood (Groppeli et al., 1992, Oncken et al., 2001, Pandey et al., 2009). Around half of those patients in the AT group were following a low salt low fat diet, more than half of participants in this study were non-smokers (around 60%) at baseline, and the both groups (AT and TAU) had identical BP at baseline. However, we cannot assume any effect for AT in these factors and on the patients’ life style modification at the end of the study. It is possible, that by examining patients’ health behaviours and beliefs in general this may have prompted specific changes in diet and smoking behaviours. But AT did not specifically target these issues and so we did not measure these behaviours at the 7 weeks end point. During the therapy a number of patients discussed changing lifestyle behaviours as a way of managing BP to enhance the effects of medication. Although some of the change observed in our study may be due to diet and smoking, we have no data to support this hypothesis. Therefore their effect on the observed reduction in BP is questionable and requires confirmation in future research.

### Adherence

AT improved adherence to a level of 97% compared with the TAU group's level of 71%. This may result from the ability of AT in emphasizing personal choice and responsibility that has helped patients enhance their self-motivation with regard to changing their medication taking behaviours (Gray et al., 2006, Hardy, 2009). AT's components have the ability to increase a patient's readiness to change, enhance self-efficacy, self-esteem and confidence in their ability to overcome barriers necessary to achieve a desired outcome (which was medication taking behaviour) (Gray, 2003, Ogedegbe et al., 2008).

Although results from recent reviews indicate the positive effect of combined motivational interviewing and cognitive behavioural approach on psychological, physiological and life style change outcome in patients with chronic diseases (Friedman et al., 1996, Ogedegbe, 2008, Schroeder et al., 2004), only one study has previously assessed the effect of AT in a sample of people with schizophrenia. This was in Thailand (Maneesakorn et al., 2007). In this study, the AT group reported a significant improvement in overall psychotic symptoms, attitudes towards and satisfaction with medication compared to TAU. However, the effect of AT on medication adherence was limited by small number of patients (n=32). Another limitation of Maneesakorn's study is the degree of adherence for participants before entering the trial was not known and they made no direct reliable measurement of the adherence measure used. They assessed improvement in psychopathology and attitudes towards medication since these outcomes strongly influence medication adherence. In our study, 136 patients were non-compliant at baseline and were assessed for change in SBP as the primary outcome and change in DBP, adherence rate and attitudes and beliefs as secondary outcomes. We measured all of these outcomes because we have concerns regarding the accuracy of methods which we used to assess adherence rates (as we discussed no accurate adherence measure is recommended) and because changes in BP should logically be the direct clinical effect of improved adherence to antihypertensive drugs.

The only study that has previously tested the effect of a motivational interviewing (MI) intervention among hypertensive patients is Ogedegbe et al (2008). This study reported that the MI led to a significant steady maintenance of adherence in hypertensive African Americans, over 12 months compared to a significant adherence reduction demonstrated in the usual care group.

Furthermore, the significant increase in the level of adherence in this study might be because AT includes sub-interventions (see Figure 5, Chapter 7). For example, identifying a patient's history and previous events have been shown to increase adherence levels (Wai et al., 2010). AT also has a problem solving intervention that helps patients to deal with medication related problems. This strategy had a positive impact on enhancing medication taking behaviours (WHO, 2003a). Moreover, adherence behaviours have been shown to significantly improve when patients’ attitudes and beliefs are explored (Morrison et al., 2000, Nunes et al., 2009). This was the core of our intervention (AT).

One factor that is known to reduce adherence is, having to take more than one drug per day. A meta-analysis review of eight studies reported that the adherence level for mono-therapy drug was significantly higher than for multiple daily dosing (91.4% vs. 83.2%, respectively, P < 0.001) (Iskedjian et al., 2002). Similarly Schroeder et al’s (2004) systematic review of RCTs reported that adherence improved through the use of once daily instead of twice daily dosage regimens. An inverse relationship was observed between adherence and the number of pills prescribed in Hashmi et al (2007); the study which was conducted among Muslim Pakistani hypertensive patients. Mean adherence was 79% for once daily dosing compared to 90% for those on three drugs or more (P < 0.02) (OR; 95% CI, 0.3; 0.1–0.6) (Hashmi et al., 2007). Currently it is recommended that two antihypertensive medications should be prescribed for most people with hypertension in order to maximize BP control (Williams et al., 2004). However our results showed no significant difference in the average adherence rate between individuals on mono-therapy compared to those prescribed two or more antihypertensive drugs in either the AT or TAU groups. This is consistent with Inkster et al (2006) who found that there is no relationship between number of drugs and poor adherence (Inkster et al., 2006).

### Change in patients attitudes and beliefs toward medication

Theunissen et al (2003) claimed that exploring patients emotional and cognitive illness representations, lowered their concerns about the harmful effects of medicines and encouraged them to take positive steps to manage their BP (Theunissen et al., 2003). Furthermore, a systematic review of 30 RCTs was conducted by Zygmunt et al (2002) who examined the psychosocial interventions for improving medication adherence among schizophrenia patients. They reported a significant positive effect on patients’ attitudes and beliefs for the interventions that used cognitive and motivational interviewing techniques in improving adherence (Zygmunt et al., 2002). AT in this trial encouraged patient to articulate their negative beliefs and ambivalence about BP lowering medications (G-H -5.7) while focusing on adaptive behaviour and the benefits of medication drugs (G-B 2.7) in order to stay well.

### Causal mechanism

The hypertensive patients desire to adhere was not assumed and all began the study with relatively neutral beliefs about medication, but poor adherence behaviours. In AT sessions a personal construction of meaning was emphasized. Therefore, those in the AT group shifted their opinions so that overall they disagreed with statements regarding the intrinsically harmful nature of medicines, and overall agreed with statements regarding the intrinsically beneficial nature of medicines. This shift in beliefs led to a change in adherence behaviour (37% improvement in the number of pills taken over 1 month), which subsequently reduced the BP to close to the usual target ranges (Mean SBP/DBP 143/88 mm Hg). No such shift in medication beliefs or adherence behaviours was observed in the TAU group, and their endpoint BP had barely changed from baseline (Mean SBP/DBP 164/102 mm Hg). That we have been able to demonstrate how AT has impacted on BP is important and particularly pleasing because few, if any, previous adherence studies have been able to establish this. To an extent this observation also counters one of the major weaknesses of our trial; a lack of a control intervention that addresses the non-specific attention (Hawthorne) effects of the therapy.

### Size of effect

The comparison of the magnitude of the effect sizes of experimental treatments from one experiment to another are especially important (Warsi et al., 2004).

Although the sample size of 136 patients was modest the confidence intervals for the effect are narrow due to the small variation in BP in this population. A previous Cochrane systematic review of RCTs of adherence therapies in hypertension (Schroeder et al., 2004) had demonstrated up to a 41% increase in adherence, and reductions of up to 19.5 mm Hg in SBP, and 12.7 mm Hg in DBP. The duration of the follow-up was short (4 weeks) so the impact of the AT was maximised and may not have suffered from decay in effect that might be expected with a longer follow-up period.

### Adjustments to prescriptions

In the current trial there was no significant difference in the rates of prescribing adjustments in either group, although the TAU group did change their medication more often. This study had a short period of follow-up (one month) which may have reduced the likelihood of us detecting differences in the rates of medication adjustment between the two groups. It is consistent with the Barrios et al (2007) trial which was conducted over 12 weeks to test the effectiveness of MEMS. However, Ogedegbe et al (2008) reported a greater frequency of adjustments in medication in the usual care group in hypertensive African Americans compared to the motivational interviewing intervention group, over 12 months follow up. In addition, Wetzles et al (2007) conducted a five month trial that tested the effect of MEMS among hypertensive patients in the Netherlands, which showed that medication adjustment was higher for the usual care group compared to those in whom adherence was monitored (P < 0.01) (Wetzels et al., 2007). This reflects that no clear association between follow-up duration and adjustment of treatment exists. Thus with a longer follow-up period it was not possible to predict if similar changes or not would have been observed.

### Cultural issues

Ideally an effective intervention should be effective irrespective of the ethnic and racial settings in which it is used. Thus such interventions should produce widely applicable findings for improving health status (Morisky et al., 2002). To the knowledge of the research team this is the first RCT that has tested the effect of AT on reduction in BP and medication adherence among mainly Muslim hypertensive patients. Griffiths et al (2005) has suggested that a belief in the predetermination (‘takdir’ or destiny) of the Islamic life-course can present a barrier to the uptake of interventions that aim to improve health behaviours. In fact, Islamic religious beliefs encourage healthy behaviours for Muslims in all aspects of life (Padela, 2007, Sarhill et al., 2001). In addition, the success of the current intervention refutes Griffiths et al’s (2005) hypothesis, although we acknowledge that Islamic beliefs and behaviours vary across the world and the fact that the therapist (FA) is from Jordan meant that she undoubtedly presented the AT in a culturally acceptable manner.

### Global impact of hypertension

Hypertension was estimated to be present in 26% of the adult population in 2000, which represents 972 million patients. The number of adults with hypertension in 2025 is predicted to increase by about 60% to a total of 1·56 billion (Kearney et al., 2005). It has been estimated that the cost of hypertension was US$ 370 billion globally in 2001, and indirect costs could be as high as US$ 3600 billion annually. This represents about 10% of the world’s overall healthcare expenditure (Gaziano et al., 2009).

Although a formal evaluation of cost effectiveness could not be conducted with the data collected from this study, it was calculated that the price of a course of AT would be approximately US$ 130 per person. Considering the substantial costs of treating hypertension outlined above and the fact that observational studies have predicted that a long term reduction of 10 mm Hg DBP would be predicted to lead to at least a 56% reduction in strokes and a 37% reduction in chronic heart disease (MacMahon et al., 1990), even a small reduction of BP by 3 mm Hg can decrease the risk of stroke by 34%, and by 21% of ischemic heart diseases (Law et al., 2003), it would seem reasonable to suggest that this intervention is likely to be cost effective.

AT could be considered a cost saving and if the AT did have a longer term impact on the character of prescriptions, or the rate of utilisation of medical services (e.g. visits to their family practitioner or to the emergency centre at the hospital) then this would have to be incorporated into the cost analysis. However, for this study, the simple cost calculation included just nurses’ time, employer costs, and the hire of a suitable venue. This means we took basic medical costs into account. There is a need to take into account in addition to these factors the following cost aspects in future research (Goossens et al., 2000):

1. Healthcare costs: such as cost of antihypertensive drugs, physician, pharmacist, therapist transportation, cost of adherence and BP measurement.

2. Patients costs: such as travel cost incurred by patients in obtaining medical care and AT sessions.

3. The societal costs: which include non-medical costs and health effect regardless of who incurs the costs and who obtain the effect was not included.

In addition, longer term health economic modelling of predicted savings associated with a lowered rate of complications resultant from hypertension would be helpful to allow for the assessment of the value of such an intervention to the healthcare system and society as a whole. Cost of TAU also should be calculated to compare the cost effectiveness with AT. Therefore, future cost effective analysis should address all these points to determine the real cost saving merit of AT.

## LIMITATIONS OF THE TRIAL

### Inclusion and exclusion criteria

This trial is the first of its kind conducted on a Jordanian population. The use of a relatively homogeneous sample of patients made the results easier to interpret, so patients with other chronic diseases, mental illness, hypertension complication, and pregnant women (see exclusion criteria, Chapter 7) were not included in this trial. Therefore the translation of results into practice may be difficult, as the strict inclusion and exclusion criteria may be too "ideal" for routine practice. The trade off is that these findings can be generalised to people in Jordan and other Middle East countries who are similar to the participants in this study in the above characteristics.

### Imbalance baseline characteristics

The process of randomisation was only partially successful in balancing the baseline characteristics of the two groups as there were differences in terms of gender balance, employment status, education level and medical insurance status. Imbalance between groups in baseline characteristics may influence outcomes and can bias statistical tests (Moher et al., 2010). In this trial there were numerically important differences (but not statistical) between the two groups that could be rated as potential confounders that may limit the generalisability of the findings. The adjusted analysis which has been recommended to increase in power the analyses of the treatment effect was done (Hernández et al., 2004). However, the current trial's findings were nearly identical whether using adjusted or unadjusted analyses.

### Adherence measurement and types

The counting of pills over after one month was used to estimate the level of adherence. However we recognise that the absence of pills does not necessarily mean that the patient has correctly taken their medications. Pill counting cannot identify other types of non-adherence such as inappropriate timing or dosage. However, as has already been considered, there is no perfect measure for assessing medication adherence.

### Single therapist

Although the use of a single therapist limits the generalisability of this intervention it is believed that this was mitigated as FA was trained according to the standard manual to deliver AT and the fidelity of the delivery was confirmed. However the “halo” effect cannot be ruled out which may have resulted from the passion for the intervention and the fact that it was taking place in the context of a clinical trial. Both factors may have enhanced the effect size of the AT intervention and may not be replicable in more general practice.

### Unmasked participants

Patients were aware of the fact that they were being monitored because this was explained to them in the patient information sheet. This may have encouraged them to be more adherent with treatment than usual. The lack of change in BP in the TAU group suggests that this did not occur in this group. However, it is recognised that due to the relationship the patients in the AT group developed with their therapist (FA) during therapy, they may not have wanted to let her down, and were particularly adherent during the assessment period.

### Short time follow-up

The effect of AT on BP reduction, adherence behaviour, and patients’ attitude and beliefs may have been enhanced by the short follow up period (4 weeks). Other studies have shown that adherence to long term medications decreased over time and declined sharply in the first six months after the initial prescription (Chapman et al., 2005, Cohen, 2001).

### Reliability of the Arabic measures

All measures were translated into Arabic using a rigorous translation process. However, they were piloted with only five Jordanian patients with hypertension. Although the results of this pre-testing were encouraging, more psychometric work is necessary. However, it is encouraging that no trial participants indicated any difficulty in using the measures. Despite this, for these Arabic versions of the measures to be recommended for wider use requires further investigation with large samples to ensure the reliability of the measures.

### Lack of placebo control and lack control by mean of time and attention care

AT showed a great effect on patient's BP, adherence, and attitudes and beliefs. However, these findings are mitigated by; the lack of a control intervention to control for the time and attention that those in the AT group received. Thus the results could be derived from the Hawthorne effect in which the participant's responses and behaviours are affected to the fact they are being studied not in response to applied intervention (McCarney et al., 2007). However, not all of the influence of the lack of a control group would lead to an increase size of difference as it would also be necessary to factor in the “inconvenience” of having to find time to receive the AT, which would likely have a negative effect. Additionally some researchers have argued that there is a need to have placebo group when conducting RCTs (Cochrane, 1972, Gensini et al., 2005, Hrobjartsson and Norup, 2003, Moerman and Jonas, 2002). Placebo is medically ineffectual treatment or intervention for a disease or other medical condition intended to deceive the recipient (Gensini et al., 2005, Hróbjartsson and Norup, 2003, Moerman and Jonas, 2002). Despite this, when patients are given a placebo treatment or intervention they might have a perceived or actual improvement in a medical condition, this commonly called the “*placebo effect*”(Hrobjartsson and Norup, 2003). Placebo effect is dependent on patient’s beliefs that the intervention they are receiving is beneficial (Kaptchuk et al., 2010, Kirsch, 1985). Placebo effects often include small, short term benefits e.g. reductions in blood pressure (Kaptchuk et al., 2010, Klinger et al., 2007). In contrast, Hrobjartsson and Gotzsche (2010) claimed that the placebo interventions did not have important clinical effects in general.

In our study we were aware that we did not control for either placebo or Hawthorne effects. We did not use placebo control intervention since there was no evidence about what kind of placebo intervention would be clinically ineffective and not have any significant effect on clinical outcomes. Furthermore, the placebo intervention had to be ethical and acceptable to patients (Kaptchuk et al., 2010, David, 2008); therefore an intervention that was just “time wasting” and not a usual part of clinical practice was not acceptable to us. However, as part of this program of research we submitted a systematic review which aimed to identify the efficacy of interventions aimed at improving hypertensive medication patient adherence to the Cochrane library. We found that didactic education is not effective in improving adherence to BP lowering medication. As this sort of patient education is still frequently used in current clinical practice an argument could be made for this intervention to be used as a placebo group in future research.

## STRENGTHS OF THIS TRIAL

This trial is the first study to assess the efficacy of AT among non-compliant medication patients in Jordan. It has several strong points. First, it shows that AT can be effectively applied to hypertensive patients in Jordan by a relatively inexperienced therapist. Second, treatment fidelity was checked by an independent person who assured that the AT delivered in practice adhered to the protocol. Third, the demographic characteristics of patients were representative of hypertensive patients in Jordan. Fourth, all of the measures were translated, back translated, and tested with the target population; the current results showed that measures used have good psychometric properties. Fifth, the outcome assessors, and analysts were masked to the group assignment. Sixth, no adverse events were observed. Seventh, it shows that an intervention which was developed and practised in Western countries can be effectively applied in Muslim countries. Finally, all patients completed their therapy sessions as required, and the subsequent dropout rates were very low in comparison to previous research. All these, in addition to positive findings of the trials, make the results of the study promising and suitable to be used to inform clinical practice.

## SUMMARY

The AT seems to be an effective intervention for enhancing patients adherence to antihypertensive drugs regimen through modifying patient's attitudes and beliefs and consequently effect on clinical outcomes (BP reduction). However, there is a need to understand how AT exerted the observed effect. Therefore the next chapter presents the patients experienced AT views and issues.

# EXPLANATORY QUALITATIVE INTERVIEWS

## INTRODUCTION

Chapter 4 described several interventions that have been proposed by authors to enhance patients medication adherence. In this trial we tested the effect of an AT intervention which is characterised by a patient-centred approach of cognitive behavioural and motivational interviewing techniques. In AT the therapist practiced effective communication skills (such as working collaboratively, reducing resistance, generating discrepancy; and exchanging information) and used the key techniques (such as medication problem solving, looking back at the disease history, exploring ambivalence, and checking beliefs) to enhance the likelihood of the patient to taking their medication as prescribed. Chapter 8 reported that AT had a positive impact on a group of non-complaint hypertensive patients; AT lowered SBP by   
-23.11 mm Hg (95% CI: -25.85, -20.36) and DBP by -15.18 mm Hg (95% CI: -17.55, -12.80), improved their beliefs about medication in a favourable direction, and enhanced adherence (by 37% at 11 weeks compared to TAU). Whilst our trial may have been effective we do not understand which elements of the package are effective, which are inert, and which were valued by patients. Patients levels of satisfaction with AT was also of interest. Therefore, the aim of this part of the study was to investigate the subjective experience of hypertensive patients who received AT.

## QUALITATIVE APPROACH AND THEMATIC ANALYSIS

When evaluating complex interventions researchers often use qualitative techniques to help them to develop a better understanding and answer certain important questions about phenomena (such as the how and of why a particular phenomena has happened) (Cress, 2003, Patton, 2002). Qualitative research means a focus on qualities of process and meaning that cannot be measured in terms of quantity, amount, frequency or intensity (LoBiondo-Wood and Haber, 2006). It also implies the analysis of open-ended questions that respondents are asked (LoBiondo-Wood, et al., 2006; Polit and Beck, 2006).

There are four commonly used research traditions in qualitative research; grounded theory, case study, ethnographic, and phenomenology (LoBiondo-Wood and Haber, 2006, Polit and Beck, 2006). These methods differ in the purpose, outcome and philosophical approach upon which they are built (LoBiondo-Wood and Haber, 2006, Polit and Beck, 2006). However, all methods share such similarities (e.g. involve data that are textual rather than numerical) (LoBiondo-Wood and Haber, 2006). Phenomenology is a useful qualitative method, which is used when the researcher aims to understand an experience (Akerlind, 2005). The phenomenological approach is used to answer questions of meaning (adaptive for mapping the qualitatively different way in which people experience, conceptualise, perceive, and understand various aspect of and phenomena in, the world around them) (Marton, 1986). It is particularly useful when little is known about a particular topic (such as receiving AT) (LoBiondo-Wood and Haber, 2006). The phenomenological approach is an empirically based research design focusing on recognising and describing the limited number of qualitatively different ways that people conceptualise and experience a particular event (Svensson, 1997 ).

Data collection for qualitative research includes structured, semi, and non-structured interviews, written narratives or self reports. Semi-structured interviews are the most commonly used method of generating data. Also this helps the patient to feel relaxed and comfortable talking with the interviewer (Bryman, 2006). A set of questions to guide the interview are asked to capture as much as possible the subject's thinking about the study's topics, the interviewers follow the process of thinking, and pose new question after the answers given by the subject (DiCicco-Bloom and Crabtree, 2006). Also, semi-structured interviews can incorporate different material: video, stories, dilemmas, and practical problems to be solved, so it can be a useful tool in an intervention context (Bryman, 2006, DiCicco-Bloom and Crabtree, 2006). In data collection the focus is gathering an in depth understanding of phenomena such as human behaviour, and the reasons that evoked and motivate it through answering why and how certain practices were achieved (Maxwell, 2005). Qualitative design gives information only on the particular phenomena and any more general conclusions remain only as a hypotheses as we know, qualitative methodologies cannot be used to test a hypothesis (Cress, 2003, Maxwell, 2005). Regarding data analysis, observer interpretation is the most common way of understanding data that is gathered through a qualitative approach (Maxwell, 2005). The meaning of information collected is the main focus of the researcher, either in terms of a content analysis, more descriptive, either by response interpretation in term of levels of complexity (Ericsson and Simon, 1984, Maxwell, 2005). After coding of the interview into categories, looking for similarities and differences within the data have to be performed (Cress, 2003). Then counting the frequency of themes can follow (Cress, 2003). In this study a thematic analysis was used for analysing and encoding of qualitative information (Cress, 2003). This interpretive technique helps researchers to organize and understand their data (Maxwell, 2005, Boyatzis, 1998).

Thematic analysis is widely used by researchers because it provides an accessible form of analysis and can be used within different theoretical frameworks (Boyatzis, 1998). Also it does not require the detailed technological and theoretical frameworks that are required in other methodologies such as grounded theory (Braun and Clarke, 2006). There is no definitive description of how thematic analysis should be undertaken (Attride-Stirling, 2001, Tuckett, 2005). Thematic analysis is described by Braun and Clarke (2006) as a method of identifying, analysing and reporting patterns (themes) within data. It helps researchers to increase their ability to understand and interpret the observations (Boyatzis, 1998, Cress, 2003, Maxwell, 2005). Thematic analysis can be used to report experiences, meanings, and the reality of participation (Boyatzis, 1998).

Therefore in-depth interviews were used (Boyatzis, 1998, Cress, 2003, Maxwell, 2005) as this is best suited to achieving a deep understanding of experiences and views from the perspective of the patients who received AT sessions. Although, the philosophical background of this piece of work is not based on specific theory, it can be said that the qualitative study is nearly aligned to a phenomenological approach because;

1. There is a little known about AT.

2. There was a need to observe patient experience of the phenomena (AT) (at that time point the participants and the researcher were unaware to the RCT results).

3. Evidence about how AT could work and how patient experience of it was needed.

4. There was a need to know which elements of the therapy are appreciated by patients and overall how satisfied patients were with AT

In this study we adhered to the Consolidated Criteria for Reporting Qualitative research (COREQ), which aims to promote complete and transparent reporting, and improve the rigor, entirety and reliability of qualitative research (Tong et al., 2007).

## METHOD

### Aim

The aim of this study is to understand patient's experience of AT in a group of patients that received a seven sessions of AT as part of RCT.

### Design

The design of this study is a qualitative in-depth interview approach, using semi-structured interviews.

### Interviewer

The author was the interviewer. The author is a Jordanian nurse trained to deliver AT and had provided the hypertensive patients with seven sessions of AT in the randomised controlled trial.

### Participants

A convenience sample of the first ten hypertensive patients that agreed to be interviewed after their course of AT had finished. They were all adults’ over18 years of age, initially non-adherent to their hypertensive medications and in receipt of regular clinical follow up.

### Data collection

Interviews lasted up to 20 minutes and were audiotaped. A reflective diary was used to support the audiotaped data and to help patients feel that the therapist was interested in what they were saying. Simple language was used and technical terms were avoided. The interviews were conducted on a one-to-one basis in a private room. The patients were told that our aim was not to audit or make judgements about on practice but to understand their experience and views about AT. At the time of the interview, both the interviewer and patients were unaware of the trial results. The interview schedule explored the following broad themes of (see Appendix 11):

1. Components of the AT intervention

2. Communication style

3. The physical environment of AT

4. Patient's expectations of AT

### Data analysis:

The author (FA) transcribed the data from audiotapes in Arabic then translated these transcripts into English. Forward translation from Arabic to English was carried out by DM and FA separately then the two translation drafts were compared to identify similarities and differences. The final draft was checked by KD for English editing after discussion with FA to confirm that the exact meaning for each statement was maintained. The backward translation from English to Arabic was done by DM. The final confirmed English version of the translated interviews was then analysed using a data driven thematic approach. The data were analysed for themes in four stages; stage one involved reading through each interview 4-5 times to allow themes to emerge. Broad themes were then identified and these were then discussed and agreed by supervisors (RG, KD). Five major themes emerged from the data: modifying attitudes and beliefs, positive effect on self efficacy, motivational therapist, positive impact on wellbeing, and a well designed intervention. Under these five major themes a number of sub-themes emerged. The frequency with which each sub-theme was mentioned was counted (see Table 16). Each sub-theme was checked and opposing statements identified so as to reflect both the positive and negative views of patients, improving the robustness of the analysis.

Ideally, the findings and analysis of this study would have been checked with the interviewees to verifying their completeness, accuracy and validity. Unfortunately I was not able to do this and this represents a limitation of this study.

Table 16, Main themes with sub-themes and numbers of participants who mentioned them (n=10)

|  |  |
| --- | --- |
| Theme | N\* |
| 1. Modifying patients attitude and beliefs |  |
| AT and motivation | 10 |
| Generated discrepancy | 5 |
| Changed thoughts, beliefs and attitudes | 8 |
| Being more honest | 4 |
| Confident with medicines | 3 |
| Enhanced commitment to prescribed drug regimens | 8 |
| Met patients health expectations | 10 |
| 2. Positive effect on patient's self efficacy |  |
| Individualised care | 9 |
| Sense of responsibility | 4 |
| Gaining insight | 3 |
| Ability to make decision | 10 |
| Feeling of self worth | 7 |
| 3. Motivational therapist |  |
| Therapist communication | 5 |
| Freedom of choice | 9 |
| Getting benefit from exchanging information | 10 |
| 4. Positive impact on wellbeing |  |
| Reducing stress and anxiety | 9 |
| Recognizing the medicine works | 5 |
| Should be wider available | 8 |
| 5. A well designed intervention |  |
| Environment  Comfortable  Not comfortable | 9  1 |
| Special AT clinic | 2 |
| Content and structure | 5 |
| Beneficial sub-interventions | 8 |
| Utility and transferability of AT into real life situation | 2 |
| Time factor:  a) Need to be increased  b) Suitable | 5  5 |

\* N: Number of the patients

## RESULTS

The patients interviewed were on average 50 years old and more than half of them (6/10) were female. All participants in this study were Muslims. (Please note that the numbers in the results were used just to reflect how many people reported the theme, not for generalisation purpose).

### Modifying attitudes and beliefs

#### AT and motivation

All patients reported that AT enhanced their motivation to become adherent to their medication:

*"Certainly, I now have the self motivation and logical thinking that encourages me to be adhered to my medicine".* [Patient 5, female, 50 years]

*"These sessions are great. It’s developed the motivation in order to comply with medicine. …. these sessions developed internal motivation".* [Patient7, male, 65 years]

#### Generated discrepancy

Half of the patients (5/10) reported that AT drew the patient's attention to the disparities between their thoughts and their behaviours which in turn led them to modify their behaviours:

*"Your neutral manner encouraged me …directed me to think that there is a difference between my drug taking behaviour and my opinions.... that made me confront myself ... and my thoughts…. as I see myself in mirror".* [Patient 1, female, 44 years]

*"These meetings revealed to me that my behaviours were opposite to my thoughts….for example…. I know that the medication is important, but in fact I do not take it as prescribed….These sessions encouraged me to be clearer with myself".* [Patient 3, female, 62 years]

#### Changed thoughts, beliefs, and attitudes

AT seemed to have an effect on patients’ attitudes and beliefs about their antihypertensive medication; with eight out of ten patients reporting a change in beliefs and/or attitudes:

*"Our meetings showed me many things were wrong in my behaviour towards drugs and my thoughts towards the importance of drugs …I became more aware of my health status ... It has raised my awareness of my health and the positive aspects of medicine".* [Patient 10, female, 48 years]

*"Your sessions helped me to change, as you know changing always faces resistance… however in our meeting I did not have it…even I feel that my thoughts and beliefs toward drugs were changed".* [Patient 7, male, 65 years]

#### Being more honest

At the beginning of AT sessions, some patients (4/10) did not report that they were non-adherent to medication. However all participants in our trial were selected for being predicted to be non-adherent by two methods; they had had two hypertensive BP measurements a least a month apart despite being on appropriate antihypertensive medications, and by having a high MMAS score that predicts non-adherence. Then after AT started; they revealed that they were not taking medication:

*"At first I thought that I must show that I am fully committed to treatment. And my blood pressure is high as a result of type of medication which is not suitable for me…not as a result of my problem which is non adherence to medication… I thought the medication did not have the ability to control my blood pressure … but when we started adherence sessions….your way of communication let me speak frankly".* [Patient 2, female, 52 years]

*"At beginning, I thought that I must show that I am committed to the treatment as prescribed…and the nature of disease is the cause of high blood pressure for me… your open way of communication encouraged me to talk frankly in order to be more adhered to my medication, to get more benefit from sessions and to gain control over my blood pressure".* [Patient 8, male, 55 years]

#### Confidant with medicines

Three patients expressed that AT increased their confidence in the effectiveness of their medicines to control BP:

*"I did not think that controlling my blood pressure depended on my compliance with medicines. It meant I was not confidant in the role of medication in controlling and decreasing blood pressure therefore I was not take my medicines. But now after the sessions I noticed that when I committed to taking the medicine, my blood pressure was controlled"* [Patient 8, male, 55 years]

*"I was not convinced that the control of my high blood pressure was much affected by medication...now after my commitment to taking medication I noticed that… Adherence therapy has raised my awareness of my health and the positive aspects of medicine … that increased my confidence with drugs".* [Patient 9, male, 43 years]

#### Commitment to prescribed drug regimen

The majority of patients (8/10) reported that AT enhanced their commitment to take medication as prescribed:

*"AT sessions increased my commitment to take medication….medication has become an important part of my life and routine…. is essential for me ... like water".* [Patient 9, male, 43 years]

*"These sessions have increased my commitment to take medication as prescribed".* [Patient5, male, 50 years]

#### Patient health expectations

All patients reported that AT sessions met their health expectations:

"I think adherence therapy *helped me to be in a good health condition and to control over blood pressure …that met and exceeded my health expectations as I told you before….I did not expect that I am the one who would do everything ... I'm the one who plans …chooses the best solution".* [Patient 1, female, 44 years]

*"I expected that I would get information about hypertension medications. I did not expect that I could control my blood pressure and maintain health by myself without help from others. Yes adherence therapy met my health expectations to have a good health".* [Patient 2, female, 52 years]

### Positive effect on self efficacy

Patients reported that AT seems to have an impact on their self efficacy

#### Individualised care

The majority of patients (9/10) reported that AT was different to general health education and is about individualised care, enhancing their self efficacy and consequently improving adherence to medication:

*"I thought that you would just give me a scientific information no more than, I said why not? I will increase my knowledge…so I agreed to participate, but after that I felt that these sessions designed for me …to solve my problems… I got internal awareness; logical thinking ….I got more than knowledge from this study experience… ".* [Patient 5, female, 50 years]

#### Sense of responsibility

Four of ten patients found that a sense of personal responsibility was also initiated by AT sessions:

*"When we started the session I found that I am responsible and the key factor in each session; I am the one who discussed, planned for next meeting’s content…etc… so I looked forward to the next session date".* [Patient 10, female, 48 years]

#### Gaining insight

Three out of ten patients reported that AT helped them to develop insight into their illness:

*"The sessions encouraged me to think and learn….how I should deal with my disease….medicine and how I should adhere to it … helped me to know what are the problems in my adherence to medication…What are the factors that affect my adherence ... and how to solve them properly ….so I gained insight".* [Patient 1, female, 44 years]

*"These sessions made me gain insight".* [Patient 7, male, 65 year]

#### Ability to make decision

All patients confirmed that AT helped them to be a medication decision maker:

*"Definitely these sessions supported me to become the decision maker with regard to taking my medications".* [Patient 1, female, 44 years]

*"Of course, these sessions helped me to take right decision to take my medication... in more than one session I felt that ... In problem solving; I was the one who identified the problem and decided what should be done to address it… in looking back at the intervention I was the one who talked about my experience with medicine and evaluated it. In every meeting I was the decision maker ... this is what I felt".* [Patient 10, female, 48 years]

#### Feeling of self worth

Seven out of ten patients felt increased self worth when participating in their own care:

*"I did not expect that I would be the one who would do everything ... I'm the one who plans …who chooses the best solution…. I've been a key partner in everything... …so I feel …my thought and concerns are valued and important…. I felt that we are, (you and I), sharing knowledge… I have the right to say and to do what I want…..without any force or pressure…. I felt I was the builder, decision-maker and controller over the way and the course of discussion…I saturated my self esteem".* [Patient 1, female, 44 years]

*"I did not think I would be participating and practicing….your way of communication was very attractive ...you valued me and I valued all of that... really that encouraged me to continue these sessions".* [Patient 9, male, 43 years]

### Motivational therapist

#### Therapist communication style

The ability of the therapist to deal with resistance was a key to keeping patients engaged in the therapy; and was commented on by 5 out of 10 patients:

*"To be honest your communication style was one of the reasons that made me complete these meetings. In many cases, I was sharp in the speech, but you were there with your smile and your style of communication, you let me calm down. This was clear in our discussion about my beliefs and views about medication…. Your neutral manner encouraged me …directed me to think that there is a difference between my drug taking behaviour and my opinions".* [Patient 1, female, 44 years]

*"More than once I felt I am reaching a point of contention and conflict with you, but your style has always been to rise above this conflict. You were an active listener to my speech… at the end of each session you made a summary and you asked me to clarify my meanings if my words have more than one meaning".* [Patient 6, male, 45 years]

#### Freedom of choice and equity of expertise

Most patients (9/10) felt that the therapist was aiming to facilitate and not to impose decision making:

*"You did not deal with me from the stand point that you are the expert and knowledgeable one…. and I should accept what you talking about …without a doubt or discussion".* [Patient 7, male, 65 years]

*"I have the right to say and to do what I want…..without any force or pressure".* [Patient1, female, 44 years]

#### Getting benefit from exchanging information

All patients reported that they derived considerable benefit from the therapist’s way of exchanging information about medicines. This affected their engagement and satisfaction with AT and consequently helped them to adhere to drug regimen:

*"I did not think I would be participating and practicing…your way of communication was very attractive ... it encouraged me to continue these sessions…it was built on exchange of information …so I benefited …. I am satisfied with these sessions".* [Patient 9, male, 43 years]

### Positive impact on wellbeing

#### Reducing stress and anxiety

Most patients (9/10) said that AT helped reduce their stress and anxiety by reducing their suffering from medication side effects, disease complications, hospitalization, and worries:

*"I wish that these sessions have been carried out earlier, so I would know how I can adapt to adverse events from medication,…even I would not have entered the hospital….that made my family to become so worried about my health, they were afraid that I would die".* [Patient 3, female, 62 years]

*"When we started our sessions I noticed that when I start to adhere to anti-hypertension medication, my blood pressure started to be under control….that’s something I have wanted to happen for a long time….. I was having recurrent admissions to hospital…. which impacted on my family and my normal activities of life".* [Patient 2, female, 52 years]

#### Reinforcement and monitoring

Half of patients (5/10) reported that AT drew attention to the link between adherence, medication and their ability to maintain BP control:

*"When we started our sessions I noticed that when I start to adhere to anti-hypertension medication, my blood pressure started to be under control….that’s something I have wanted to happen for a long time".* [Patient 2, female, 52 years]

*"I was not convinced that the control of my high blood pressure was much affected by medication...now after my commitment to taking medication I noticed that"*. [Patient 9, male, 43]

#### AT should be widely available

Patients generally agreed that AT should be more widely available; 8 of 10 patients suggested health organisations adopt AT to enhance community wellbeing:

*"I expected that if the adherence therapy sessions adopted by health services, patient’s adherence to their medication will be increased, blood pressure control will be maintained, in addition hypertension complications will be decreased…when that happens I will be happy"*[Patient 4, female, 36 years]

*"I hope that they hold these sessions for all patients… because my father is sick and not sticking to his medicine …his health suffered …then he was admitted to the hospital more than once. I am worried about him. I expected that if there was any awareness about consequences of non-compliance with medication then this might not have happened to him"* [Patient 10, female, 48 years].

### A well designed intervention

All patients talked about AT as being a well designed intervention.

#### Environment

Patients had a choice over where AT was delivered either in an outpatient clinic or in their homes. The majority of patients (9/10) said that the environment, in which AT was offered, was comfortable:

*"Because I was in my home I felt more freedom to speak and so I was more satisfied and convinced with adherence session".* [Patient 4, female, 36 years]

*"I felt comfortable when we met in clinics, because there was no one I knew noted what I said I was able to talk freely. Like my mother if she heard that she would blame me when I become tired from high blood pressure".* [Patient 5, female, 50 years]

However, one patient who was met in outpatient clinic during AT sessions reported that the environment was noisy:

*"The location…should be more calm and away from the outside noise".* [Patient 10, female, 48 years]

#### Special AT clinic

Two out of ten patients suggested that having a special clinic for AT would be an improvement:

*"I would have preferred it if there was a special permanent office for all patients. Because there were sometime interruptions; when someone was knocking on the door, the discussion was cut short".* [Patient 7, male, 65 years]

#### Content and structure

Half of the patients (5/10) felt that the content and structure of sessions motivated them to continue the whole sessions and to be more satisfied with AT:

"*The nature and content of the sessions …let me be more satisfied with adherence sessions …….when the sessions began I had a significant and basic role in each one; I decided… planned… and discussed ... this is what attracted me to continue these sessions to the end".* [Patient 6, male, 45 years]

#### Beneficial key-interventions

The key interventions in AT are: problem solving, looking back, and exploring ambivalence and beliefs about medication. Patients’ feelings of getting benefit from key-interventions of AT increased satisfaction with AT and aided adherence to medications (8/10):

*"In each session there was something to learn. I learned how to confront the problems, solve them in a proper manner, how to balance the advantages and disadvantages of taking and not taking my medication, to learn from my experiences with the medicine, and to organize my time. To be honest, I learned and became aware of the many things that may help me a lot through my life".* [Patient 9, male, 43 years]

#### Utility and transferability of AT into real life situations

Particularly, the problem solving intervention was reported by two patients to be the most beneficial intervention because the utility and transferability of AT into real life situation:

*"I got most benefit through the problem solving session; since I now have the ability to deal with any other problems I may face in future, whether with medication or other".* [Patient 5, female, 50 years]

#### Time

Although all patients said that they appreciated the time given in AT; half of them (5/10) said that they would be more satisfied if they had more time in AT:

*"I thought the duration of sessions should be longer than 20 minutes or the number of them should be increased, in order to encourage the patients to talk more freely and allow them to talk without consideration of the time as a barrier".* [Patient 5, female, 50 years]

*"In my opinion, the duration of meetings must either be longer ... or that the number of meetings over [seven]... it allows the patient to understand and respond more to the therapist, in order for the patient to feel comfortable and able to talk freely… that leads to reaching the objective of the sessions and help patient to gain more benefit".* [Patient 9, male, 43 years]

Meanwhile, half of patients (5/10) reported that the AT time was suitable:

*"I do not think there is a reason to increase or decrease the number of meetings. These sessions were distributed very appropriately. I consider the number is suitable to harness the hearing and thinking, also for some entertainment".* [Patient 10, female, 48 years]

## DISCUSSION

In this study five major themes about patients’ experiences of AT were identified; modifying attitudes and beliefs, positive impact of self efficacy, motivational therapist, positive impact on wellbeing and a well designed intervention. The views and attitudes which were expressed by participants in this study helped us understand how AT exerts its effect on this group of hypertensive patients.

The findings of this study were consistent with previous studies which highlighted the importance of modifying patients attitudes and beliefs, enhancing self efficacy, and therapist communication style for improving patient's adherence behaviour (Gravel et al., 2006, Gu et al., 2008, Guyatt et al., 2008, Nunes et al., 2009, Sullivan et al., 2008).

There is a positive association between patient adherence and satisfaction (Sullivan et al., 2008, Gu et al., 2008, Krousel-Wood et al., 2005). Patients were satisfied with interventions which improved adherence and BP (Gravel et al., 2006, Krousel-Wood et al., 2005). Benson and Britten (2002) found that 42% of patients were dissatisfied with their medication, preferring to discontinue and use alternative natural treatments. Moreover, Dezii (2000) and Touchette and Shapiro (2008) studies reported that patients’ dissatisfaction was associated with lack of perceived benefits from being complaint with the medical interventions advised. We also noted that patients in this study reported many factors that enhanced their satisfaction with the AT intervention, encouraged them to continue all sessions, and adhere to their conventional medications. Also, the themes which emerged from participants views in this study reflects their satisfaction with AT.

### Modifying attitudes and beliefs

Interventions which modify patients’ attitudes and beliefs significantly increased adherence to in antihypertensive drugs (Gravel et al., 2006, Martin et al., 2005, Morrison et al., 2000, WHO, 2003a). Indeed, in this study discussion of patients attitudes and beliefs seem not only to help them to reappraise their views and enhance satisfaction but also increase adherence behaviour.

Patients’ confidence with medicines also seems to affect adherence behaviours (Benson and Britten, 2002, Dezii, 2000, Qureshi et al., 2007). The interventions which aimed to increase patients’ adherence should be able to enhance their confidence with medication to achieve the desire goal (Benson and Britten, 2002, Dezii, 2000, Qureshi et al., 2007). Theunissen et al (2003) reported that when discussing illness representation with patients, they became less confidence that they were able to take medication as prescribed. In the current study, patients reported that AT helped them to recognise the drugs ability to control BP therefore they became more confident with medicines and more honest about their adherence behaviour.

Overall patients’ adherence behaviour was affected by the ability of adherence intervention to meet their health expectation (Gu et al., 2008, O’Connell et al., 1999). AT sessions met the health expectations of this study's group of participants; they reported that adherence therapy helped them to adhere to a medication regimen and consequently to have better health (lower BP).

### Positive impact on self efficacy

Patients in this study stated that AT enhanced their self efficacy through enhancing self esteem, self motivation, sense of responsibility, developing insight and helping them to be a decision maker for taking medication behaviour and controlling their BP. Moreover, AT in this study increased participants health and illness awareness so they continued AT to the end and they became adherent with the drug regimen. This is consistent with observations by Hamet et al (2003) and Gravel et al (2006) they found that the reason for discontinuation of intervention was lack of self efficacy, and health awareness. Our findings also supported the provision of individualized care (Herborg et al., 2008, Hunt et al., 2004, Oparah et al., 2006), and participation of patients in their health care (Martin et al., 2005, Nunes et al., 2009) led to improved adherence to drug regimens.

### Motivational therapist

A positive patient experience of health care providers (HCPs) also enhanced their adherence behaviour (Gravel et al., 2006, Qureshi et al., 2007, Schroeder et al., 2004, Schroeder et al., 2005). Indeed the therapist’s communication style was identified by this study's participants as a factor that enhanced their adherence. They reported that the therapist's communication style was non-threatening, discouraged resistance, and made them feel equality of expertise. Despite 50 % of our patients wanting AT duration to be longer than the seven weekly 20 minutes AT sessions provided, the RCT showed it to be highly effective at this "dose" at least in the short term. This finding is consistent with Sookaneknun et al (2004) and Vivian (2002) who reported that interventions which provide time and opportunity for HCPs to discuss patients medication use problems, and helped them in resolving these problems, enhanced their medication taking behaviour. In contrast, Schroeder et al (2005) and Hunt (2008) reported that medication taking behaviours were not affected by providing counselling time for patients to talk about any problems related to their antihypertensive drugs. Thus it appears that the content and aim of the conversations is important for them to have efficacy.

### Positive impact on wellbeing

The WHO (2003) and the English National Institute for Health and Clinical Excellence (NICE) reported that increasing patient adherence to a therapeutic regimen should positively influence patients’ wellbeing (Nunes et al., 2009, WHO, 2003a). However, other studies reported that patients who felt that they had strong ability to control their BP, tried to decrease their reliance on drugs, and therefore, became non-adherent to their medications (Patel and Taylor, 2002, Wai et al., 2010). AT appears to have a positive impact on patient's wellbeing that includes; reduced stress and anxiety, disease complications, and hospitalization. Patients recommended adoption of AT by healthcare providers to enhance the health of the community. Also, in this study patients reported that improving their ability to have a control over their health condition and BP were positively associated adherence. This finding agreed with the study of Ross et al (2004).

### A well designed intervention

Based on interviews with patients that experienced AT, there was evidence that our approach addressed many of the elements of an effective intervention that have been proposed by many authors (Ali and Horne (1996), Gravel et al (2006), Nunes et al (2009) and WHO(2003)) and the systematic reviews of Schroeder et al (2004) and Haynes et al (2008). AT's component and structure, beneficial, utility and transferability into real life situation, time, and environment helped this study's participants to be satisfied with provided sessions, adhere to their drug regimen and to complete all AT sessions.

In this study the surprising thing is that the study's participants’ views reported all theoretical principles upon which AT was built; motivational interviewing (Miller and Rollnick, 2002), and cognitive behavioural therapy (Kemp et al., 1996). In addition, the patients’ views in this study emphasized the importance of therapist skills and communication style, which is described in detail in the AT manual. All these reasons reflect the ability of AT to translate the theory into practice and supports the applicability of AT as an effective intervention to enhance adherence.

## IMPLICATION OF THIS STUDY

This study was undertaken because of the belief that understanding why and how AT works is essential in refining and further developing the intervention. The five themes which were explored by the patients interviewed could be adopted by researchers for developing a new effective intervention for enhancing patient adherence to drug regimens. Indeed, it could be argued that AT should be introduced to the nursing curriculum of education since non-adherence is such a common problem and higher adherence to all medication regimens is predicted to have substantial benefits for patients and substantial cost implication for healthcare providers (Nunes et al., 2009, WHO, 2003a). Future research is needed to understand how patients from different cultures and backgrounds, and disease conditions may experience AT. Half of the participants recommended increasing the duration of AT sessions; therefore future research should be done to examine different AT session's time duration (dose finding studies). Other research should examine modes of delivery such as group versus one to one, face to face versus telephone therapy plus SMS text message reminders etc.

## STUDY LIMITATIONS

This qualitative study may be liable to positive bias since the author (FA) was the one who delivered the AT sessions and also conducted the interviews so the participants may have been reluctant to raise negative views and presented "acceptable" views because they wanted to please FA. The subjectivity of qualitative research in this study is affected by many factors which may threaten the quality of collected information, processing, and analysis, such as mood and style of the researcher. The characteristics of participants also could limit the generalisability of this study; since findings were related to a group of hypertensive Muslim patients, and they might differ from other cultures and diseases. Although the forward- backward translation process was done for the interviews, this study is liable, moreover, to have trans-cultural effect bias. Finally, it was not possible to conduct a member check of the analysis and that might affect the internal validity of this study.

## SUMMARY

This study explored how and why AT exerted the observed significant effect on clinical health outcomes among a group of hypertensive patients. The information gathered through the interviews revealed that the key foundations for an effective intervention are; modifying attitudes and beliefs, enhancing self efficacy, effective communication style, having a positive impact on patients’ wellbeing, and having a well designed intervention. Identifying a patient's experience and recognising these five elements helps in providing a target for interventions designed to tailor care provision for enhancing adherence according to individual needs. Therefore the next chapter provides summary of this thesis with its implications.

# IMPLICATIONS AND CONCLUSION

In chapter 8 and 9 the positive effects of an AT intervention among hypertensive patients in Jordan was presented. Chapter 10 provided a rational of how and why AT exerted these effects. In this chapter the implication of AT for clinical practice, future research and health policy are considered. Future research and dissemination plans will also be discussed.

## Association between this study and issues identified in Cochrane systematic review chapter (4)

This study is only the second behaviourally targeted intervention based on motivational interviewing technique that has evaluated in hypertensive patients (Ogedgbe et al 2008). Both have had positive effects on adherence with antihypertensive drugs. The trial is the most robust in terms of quality of reporting (CONSORT guidelines for reporting of RCT was followed) and has the largest size of effect. Also the study showed the effects on clinical outcomes (BP reduction). There are caveats regarding the short follow up period, single therapist and relatively small sample size. Till now no new RCTs has tested the assumption of the presence of relationship between modifying patients attitudes and beliefs and adherence behaviours. This study confirmed this evidence and proposed that if patients’ attitudes and beliefs have been explored, the adherence behaviour will be improved. Finally, the current trial fulfilled all assessment of risk of bias quality criteria in comparison to all systematic review RCTs which did not achieve this goal.

## IMPLICATION OF THE STUDY

### Implication for clinical practice

From the current trial findings it can be concluded that a relatively short dose of AT is sufficient to reduce BP and improve adherence to medication for at least one month. It is possible that these results reflected changes in patients’ behaviour, attitudes and beliefs that would lead to regular drug intake eventually becoming a habitual behaviour. AT is a patient-centred approach that provides opportunity for patients to explore their ambivalence towards antihypertensive drugs and their problems with taking these medicines. It also encourages the patients to make informed decisions about their treatment through cooperation with healthcare professionals. Providing a patient centred approach with exchanging information and reducing resistance are the main key therapist's skills for getting active participation from patients and for enhancing behavioural change.

In the qualitative chapter (10) it was feasible to identify which components of AT are effective and how AT exerted the observed effects. Patients reported that all adherence therapy's components were effective and important; key interventions (problem solving, looking back, exploring ambivalence and beliefs about medication) and therapist skills (reducing resistance, exchanging information, listening reflectively). Health care professionals should be able to integrate all these techniques together with their existing skills into their practice to get a better understanding of patients’ beliefs, attitudes and perspectives in order to improve adherence behaviour. We also established that AT was an acceptable intervention in Muslim culture. Since AT was previously tested among UK and Thai cultures this reflects its probable utility in different cultural groups.

### Implications for future research

All of the AT sessions in this study were delivered by a single person (FA). This reduces the ability to state that its effect could be as easily achieved by other clinicians. Future research should be conducted with more therapists to counter the potential “halo” effect of a single highly motivated nurse delivering treatment. Future studies should also follow more participants over a longer period to increase understanding of the duration of the effect in a larger and potentially more diverse population. Moreover, since a restricted inclusion criterion was used in the current trial, future studies should make the inclusion criteria more pragmatic and reflect general practice more (e.g. include patients with co-morbidities such as diabetes). Adherence to medication is complex and future trials may wish to determine if drug doses were taken in the correct amount and at the correct time. Future studies should also collect data to enable a cost effectiveness analysis to be conducted. An important question when applying AT in clinical practice is whether a short-term intervention (one session per week over seven weeks) is sufficient to maintain BP lowering effect over time. Other aspects of AT need to be tested to determine the robustness and genralisability of this therapy; aspects to be tested could include frequency and intensity of the therapy, the location of its delivery, the mode of delivery (e.g. by telephone), the numbers to whom it is delivered (e.g. one-to-one or group sessions), the character of the person delivering the AT (e.g. lay advisors or health care professionals), and whether the duration of effect could be enhanced by the use of top up sessions. Since non-adherence is a common problem not only for hypertensive drugs but also in other long-term conditions (e.g. diabetes, asthma) and for other health care interventions (e.g. exercise, dietary regimens, clinic attendance), future research should address the effectiveness of AT in these illnesses.

### Implication for health policy

WHO (2008) reported that the non-communicable diseases are increasing sharply in developing countries, consequently the number of deaths resulting from them will also increase substantially over the next twenty years. This will lead to an increase in economic expenditure and a negative global burden. Policymakers should recognise the importance of addressing medication adherence and its effect on BP control to prevent hypertension complications (e.g. stroke). Furthermore, AT reflects all WHO (2003a) and NICE (2009) recommendations for adopting a patient-centred approach to enhancing medication adherence. This study has provided evidence that nurses could effectively conduct AT to improve the clinical outcomes of patients. The implementation of AT by nurses will facilitate the wide-spread of intervention (AT). Therefore, it can be used in other disease conditions and different settings, not only hypertension or out-patient clinic. Although AT has been developed and tested in Western countries, it was proven to be acceptable to those with Muslim beliefs and culture. Health policymakers in Muslims countries, and in particular Jordan, can adopt the AT intervention without fearing significant culturally based resistance.

### Future plans

Although the current trial included only 136 hypertensive patients in three outpatient clinics in governmental hospital, AT demonstrated promising results with the potential to benefit the hypertensive patients in Jordan and adult health practice. The AT findings encouraged me to consider undertaking further research when I start working as a nurse lecturer in Jordan. I have published the results of the current trial in an English journal. However, I additionally need to publish it along with the Arabic version of the AT manual in Arabic journals, to allow its application in Jordan and other Arabic countries. I need to convince policymakers of the cost saving merit of AT in order to adopt it. Therefore, a cost-effective analysis of AT should be conducted in cooperation of the Jordanian Ministry of Health, Economic and Nursing departments. If the results are satisfactory, then I will be able to carry out a large-scale trial in Jordan, which will require the cooperation of Jordanian colleagues and the Ministry of Health in terms of policy, workforce development, time management, resources, and funding. After gaining their support, I need to assess the Jordanian nurses existing skills, knowledge, attitudes about adherence improvement, and training needs. Once I determine that, I can develop a training package based on their skills in relation to AT. I can use and modify the training package which was developed by Gray (2003) to suit the needs of my Jordanian colleagues. The Departments of Non-communicable Diseases and Continuing Education in the Ministry of Health will be consulted on the proposed training curriculum. Interested colleagues will be invited to participate in developing the curriculum. The proposed training package will be tested before getting the final version to get feedback from participants. The final step is an RCT to assess the effectiveness of training over a longer timescale (e.g. 12 months). If we get satisfactory outcomes, then the distribution of the training to nurses on a broader scale will be done.

## DISSIMENATION OF FINDINGS

The dissemination of findings of this study included the following:

1. The current RCT (Chapter, 7, 8. 9, 11) was published in the *Journal of Human Hypertension* see appendix (12).

2. A manuscript for the *Journal of Clinical Nursing* for the qualitative study findings (Chapter 10) was submitted in March 2012.

3. A manuscript for the *Journal of Advanced Nursing* discussed the development of a conceptual model of factors affecting adherence for antihypertensive drugs (Chapter 3) will be submitted in August 2012.

4. A systematic review for RCT interventions that aimed to enhanced adherence for BP lowering drugs (Chapter 4). We submitted it to Cochrane Database of Systematic Reviews, this update includes our study in the review.

5. A poster presentation was done in UEA Postgraduate Showcase Event 17th June 2010.

## CONCLUSIONS

Different types of antihypertensive drugs are prescribed to treat hypertension. However, poor adherence to prescribed drug regimen is common. I therefore conducted a review of the previous studies about factors affecting adherence to BP lowering medication. The main factors that affect adherence behaviours to BP lowering drugs are patient-related factor, healthcare professional, medications, and disease condition related factor. A conceptual model was developed. This model reflected how these factors related to each other to form adherence behaviour. Then I carried out a systematic review of RCTs that explored interventions to enhance adherence to antihypertensive medications. From this review we were unable to recommend a single approach intervention to enhance adherence behaviour since the included RCTs have poor quality design and unclear reporting. However, a need for testing patient-centred behaviourally targeted interventions that modify attitudes and beliefs toward medications through a robust design was highlighted.

The literature review showed me that:

• Hypertension disease is common among Jordanian population, but there was no intervention to enhance adherence to its treatment.

• Muslims only take-up and accept interventions which agree with their faith, beliefs, and culture.

• Several international interventions were recommended to increase adherence but none applied to Middle East countries.

• Intervention based on a patient-centred approach such as modifying attitudes and beliefs through cognitive behavioural and motivational interviewing techniques aimed at improving medication adherence have never been applied whether in Jordan or other Middle East countries.

• AT requires a short training period for therapists.

AT was developed as a way to help patients modify their negative attitudes and beliefs toward illness and its treatment, explore ambivalence and sort out practical problems about medications, work out solutions to problems with medication, develop an awareness and make an informed decision about medication (Gray et al. 2003). Having been trained in AT, I decided to find out whether AT could be used effectively in Jordan. I conducted a RCT and we observed that AT could be a successful intervention to improve medication taking behaviour in noncompliant hypertensive patients in Jordan. The results showed that in comparison to TAU at 11 weeks, AT significantly:

• Reduced systolic BP.

• Reduced diastolic BP.

• Improved adherence to antihypertensive drugs.

• Improved patients’ attitudes and beliefs in a favourable direction toward taking their medications.

Following the RCT, in-depth qualitative semi-structured interviews were conducted with a convenience sample of ten patients from the AT group to explore their experience and views about AT and to understand how AT exerted the observed effects. Five themes merged:

• Modifying attitudes and beliefs.

• Enhancing self efficacy.

• Effective communication style.

• Having a positive impact on patients’ wellbeing.

• Having a well designed intervention.

Collectively, these results demonstrate that AT is an effective therapeutic intervention for non-compliant hypertensive patients in Jordan. AT modified patients negative attitudes and beliefs toward hypertension and its treatment, it changed adherence behaviour in a favourable direction which subsequently reduced BP. Indeed, the results of qualitative interviews helped us to get a greater understanding of the RCT's findings. Patients should be guided to have an active role in the management of their hypertension and, therefore, behavioural changes should be a goal of any intervention. Further issues concerning identification of barriers to adherence with hypertensive drugs, should be discussed and disclosed. This will help re-design and tailor strategies to finally enhance patients’ adherence to a prescribed regimens. However, a large-scale RCT with a larger sample of patients and longer follow-up, is needed to assess the "Real world" actual effect of AT. The broader application of this intervention in daily clinical practice would be valuable step in improving hypertension care and reducing its complications in Jordan.

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**APPENDICES**

Appendix 1, Table Key Words and Search Results

|  |  |  |
| --- | --- | --- |
| **Search** | **Key words** | **Results** |
| 1 | patient compliance/ | 37786 |
| 2 | medication adherence/ | 1033 |
| 3 | patient dropouts/ | 5282 |
| 4 | ((patient$ or treatment$ or medication or pharmaceutical or prescription) adj2 (compliance or noncompliance or complied or comply$ or noncomply$ or adher$ or nonadher$ or cooperat$ or co-operat$ or discontinu$ or abstention or abstain$ or stop$ or abandon$)).tw. | 37580 |
| 5 | or/1-4 | 71634 |
| 6 | exp hypertension/ | 246368 |
| 7 | hypertens$.tw. | 246368 |
| 8 | exp blood pressure/ | 217805 |
| 9 | (blood pressure or bloodpressure).tw. | 171568 |
| 10 | or/6-9 | 492361 |
| 11 | (education$ adj2 (program$ or intervention? or meeting? or session? or strateg$ or workshop? or visit?)).tw. | 30315 |
| 12 | (behavio?r$ adj2 intervention?).tw. | 4339 |
| 13 | \*pamphlets/ | 1150 |
| 14 | (leaflet? or booklet? or poster or posters).tw. | 15204 |
| 15 | ((written or printed or oral) adj information).tw. | 1071 |
| 16 | (information$ adj2 campaign).tw. | 290 |
| 17 | (education$ adj1 (method? or material?)).tw. | 3609 |
| 18 | counseling | 42270 |
| 19 | (counselling or counseling).tw. | 42270 |
| 2 | outreach.tw. | 5207 |
| 21 | ((opinion or education$ or influential) adj1 leader?).tw. | 621 |
| 22 | facilitator?.tw. | 8310 |
| 23 | ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 training program$).tw. | 380 |
| 24 | reminder systems/ | 827 |
| 25 | reminder?.tw. | 4453 |
| 26 | (recall adj2 system$).tw. | 291 |
| 27 | (prompter? or prompting).tw. | 2947 |
| 28 | \*feedback/ or feedback.tw. | 54197 |
| 29 | compliance.tw. | 58090 |
| 30 | (diary or diaries).tw. | 10513 |
| 31 | ((followup or follow-up) adj appointment?).tw. | 695 |
| 32 | blood pressure monitoring, ambulatory/ | 4919 |
| 33 | (monitor$ or surveillance or telemonitor$).tw. | 421049 |
| 34 | self-management.tw. | 4212 |
| 35 | (medication adj2 manag$).tw. | 1218 |
| 36 | drug regimen$.tw. | 4679 |
| 37 | or/11-36 | 658036 |
| 38 | financial incentive$.tw | 1579 |
| 39 | cost shar$.tw. | 823 |
| 40 | (copayment? or co payment?).tw. | 806 |
| 41 | \*hospital charges/ | 718 |
| 42 | or/38-41 | 3765 |
| 43 | physicians, family/ | 13276 |
| 44 | primary health care/ | 40865 |
| 45 | (primary adj2 (health or care or healthcare)).tw. | 59412 |
| 46 | ((health or healthcare) adj2 practitioner?).tw. | 3559 |
| 47 | \*nurse clinicians/ | 5051 |
| 48 | nurses/ | 24620 |
| 49 | \*nurse midwives/ | 4163 |
| 50 | nurse practitioners/ | 9229 |
| 51 | (nurse adj (rehabilitator? or clinician? or practitioner? or midwi$)).tw. | 7846 |
| 52 | \*pharmacists/ | (5062) |
| 53 | pharmacist?.tw. | 13901 |
| 54 | paramedic?.tw. | 2397 |
| 55 | (case adj1 management).tw. | 5754 |
| 56 | exp \*ambulatory care facilities/ | 20970 |
| 57 | \*ambulatory care/ | 12955 |
| 58 | outpatients/ | 5932 |
| 59 | (outpatient? or ambulatory).tw. | 121887 |
| 60 | or/43-59 | 282525 |
| 61 | \*home care services/ | 16932 |
| 62 | \*hospices/ | 2907 |
| 63 | \*nursing homes/ | 16789 |
| 64 | \*office visits/ | 1665 |
| 65 | \*house calls/ | 1066 |
| 66 | \*day care/ | 2663 |
| 67 | \*aftercare/ | 2381 |
| 68 | \*community health nursing/ | 13503 |
| 69 | domiciliary.tw. | 1875 |
| 70 | (home adj1 treat$).tw. | 1076 |
| 71 | or/61-70 | 56389 |
| 72 | \*program evaluation/ | 5195 |
| 73 | exp \*"Referral and Consultation"/ and "consultation"/ | 15367 |
| 74 | \*drug therapy, computer assisted/ | 840 |
| 75 | near patient testing.tw. | 156 |
| 76 | \*medical history taking/ | 3761 |
| 77 | \*telephone/ | 3467 |
| 78 | (physician patient adj (interaction? or relationship?)).tw. | 1523 |
| 79 | \*health maintenance organizations/ | 9162 |
| 80 | or/72-79 | 39089 |
| 81 | (program$ adj2 (reduc$ or increas$ or decreas$ or chang$ or improv$ or modify$ or monitor$ or care)).tw. | 26271 |
| 82 | (program$ adj1 (health or care or intervention?)).tw. | 20750 |
| 83 | ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 treatment program$).tw. | 240 |
| 84 | ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 care program$).tw. | 107 |
| 85 | ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 screening program$).tw. | 372 |
| 86 | ((effect? or impact or evaluat$ or introduc$ or compar$) adj2 prevent$ program$).tw. | 298 |
| 87 | (computer$ adj2 (dosage or dosing or diagnosis or therapy or decision?)).tw. | 2805 |
| 88 | ((introduc$ or impact or effect? or implement$ or computer$) adj2 protocol?).tw. | 1549 |
| 89 | ((effect or impact or introduc$) adj2 (legislation or regulations or policy)).tw. | 1030 |
| 90 | or/81-89 | 45764 |
| 91 | 37 or 42 or 60 or 71 or 80 or 90 | 1004715 |
| 92 | randomised controlled trial.pt. | 282431 |
| 93 | controlled clinical trial.pt. | 80204 |
| 94 | randomised.tw. | 205206 |
| 95 | placebo.tw. | 119222 |
| 96 | drug therapy/ | 28360 |
| 97 | randomly.tw. | 139792 |
| 98 | trial.tw. | 240451 |
| 99 | groups.tw. | 964692 |
| 100 | or/92-99 | 1456716 |
| 101 | animals/ not (humans/ and animals/) | 3357634 |
| 102 | 100 not 101 | 1185856 |
| 103 | 5 and 10 and 91 and 102 | 1142 |
| 104 | limit 103 to ed=20020101-20100312 | 519 |

This search strategy was amended slightly for further searches of MEDLINE, EMBASE and CINAHL

**Appendix 2, Characteristics of included, excluded and ingoing studies**

### Characteristics of included studies

### Amado Guirado 2011

|  |  |
| --- | --- |
| Methods | Multi centre prospective cluster controlled trial, 12 months follow-up duration, ITT used, power calculation done. |
| Participants | 487 patients in each group were needed, however, actual sample size was 996 (515 in the IG and 481 in the CG), with mean age 63 years, most of them female, and 2/3 of them had no formal education. 1/2 had poor control of their BP at baseline. No significant differences in adherence rate at baseline, and no significant differences in demographical characteristics at baseline just BMI in IG was higher than the CG. Setting: Spain (primary centre) |
| Interventions | Educational intervention: Intervention consisted of personalised information by trained nurse (training focused on adverse events, pharmacological interactions, and patients centring with a special focus on comorbidity) and written leaflets (information about disease, medication, healthy lifestyle habits). CG: received their usual care |
| Outcomes | Self report, Pill count, MMAS  1- Treatment adherence measured by MMAS increased by 9.6% (95% CI: 5.5-13.6) in the IG and 8.8% (95% CI: 4.9-12.6) in the CG.  2- There were NS difference in adherence on the other tests used (pill count and Haynes-Sackett).  3- NS difference in BP. |
| Notes | Taken medication between 80%- 110% considered as good adherence. Reasons for loss of follow-up, ethical approval and source of funding were reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | Insufficient details |
| Blinding (performance bias and detection bias) outcome assessors |  | Insufficient details |
| Blinding (performance bias and detection bias) Data analysts |  | Insufficient details |
| Incomplete outcome data (attrition bias) |  | Used ITT and LOCF. Reasons of lost of follow up reported |
| Selective reporting (reporting bias) |  | Insufficient details |
| Other bias |  | Insufficient details |

### Andrejak 2000

|  |  |
| --- | --- |
| Methods | Parallel trial, study duration six months, follow -up at six months |
| Participants | 162 participants with mild to moderate hypertension, 65% women, mean age 57 years. Setting: multi-centre, France |
| Interventions | Simplification of dosage regimen: Once daily trandolapril 2mg vs twice daily captopril 25mg |
| Outcomes | Pills count and MEMS: Percentage of correct dosing 94% in intervention group compared to 78.1% among controls, P value < 0.0001. |
| Notes | Study compared two different drugs. Ethics reported, imbalance in term of age |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Allocation according to enrolment order and randomizations list |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Non blinding ensured |
| Blinding (performance bias and detection bias)Data analysts |  | Non blinding ensured |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | No description |

### Asplund 1984

|  |  |
| --- | --- |
| Methods | Cross-over trial, intervention four months on each regimen, follow-up at eight months |
| Participants | 160 participants with treated and controlled hypertension, 39% women, mean age 51 years. Setting: hospital outpatients in Sweden |
| Interventions | Simplification of dosage regimen: Pindolol 10mg and clopamide 5mg once daily in one combination tablet vs two tablets |
| Outcomes | Pill count and self report: 40.8% never forgot a tablet in the experimental group vs 69% in the control group (not statistically significant, but no exact P value reported) Net increases of 2.8 mm Hg systolic and 3.0 mm Hg diastolic (not statistically significant, no exact P value reported) |
| Notes | Dropouts not clearly reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgment | Support for judgment |
| Random sequence generation (selection bias) |  | Insufficient information |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No protocol |
| Other bias |  | Bias related cross over study |

### Baird 1984

|  |  |
| --- | --- |
| Methods | Parallel, study duration eight weeks, follow-up at 10 weeks |
| Participants | 389 participants with treated and controlled hypertension, 30% women, mean age 54 years. Setting: primary care, Canada |
| Interventions | Simplification of dosage regimen: Metoprolol 200mg once daily vs metroprolol 100mg twice daily |
| Outcomes | Pill count and urine test: 96% took more than 80% of medication in the intervention group (once-daily regimen) compared to 90% in the control group (P = 0.059). 93% took more than 90% of medication in the intervention group compared to 82% in the control group (P = 0.009). 1 mm Hg net reduction in SBP and no net reduction for DBP (NS, no exact P value reported) |
| Notes | Detailed reasons for loss to follow-up reported. Randomisation procedure and blinding to outcome assessment unclear. Ethics and source of funding reported. No imbalance at baseline |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | In sufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias) Data analysts |  | Insufficient details |
| Incomplete outcome data (attrition bias) |  | No description |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Barrios 2007

|  |  |
| --- | --- |
| Methods | Multicenter randomised, open label study duration 12 weeks, follow up 12 weeks, power calculation done; number expected to be recruited 400 in usual care, 800 in MEMS. |
| Participants | They actually recruited1523 outpatients with mild- to - moderate essential hypertension. 48% women, 61% aged >60yrs. 33% were current smoking, 29% hypercholesterolaemia. Setting: Multicenter in Spain. |
| Interventions | Intervention to support adherence behaviour (Reminder): MEMS  Lercanidipine providing through Electronic monitoring (MEMS) vs pills counting. Done by research investigators |
| Outcomes | MEMS and Pill count.  No significant differences in compliance and BP reductions between two groups, compliance: MEMS group 92% vs 91% of usual group. SBP was reduced 21.6 ± 14.8 mm Hg in the MEMS group vs 22.2 ± 13 mm Hg in the usual-care group, DBP 12.8 ± 9.2 s 13.8 ± 7.8 mm Hg. No changes in baseline or final HR. There was a low incidence of adverse events (5.4%) |
| Notes | Above 80% compliance defined as a good adherence |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient information about the sequence generation |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Open-label study |
| Blinding (performance bias and detection bias) Data analysts |  | Open-label study |
| Incomplete outcome data (attrition bias) |  | No description |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Becker 1986

|  |  |
| --- | --- |
| Methods | Parallel, study duration one year, follow-up at one year |
| Participants | 180 participants with treated and uncontrolled hypertension, primarily middle aged black women, less than 20% employed, primary care in USA |
| Interventions | Intervention to support adherence behaviour (reminders): Special unit dose reminder packaging vs usual medication vials |
| Outcomes | Pill count and self report:  84% adherent in the intervention group compared to 75% among the controls (NS, no exact P value reported). Net reduction in DBP 0.2 mm Hg (NS). |
| Notes | Physicians blinded to treatment allocation, aware that compliance study was in progress but unaware of the aims of the study. No imbalance. Funding reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | No description |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Birtwhistle 2004

|  |  |
| --- | --- |
| Methods | Equivalence controlled study, 3 years study duration, followed over an average 33.6 months at 0, 12, 24, 36 months. Power calculation done |
| Participants | 609 hypertensive patients (302 three months/ 307 six months) baseline variables were similar in both groups, with age average 55.8 years. 43.5% male. Setting: 50 family centre in Canada |
| Interventions | Intervention to support adherence behaviour (regular follow up):  Follow up every 6 months vs 3 months |
| Outcomes | Questionnaire and pill count:  -The BP measurements by doctor were equivalent between the groups and was similar to the home BP measurement which measured by nurses P value and effect size were not reported.  -Both groups were equivalent in satisfaction with medical care; just 6 month group reported that the doctor did not take BP problem seriously towards the end of the study.  -Adherence to treatment was equivalent between groups. Pill counts in this pragmatic trial were unreliable with patients who were taking multiple drugs. Self report adherence was equivalent between group however more patients in the three month group forgot to take their blood pressure drug P value and effect size were not reported  - The number of patients who did self monitoring for BP was increased for both 6 and 3 months groups (39% to 47%, 36% to 52%) |
| Notes | Adherent patient if >= 80%. Source of funding and ethical approval were reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Random number table |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Blinding of outcomes assessors ensured |
| Blinding (performance bias and detection bias) Data analysts |  | Blinding of statistician ensured |
| Incomplete outcome data (attrition bias) |  | Missing data have been imputed using appropriate methods. They used ITT, The reasons for loss of follow up were listed and were similar for both groups. |
| Selective reporting (reporting bias) |  | Not all of the study’s pre-specified primary outcomes have been reported (cost) |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Blenkinsopp 2000

|  |  |
| --- | --- |
| Methods | Cluster-randomised parallel, study duration six months follow up after 6 months |
| Participants | 180 participants with treated hypertension, 62% age 60 or over,  Setting: 20 community pharmacy sites, UK |
| Interventions | Complex combined intervention: Structured brief questioning protocol on medication problems, including advice, information and referral to general practitioner by pharmacists three times at two-month intervals vs control (not defined well) |
| Outcomes | Self report:  62% adherent in the intervention group compared to 50% in the control group (P < 0.05). 35.7% of uncontrolled patients became controlled in the intervention group compared to 17.1% in the control group (P value < 0.05) |
| Notes | Complete data on BP only available on 100 participants, high likelihood of bias. Ethics and funding were reported, no imbalance between groups at baseline. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | Insufficient details |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias) Data analysts |  | Non blinding ensured |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | Insufficient details |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Boissell 1996

|  |  |
| --- | --- |
| Methods | Parallel, study duration three months, follow up at three months |
| Participants | 7272 participants, 50% women, mean age 61 years.  Setting: primary care, France |
| Interventions | Simplification of dosage regimen: Nicardipine 20 mg thrice daily vs nicardipine SR 50 mg twice daily |
| Outcomes | Self report:  82% of participants in intervention group reported excellent adherence compared to 76% among controls (P < 0.001). Net reduction in BP 0.2 mm Hg (systolic) and 0.3 mm Hg (diastolic). NS, no exact P value reported. |
| Notes | No differential loss to follow-up reported, high participant number due to large number of participating general practitioners, bias likely. Ethics and funding were reported, no imbalance. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computer generated |
| Allocation concealment (selection bias) |  | Centralized by telematics |
| Blinding (performance bias and detection bias) outcome assessors |  | Open study |
| Blinding (performance bias and detection bias). Data analysts |  | Open study |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | Insufficient information |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Bosworth 2005

|  |  |
| --- | --- |
| Methods | Parallel RCT, 2 year duration, 6 months follow up. Based on simulation study they expected to recruit 544. |
| Participants | 588 hypertensive patients, 294 per each group were actually recruited, both group were similar with mean age 63 years, 2% female, 41% African-American, 57% white, 67% married, 22% lived alone, 50% had high school education or less, 22% had adequate income, 25% employed, 66% had at least one parent with hypertension. Setting: 30 continuity care providers at Durham VAMC primary care clinic in united states |
| Interventions | Complex/ combined intervention: Tailored intervention (nurses answer the patients questions related to their hypertension which focus on; perceived risk of hypertension, memory, literacy, social support, patient's relation with health care providers, drug's side effects, pill refill, missed appointment and health behaviours) bi monthly for 2 years vs Usual care group who received routine care and completed the same measurement as intervention group (both groups well defined). |
| Outcomes | Self report:  -NS change in overall proportion with self-reported medication adherence between two groups (0.0074, 95% CI: -0.062-0.076). Among the 200 patients who were not adherent at baseline, 46% of the nurse intervention group were adherent at follow up while 34% of the usual care group were adherent at follow up (P = 0*.*08). BP not reported. |
| Notes | > 80% adherence, they reported the ethical approval and source of fund, |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computer generated |
| Allocation concealment (selection bias) |  | Sealed envelopes |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias). Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | No description |
| Selective reporting (reporting bias) |  | In the protocol they reported the BP as primary outcome, but they didn't provide results |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Bosworth 2009

|  |  |
| --- | --- |
| Methods | 2\*2 RCT, stratified by site of enrolment and health literacy status of the patient, 3 years duration, with 2 years follow up, they did the power calculation; they expected to recruit 570 |
| Participants | 636 hypertensive patients were actually recruited, the two group were had similar characteristics; mean age was 61 years, 49% were African-American, 665 female, 19% had in adequate income, 73% had their BP under control. Setting: 2 primary health care clinics at Durham, USA. |
| Interventions | Complex/Combined intervention: three groups  1- Tailored behavioural self management intervention included perceived risk for hypertension, memory, literacy, social support, patient’s relationships with their health care providers, and side effect of anti-hypertension medication. In addition to on improving adherence to the dietary approaches to stop hypertension, weight loss, reduce sodium intake, regular- moderate intensity physical activity, smoking cessation, and moderation of alcohol intake. 2- Home BP monitoring received an Omron HEM 773AC arm monitor. 3-combined intervention received a home BP monitor, training on its use, and the behavioral self-management intervention, vs control group; not provide home BP monitors and did not have access to the nurse administered behavioural intervention. Well defined all groups. |
| Outcomes | Self report:  - The greatest increase in the proportion of BP control was in the combined intervention, at 24 months, the usual care group were 4.3% (95% CI, \_4.5% to 12.9%) in the behavioral intervention group, 7.6% (CI, \_1.9% to 17.0%) in the home BP monitoring group, and 11.0% (CI, 1.9%, 19.8%) in the combined intervention group.  - Compare to usual care. the 24months difference in SBP was 0.6 mmHg (CI, -2.2 to 3.4mm Hg), for the behavioural intervention group, -0.6 mm Hg (CI, -3.6 to 2.3mmHg) for the BP monitoring group, and combined intervention had statistically lower mean SBP than usual care group -3.9 mmHg (CI. -6.9TO -0.9 mmHg, P =0.010)  - The out patients encounter number was similar for the 4 groups, the hospitalised individuals proportion was similar (P = 0.91).  - The mean 2 years medical cost was $15 641(SD, $25 769; median, $6698), the intervention cost; behavioural $345, home BP monitoring $90, combined $416.  - Not statistically significant increased of adherence for interventions group P value not reported |
| Notes | They reported the ethical approval and source of funding. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computer generated |
| Allocation concealment (selection bias) |  | Sealed envelope |
| Blinding (performance bias and detection bias) outcome assessors |  | Blinding of the outcome assessors ensured |
| Blinding (performance bias and detection bias). Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Missing data have been imputed using appropriate methods. |
| Selective reporting (reporting bias) |  | Not all of the study’s pre-specified primary outcomes have been reported (knowledge, self efficacy, hypertension knowledge) |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping . |

### Burrelle 1986

|  |  |
| --- | --- |
| Methods | Parallel, study duration eight weeks, follow-up at eight weeks |
| Participants | 16 participants with treated hypertension and non-adherent, 75% black, 75% female, mean age 69 years. Setting:hospital outpatients and primary care, USA |
| Interventions | Complex/ combined intervention: Home visits, education, special dosing devices versus usual care |
| Outcomes | Pill count and self report:  Percent of pills taken: 92% in the intervention group compared to 71% in the control group (P < 0.0001). Net reduction in blood pressure 7 mm Hg (systolic) and net increase of 7 mm Hg in diastolic blood pressure (P > 0.05). |
| Notes | Small study, likelihood of bias. Ethics reported, and no imbalance at baseline between groups. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias). Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | No description |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Burris 1991

|  |  |
| --- | --- |
| Methods | Parallel, study duration eight weeks, follow up at eight weeks |
| Participants | 58 participants with treated and uncontrolled hypertension, mean age 67/68 years (intervention/control), 24/34% female (intervention/control). Setting: hospital outpatients, USA |
| Interventions | Simplification of dosage regimen: transdermal clonidine 0.1mg per day with placebo tablets vs verapamil SR 120mg daily plus transdermal placebo |
| Outcomes | Pill count and visual assessment: 96 to 100% of participants wore the active patch at every visit compared to 100% using the placebo patch. 68 to 88% had optimal tablet counts in the verapamil SR group compared to 11 to 37% in the control group (P values not reported). Net reduction 5 mm Hg (systolic) and 1 mm Hg (diastolic), P < 0.05. |
| Notes | No probability values reported for adherence outcome. Study compared different drugs. Different methods used to assess adherence in both groups. High likelihood of bias. Similar at baseline. Ethics reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Random table |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Double blind |
| Blinding (performance bias and detection bias). Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No information |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Christensen 2010

|  |  |
| --- | --- |
| Methods | Crossover RCT. No power calculation. 12 months follow-up duration, |
| Participants | 1577 newly diagnosed hypertensive patients, 398 patients included in analysis (219 group1, 179 group2), with range of age 45-75years, most of them female. Setting: Poland. |
| Interventions | Intervention to support adherence behaviour (reminder): MEMS used by IG and CG received their standard care. |
| Outcomes | Self report:  1- In the half of study patients using MEMS reported 91% compliance vs 85% in CG. this difference was diminished after crossover (88 vs 86%).  2- NS difference in BP  3- Using MEMS reminder improved self reported compliance by 5.5% compared to CG. With compliance taking, dosing and timing between 45-52 in IG and 32-38 in CG. |
| Notes | Reasons for lost of follow -up, ethical approval and source of funding were reported. NS difference between groups in demographical data at baseline. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | Insufficient details |
| Blinding (performance bias and detection bias) outcome assessors |  | Ensured |
| Blinding (performance bias and detection bias). Data analysts |  | Insufficient details |
| Incomplete outcome data (attrition bias) |  | ITT not used, just mentioned reason for lost of follow up |
| Selective reporting (reporting bias) |  | Insufficient details |
| Other bias |  | Bias related to crossover design. |

### Da Costa 2005

|  |  |
| --- | --- |
| Methods | A Parallel field trial, with 3 months study duration and follow up. Power calculation was done. Number expected to be recruited 60 per each group. |
| Participants | 71 hypertensive patients were included; median age was 57 years for intervention and 59 for control; 54/ 55% were female, 67.6% were had secondary school or less. Setting: Community of Lisbon and Porto in Portugal. |
| Interventions | Intervention to support adherence behaviour (reminder): Provided a card reminder: alarm card set up to peep every day at the same time for an overall follow up period of 84 days vs control group with no reminder card. done by pharmacies well defined) |
| Outcomes | Pill count:- In both group the mean compliance rates were high at all time points. In intervention group there  was a constant compliance 97% throughout the study, whilst in the control group the compliance rate dropped from 94.9% at the beginning of the study to 87.3% at the end with P = 0.01).  - Between complaint and non compliant subjects there were no mean BP significant differences ( SBP, P = 0.580/ DBP, P = 0.175) |
| Notes | Compliant patient had compliance rates between 80% and 100%. Source of funding, and reasons for loss of follow up were reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Folded papers with the numbers 1 or 2 |
| Allocation concealment (selection bias) |  | Using an open random allocation schedule |
| Blinding (performance bias and detection bias)outcome assessors |  | The outcomes assessors were knowing the purpose of the study after attending day training course about the study |
| Blinding (performance bias and detection bias). Data analysts |  | The open label study |
| Incomplete outcome data (attrition bias) |  | Insufficient information |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping. |

### Detry 1995

|  |  |
| --- | --- |
| Methods | Crossover, study duration 12 weeks, follow up at 12 weeks |
| Participants | 320 participants with uncontrolled hypertension, age under 70 years, mean age 60 years, 48% female. Setting: hospital outpatients, Belgium |
| Interventions | Simplification of dosage regimen: Amlodipine 5mg daily vs nifedipine 20mg twice daily |
| Outcomes | Pill count and electronic monitoring: Therapeutic coverage 93.7% in the intervention group vs 75.9% in the control group (P < 0.001). Blood pressure changes not reported. |
| Notes | Patients double-counted. Randomisation procedure not reported. Study compared two different drugs. Ethics and funding reported. No imbalance at baseline between groups. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient information |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Assessors were un blind |
| Blinding (performance bias and detection bias). Data analysts |  | In dependent statistical unit |
| Incomplete outcome data (attrition bias) |  | Insufficient information |
| Selective reporting (reporting bias) |  | No information |
| Other bias |  | Cross over design bias |

### Eshelman 1976

|  |  |
| --- | --- |
| Methods | Parallel, study length and timing of follow up not reported |
| Participants | 100 participants with treated hypertension, no baseline data reported. Setting: hospital outpatients and pharmacy department, USA |
| Interventions | Intervention to support adherence behaviours (reminders): Compliance dispenser vs usual medication bottle |
| Outcomes | Pill count and self report:  63% adherent in the intervention group compared to 61% in the control group (not statistically significant, no exact P value reported) |
| Notes | Dropouts at least 33% with no differential loss to follow-up reported. Bias likely. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient information |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias). Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | No description |
| Selective reporting (reporting bias) |  | No protocol or description |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Friedman 1996

|  |  |
| --- | --- |
| Methods | Parallel, study duration six months, follow up at six months |
| Participants | 267 participants with treated hypertension, 90% white, 77% women, mean age 76 years. Setting: primary care, USA |
| Interventions | Intervention to change behaviour (counselling): Telephone linked computer counselling vs usual care (not defined well) |
| Outcomes | Pill count: 18% adherent in the intervention group compared to 12% in the control group (P = 0.03). Net reduction in BP 4.7 mmHg systolic (P = 0.85) and 4.4 mmHg diastolic (P =0.09) |
| Notes | Treatment provider blinded until baseline measurement completed. Randomisation by 'paired randomisation protocol'. Funding reported. No imbalance in demographical characteristics of both groups. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Blinding ensured |
| Blinding (performance bias and detection bias). Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Gabriel 1977

|  |  |
| --- | --- |
| Methods | Parallel, 3 1/2 months follow-up. |
| Participants | 79 participants with treated hypertension, mean age 65 years, mainly black women. Setting: pharmacy at community health centre, US |
| Interventions | Intervention to support behaviours (professional support and reminder): Daily drug reminder chart with pharmacist supervision vs not daily reminder |
| Outcomes | Pill count and self report: Mean compliance score 82.4% in the intervention group compared to 70.4% in the control group (P = 0.002).  - Positives attitudes toward the chart higher compliance significant correlation but no P value reported. |
| Notes | Small study, no power calculation reported, unreliable assessment of adherence. There was imbalance in term of income. Funding reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias)outcome assessors |  | No description |
| Blinding (performance bias and detection bias). Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | No description |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Girvin 1999

|  |  |
| --- | --- |
| Methods | Cross over, three months follow up |
| Participants | 27 participants with controlled hypertension, 36% women, mean age 62 years. Setting: general practices, Northern Ireland |
| Interventions | Simplification of dosage regimen: Enalapril 20mg once daily vs Enalapril 10mg twice daily |
| Outcomes | Electronic monitoring: 92.2% adherent in intervention group vs 72.6% in the control group (P < 0.001). 5.3 mm Hg net reduction in systolic and 1.0 mm Hg net reduction in DBP (P = 0.068 and 0.086 respectively). |
| Notes | Patient selection with potential for selection bias. Approved ethics, not reported imbalance. No power calculation. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | Insufficient details |
| Blinding (performance bias and detection bias) outcome assessors |  | Non blinding ensured |
| Blinding (performance bias and detection bias)Data analysts |  | Blinding ensured |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | Cross over design bias |

### Green 2008

|  |  |
| --- | --- |
| Methods | Parallel RCT, with 12 months study duration and follow up. Power calculation done. Number expected to be recruited 780. |
| Participants | 778 patients with uncontrolled essential hypertension, characteristics of the study groups were comparable at baseline except for sex and already having a home BP monitor; mean age was 59.125 years; 52% female; 82.7% were white. 41.6% were had some post high school, 55.9 % were full time employed. Setting: 10 Primary care medical centres in Washington and Idaho USA. |
| Interventions | Complex/ combined intervention: - Home BP monitoring and secure patient Web site ( includes the ability to refill medications, make appointments, view portions of his or her EMR such as current health conditions, laboratory test results, clinic visit summaries, and lists of allergies, immunizations, and medications and use secure messaging to contact health care team members training only)  -Home BP monitoring and secure patient Web site training plus pharmacist care management delivered through Web communications vs usual care who were told their BP was not in control and were encouraged to work with their physician to improve it |
| Outcomes | Reviewing automated data files:  -There was no difference between groups in the proportion of subjects reporting high medication adherence (67% (95/142) intervention vs. 69% (90/130) control, P = 0.77).  -Systolic BP was decreased stepwise from usual care to home BP monitoring and Web training only to home BP monitoring and Web training plus pharmacist care. Diastolic BP was decreased only in the pharmacist care group compared with both the usual care and home BP monitoring and Web training only groups. Compared with usual care, the patients who had baseline systolic BP of 160 mm Hg or higher and received home BP monitoring and Web training plus pharmacist care had a greater net reduction in systolic BP (−13.2 mm Hg [95% CI, −19.2 to −7.1]; P = .001) and diastolic BP (−4.6 mm Hg [95% CI, −8.0 to −1.2]; P = .001), and improved BP control (relative risk, 3.32 [95% CI, 1.86 to 5.94]; P = 0.001) |
| Notes | Ethical approval and source of funding were reported. Adherence was defined as patient procurement of a 60-day or longer supply of medication during a 182-day period. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Block randomizations design |
| Allocation concealment (selection bias) |  | Sealed envelope |
| Blinding (performance bias and detection bias) outcome assessors |  | Insured outcomes assessors blinding |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Missing data have been imputed using appropriate methods (observation carried- forward assumption) but the table did not show that. |
| Selective reporting (reporting bias) |  | Not all of the study’s pre-specified primary outcomes have been reported (cost) |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping. |

### Hamet 2003

|  |  |
| --- | --- |
| Methods | Parallel RCT, with 12 months study duration and follow up, power calculation was done. Number expected to be recruited 5000. |
| Participants | 4864 patients with essential hypertension were recruited. Two groups characteristics were similar; the mean of age was 58 years, 51% were female. Setting: 397 general practice centres in Canada. |
| Interventions | Complex / combined intervention:  Behavioural modification: Patients received once daily dose of irbesartan with intervention Avapromise. Had two elements; 1st attempts to reinforce medication adherence behaviours by using medication reminder letters, BP diaries, and telephone nurse counselling sessions. The 2nd addresses issues of lifestyle management through educational brochures dealing with topics such as healthy living, nutrition, physical fitness and stress management.) vs with out intervention who received usual care educational materials in their physicians office well defined for both groups. |
| Outcomes | Self report:  - Compliance was assessed by comparing the rate and time to discontinuation between these two groups.  - Overall adherence rate was 75% in both groups (approximately because 25% discontinued).  - No significant differences in the duration of irbesartan compliance between the treatment groups (23.1% in intervention group, 23.5% in non intervention. BP not reported. |
| Notes | The time to discontinuation was defined as negative response to telephone follow up question "are you taking your Avapro (irbesartan) every day?". Source of funding was reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computer generated |
| Allocation concealment (selection bias) |  | Central allocation through site of physicians office |
| Blinding (performance bias and detection bias) outcome assessors |  | Insured no blinding |
| Blinding (performance bias and detection bias)Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Missing data have been imputed with appropriate way ITT. and reasons for loss of follow up were listed |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | Early termination of the study |

### Hamilton 1993

|  |  |
| --- | --- |
| Methods | Parallel, six months follow up |
| Participants | 34 participants with treated hypertension, mean age 54 years, white, married, high school educated. Setting: hypertension clinic in tertiary care teaching medical centre, US |
| Interventions | Complex/ combined intervention: postcard reminder, nurse-led educational appointment and follow-up phone call compared with usual care |
| Outcomes | Self report: adherence score of 27.5 in intervention group compared to 24.5 in control group (P = 0.12). Net reductions of BP 17.3 mm Hg systolic and 4.7 mm Hg diastolic ( P = 0.03 and 0.22 respectively). |
| Notes | Small study. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias)Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Hawkins 1979

|  |  |
| --- | --- |
| Methods | Parallel study, 29 months follow up |
| Participants | 1148 participants with hypertension and diabetes. Mean age 60 years, 76 % women. Setting: hospital outpatient clinic, USA |
| Interventions | Complex/ combined intervention: (three groups). post-diagnostic management of patients with hypertension and diabetes by clinical pharmacist vs usual physician review |
| Outcomes | Prescription record: diuretic only: 60.5% adherent in intervention group vs 52.9% in the control group (P < 0.7), diuretic plus methyldopa: 84.6% adherent in intervention group vs 65.4% among controls (P = 0.2). Net reduction in blood pressure 4 mm Hg systolic and 0 mmHg diastolic (P < 0.001 and not significant with no exact P value reported, respectively, for both groups combined) |
| Notes | High losses to follow-up (455). Ethics and funding reported, imbalance in term of diabetes |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Random table |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | They were the investigators |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Haynes 1976

|  |  |
| --- | --- |
| Methods | Parallel, study duration one year, follow up at one year |
| Participants | 39 participants with treated and uncontrolled hypertension, male steel workers, work-site. Setting: Canada |
| Interventions | Complex /combined intervention : Self-measurement of blood pressure, medication and blood pressure charting, tailoring to daily routines, fortnightly review and rewards (financial and praise) vs no intervention |
| Outcomes | Pill count: 66% adherent in the intervention group compared to 43% among the controls (P < 0.025). Net reduction in DBP 4 mm Hg (P = 0.12) |
| Notes | Small study. Potential sources of bias well reported. Study was underpowered to detect an effect on BP, Funding reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Minimization |
| Allocation concealment (selection bias) |  | Insufficient details |
| Blinding (performance bias and detection bias) outcome assessors |  | Blinding insured |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised also no bias related to early stopping |

### Hunt 2004

|  |  |
| --- | --- |
| Methods | Parallel prospective RCT, follow up started after one year (+\_3months) from providing of the intervention. Power calculation done. 302 patients expected to be recruited. |
| Participants | 312 patients with mildly uncontrolled hypertension; with mean of age 69.2 years, 58% women, 89.8% white, 30.15% had high school graduate. Setting: 9 clinics in Portland, Oregon USA. |
| Interventions | Educational intervention: Providing educational hypertension packets through mail; first packet focused on educational materials about hypertension and lifestyle modification, 2nd packet after 3 months from 1st one, focus on drug adherence and blood pressure monitoring. versus control group with no materials provided through mail |
| Outcomes | Self report:  - No significant differences was found in mean BP between two groups (135/77 mmHg vs 137/77 mmHg; *P* = .229).  -There was no significant difference in patient-reported medication compliance (0.35 intervention vs 0.35 control; *P* = ns)  ***-*** Subjects in the intervention arm scored higher on knowledge quiz (mean 7.48 ± 1.6) as compared to 7.09 ± 1.6 in the control arm ( *P* = .019). also reported higher satisfaction with their care. |
| Notes | 4 points of self reported questionnaire represented good medication compliance. Ethical approval and source of funding were reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computer generated |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Insufficient description |
| Blinding (performance bias and detection bias) Data analysts |  | The data analysis done by the study investigators |
| Incomplete outcome data (attrition bias) |  | No description they didn't report ITT analysis however the table showed that they included all patient in analysis. no description for the reasons of loss of follow up |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | No bias related to particular trial designs (e.g. carry- over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping. |

### Hunt 2008

|  |  |
| --- | --- |
| Methods | Parallel prospective RCT, with 12 months duration and follow up. Power calculation done. 151 patients were required. |
| Participants | 233 hypertensive patients in control group and 230 treatments, total 463 patients with un controlled BP; both groups characteristics were similar at the baseline with exception of history of stroke which was 7% in intervention group compared to 3% in control with P = 0.04. Mean of age was 68%, 64.5% were female, 66% had medicaid or medicare insurance, 64.5% had college education, 18.5 were currently smoker. Setting: 9 Primary care clinics in Oregon, USA |
| Interventions | Complex/ combined intervention: Participating of pharmacy practitioners in the hypertension management through reviewing the patients medication, and lifestyle habits, assessing barriers to adherence provide education, scheduled follow up appointment etc, vs usual care group who continued their normal schedule of care. well defined both groups |
| Outcomes | Self report:  - SBP decreased by 6mm Hg (P = 0.007) and DBP by 3mm Hg (P = 0.002) were lower in intervention group compared to control group.  - 62% of intervention group achieved target BP compared to 44% of control group (P = 0.003).  - Minimal difference between both groups in the proportion of reporting high medication adherence (67% (95/142) intervention vs 69% (90/130) control ( P = 0.77). |
| Notes | Ethics and funding source were reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computer generated |
| Allocation concealment (selection bias) |  | Insufficient information |
| Blinding (performance bias and detection bias) outcome assessors |  | Blinding of nurses who assessed outcomes |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Missing data have been imputed by using appropriate way (ITT) reason of loss of follow up was reported |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping. |

### Johnson 1978

|  |  |
| --- | --- |
| Methods | Factorial, study duration six months, follow up at six months |
| Participants | 204 participants with treated but uncontrolled hypertension, 60% women, mean age 54/52 years (men/women), primary care, Canada |
| Interventions | Complex/ combined intervention : Four groups : self-recording of blood pressure and monthly home visits, self-recording only, monthly home visits only versus no intervention |
| Outcomes | Interview and pill count: Increase in adherence 10% (self-monitoring plus visits), 12% (self-monitoring only) and ten % (home visits only) compared to one% decrease in the control group (not significant, no exact P value reported). Reductions in DBP 1mm Hg (self-monitoring plus home visits), 2 mm Hg (self-monitoring only) and 2 mm Hg (home visits only), all not statistically significant, but no exact P value reported. |
| Notes | Power calculation not reported but probability of type II error quantified in the discussion. no imbalance. Funding reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | insufficient details |
| Allocation concealment (selection bias) |  | no description |
| Blinding (performance bias and detection bias) outcome assessors |  | blinding ensured |
| Blinding (performance bias and detection bias) Data analysts |  | no description |
| Incomplete outcome data (attrition bias) |  | insufficient details |
| Selective reporting (reporting bias) |  | no description or protocol |
| Other bias |  | no bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Kerr 1985

|  |  |
| --- | --- |
| Methods | Parallel, study duration one day, follow up at three months |
| Participants | 235 employees, 43% women, mean age 50.3 years. Setting: work-site, USA |
| Interventions | Complex/ combined intervention: Education and self-monitoring, self-monitoring only, education only versus no intervention |
| Outcomes | Self report: Per cent of pills taken: 100% (education and self-monitoring), 84% (self-monitoring only) and 81% (education only) vs 100 % (control), not statistically significant. Reduction in DBP zero mm Hg (education and monitoring) and increases in DBP of 1 mm Hg (self-monitoring only) and 5 mmHg (education only), not statistically significant. |
| Notes | Large dropouts in all groups, inconsistencies between denominators in tables and dropouts that vary for blood pressure and adherence outcomes. Funding and ethics were reported. No imbalance |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Kirscht 1977

|  |  |
| --- | --- |
| Methods | Parallel, study duration one day, follow up at three months |
| Participants | 400 participants with treated hypertension, nearly all white, 78% age over 50, Setting: primary care, USA |
| Interventions | Complex/ combined intervention : Four sequential interventions four months apart: Education, nurse phone calls, self-recording of blood pressure, social support versus usual care |
| Outcomes | Self report: Percentage of maximum adherence score achieved (intervention vs control): Educational material 91 vs 90% (not significant), nurse phone calls 96 vs 91% (not significant), self-monitoring 94 vs 94% (not significant) and social support 98 vs 93% (P <= 0.05). Blood pressure changes not reported. |
| Notes | Results difficult to interpret due to unclear reporting of adherence scores. Funding reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Leenen 1997

|  |  |
| --- | --- |
| Methods | Parallel, study duration 20 weeks, follow up at 20 weeks |
| Participants | 198 participants with newly diagnosed hypertension, 40% women, mean age 55 years. Setting: primary care, Canada |
| Interventions | Intervention to support adherence behaviour (reminder): Amlodipine 5mg daily vs diltiazem SR 60mg twice daily |
| Outcomes | Medication event monitoring system: 90% adherent in intervention group compared to 82% in the control group (P < 0.01). Net reduction in SBP 6 mm Hg (P < 0.01) and DBP 1 mm Hg (not statistically significant, no exact P value reported) |
| Notes | Study compared two different drugs. Bias likely. Ethics and funding were reported. No imbalance at baseline |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computer generated |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Blinding ensured |
| Blinding (performance bias and detection bias) Data analysts |  | Non blinding ensured |
| Incomplete outcome data (attrition bias) |  | No description |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Logan 1979

|  |  |
| --- | --- |
| Methods | Parallel, study duration six months, follow up at six months |
| Participants | 457 volunteers from business, newly diagnosed hypertension, 88% white, 21% female, mean age 47 years. Setting: work-site, Canada |
| Interventions | Complex combined intervention: Nurse-led work-site care versus usual care (well defined) |
| Outcomes | Pill count: 67% adherent in the intervention group compared to 49% in the control group (P < 0.005). Reduction in blood pressure 4 mm Hg diastolic (P < 0.001) |
| Notes | Differential loss to follow-up well reported, no imbalance at baseline. Funding reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Technician unaware of group allocation |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Logan 1983

|  |  |
| --- | --- |
| Methods | Parallel, study duration one year, follow up at one year |
| Participants | 194 participants, uncontrolled hypertensive business employees, 84% white, 27% female, business employees. Setting: work site, Canada |
| Interventions | Complex combined intervention: Nurse-led care versus usual care (well defined) |
| Outcomes | Pill count: 55% adherent in the intervention group compared to 56% in the control group (not statistically significant, no exact P value reported). Net reduction in diastolic blood pressure 3 mm Hg (not significant). |
| Notes | Randomisation process unclear. No imbalance. Funding reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Blinding ensured |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Marquez-Contr. 1998

|  |  |
| --- | --- |
| Methods | Parallel, study duration six months, follow up at six months |
| Participants | 110 participants with newly diagnosed and established treated hypertension, 71% women, mean age 59 years. Setting: primary care, Spain |
| Interventions | Complex/ combined intervention and patient education: group sessions with information about blood pressure management and postal education (with information on blood pressure and the importance of compliance, sent at months one, three and five) versus usual care (defined well) |
| Outcomes | Pill count: 93% adherent in the intervention group compared to 69%in the usual care group (P <0.002). Reduction in blood pressure not reported. |
| Notes | Differential loss to follow-up in both treatment arms not reported. Funding and ethics were reported. No imbalance at baseline |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Marquez-Contreras 2005

|  |  |
| --- | --- |
| Methods | A prospective multicenter RCT, 18th months study duration, 6 months follow up, |
| Participants | 636 patients with mild to moderate hypertension, no difference in characteristics of patients between groups; with mean age 60.9 years, 51.5% female. Setting: 85 primary care clinics in Spain |
| Interventions | Complex/ combined intervention: 1- TIG, Telephone intervention group done by nurses; received controlled intervention by 3 telephone calls to reinforcing compliance and reminding the subjects of the scheduled visits. During these telephone calls the patients answered questions related to their antihypertensive medication such as name, dosage and timing ...etc  2- Mail intervention group(MIG): in addition to CG intervention, received three mailed communications at home (health education about hypertension included information about hypertension; definition, diagnosis, signs and symptoms…etc).This done by 2 investigators not included as field investigators. Versus Control group CG; they received routine canter primary care (not defined well). |
| Outcomes | Pill count:  -85.5% were compliers (CI= 82.5%- 88.5%; n=460); they represented 69.2% of CG, 91.3% of MIG , and 96.2 of TIG  - Mean percentage compliance (MPC) was 95.1+- 19.6%b(CI =93.28-96.92); MPC for CG was 89.6%+-15, for MIG 96.6%+\_12, and for TIG was 99.1%+\_26.8 (P = 0.0001).  - The percentage of patients controlled was 63..3% in TIG( 95% CI 56.4-70.2%) , 61.3% in MIG (95% CI 54.1- 68.5%) and 47.2% in CG (95% CI 40-54.4%) with significantly superior control in TIG vs CG (P < 0.05). .  - The mean BP reductions were significant for 3 groups with significantly greater in TIG mean decrease in SBP (31.6+\_10.1, P = 0.0001) DBP 19.7 \_+ 46.7 , P = 0.0001. |
| Notes | Compliance was accepted for Percentage Compliance 80-110%. They reported source of funding and ethical approval. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | No description |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient information about calculation of missing data but reasons for loss of follow up were reported |
| Selective reporting (reporting bias) |  | No protocol was found |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping . |

### Marquez-Contreras 2006

|  |  |
| --- | --- |
| Methods | Parallel prospective multicenter Clinical trial, 12 months duration and 6 months follow up. |
| Participants | 250 Mild to moderate Uncontrolled hypertension patients; both group were similar in baseline variables; with mean of age 59.1 years, the mean of follow up 6 months, 49% were female. Setting: 40 primary care centres in Spain |
| Interventions | Intervention to support behaviour (home BP monitoring); patients received an OMRON in their homes vs control group who received standard health intervention (not well defined) |
| Outcomes | MEMS  -Compliance was 92% in IG. In CG 74% (95% CI 86.7-97.3 AND 63.9-84.1) P = 0.0001)  - PC ( percentage compliance) OF 93.5 % AND 87.6% (95%  CI 88.7-98.3 and 81.2-94.0) P =0.0001)  - The percentage of correct day were 83.6 for CG and 89.4 % for IG.  -The percentages of subjects  who took the medication at the prescribed time  were 79.89 and 88.06 %.  -The levels of therapeutic cover were 86.7 and 93.1%  - The number needed to treat to avoid one case of non compliance was 5.6 patients.  - The differences in the mean decrease in BP were significant for DBP with greater decrease observed in the IG ( 12.8+-9.9mm Hg)CG (9.7+- 9.8mm Hg) with P <0.05  - The percentage of patients controlled of BP at the end of the study was 56 % in CG and 67 % in IG with no significant  - ARR WAS 18%, RRR WAS 70%, NNT WAS5.6 patients Relative risk was 0.3 |
| Notes | Adherence if their drug consumption of 80-100%. Ethical approval reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Random number tables |
| Allocation concealment (selection bias) |  | Centralized randomisation |
| Blinding (performance bias and detection bias) outcome assessors |  | Insufficient information |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient information about missing data but reasons of loss of follow up was reported. |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping |

### McKenney 1992

|  |  |
| --- | --- |
| Methods | Two-phase parallel, study duration two times 12 weeks, follow up at 12 and 24 weeks |
| Participants | 70 participants, 70% white, 59% women, mean age 73 years |
| Interventions | Intervention to support behaviour (reminder): electronic medication aid cap with recording card and BP cuff vs usual drug bottle. Setting: Virginia, USA |
| Outcomes | Pill count: PHASE I: Mean adherence 95% in the intervention group compared to 78% among controls (P = 0.0002). Net reduction in BP intervention vs control 4.8 mm Hg systolic (P = 0.0006) and 8.6 mmHg diastolic (P < 0.001) PHASE II: Mean adherence rates 93.6% for cap only (P = 0.003), 98.7 5 for cap and card (P < 0.001), 100.2% for cap card and cuff (P < 0.001) vs 79% in the control group. Net BP reduction 12.3 mm Hg systolic (P < 0.01) and 19.2 mm Hg diastolic (P = 0.0001) for cap and card. Net BP reduction 19.5 mm Hg systolic (P = 0.0006) and 12.7 mm Hg diastolic (P = 0.0006) for cap, card and cuff. |
| Notes | Nine patients required change of medication during second phase, and their blood pressure measurements were not included in the analysis. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Insufficient details |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No protocol or description |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Mehos 2000

|  |  |
| --- | --- |
| Methods | Parallel, six months follow up |
| Participants | 41 participants with uncontrolled hypertension, mean age 59 years, 70% women. Setting: single family medicine clinic, US |
| Interventions | Complex/ combined intervention: Home BP measurement, diary, instruction to measure BP, information on hypertension and risk factor with subsequent evaluation by clinical pharmacist vs usual care (well defined) |
| Outcomes | Prescription data refill: Mean adherence 82% in intervention group vs 89% in the control group (P = 0.29). Blood pressure net reduction 10.1 mm Hg systolic (P = 0.069) and 6.7 mm Hg diastolic (P = 0.02) |
| Notes | Patients randomised using a 'deck of cards'. Funding and ethics were reported, no imbalance at baseline. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Morgado 2011

|  |  |
| --- | --- |
| Methods | Parallel RCT (1:1), 9 months follow-up duration. Power calculation was reported. Used ITT. |
| Participants | Expected to recruit 90 patients/ group, however, 99 CG and 98 in IG, with mean age 59.5 years, around 60% were female. Both groups were comparable in their characteristics with no significant differences at baseline just with using of angiotensin receptor blocker was high in IG. Setting: outpatient clinic, Portugal. |
| Interventions | Complex/ combined intervention:  Counselling and education: Clinical pharmacist identified problems leading to poor BP control, provided patients education (disease, BP self monitoring, lifestyle education and counselling. Educational written material provided. CG received the traditional service provided by hospital clinic with no clinical pharmacist involvement. |
| Outcomes | MMAS  1- BP control was higher in IG (P = 0.005) at the end of the study.  2- IG had significant lower SBP (-6.8 mmHg. P = 0.006) and DBP (-2.9 mmHg, P = 0.02).  3- Adherence was significantly higher in IG (74.5% vs 57.6%, P= 0.012). |
| Notes | Used ITT analysis. Source of funding, reasons for lost of follow-up, and ethical approval were reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Ensured |
| Allocation concealment (selection bias) |  | Ensured |
| Blinding (performance bias and detection bias) outcome assessors |  | Insufficient details |
| Blinding (performance bias and detection bias) Data analysts |  | Insufficient details |
| Incomplete outcome data (attrition bias) |  | ITT and reported reasons of lost of follow-up |
| Selective reporting (reporting bias) |  | Insufficient details |
| Other bias |  | Free from bias related design and early stopping |

### Morisky 1985

|  |  |
| --- | --- |
| Methods | Sequential factorial, study duration three years, follow up at five years |
| Participants | 193 participants with treated hypertension, 91% black, 70% women, median age 54 years. Setting: USA |
| Interventions | Educational intervention: Re-enforcement interview, family member support, small groups versus usual care(not defined well). |
| Outcomes | Self report: high adherers: 53% (family support), 36% (counselling) and 40% (small group training) vs 40% in the usual care group (P < 0.05, not significant and not significant respectively). Control of BP (control being defined as equal or less than 140/90 mmHg in patients age 39 and under; equal or less than 150/95 mmHg for ages 40 to 59; equal or less than 160/100 age 60 or older) 75% (family support), 54% (counselling) and 46% (small group training) in the intervention groups compared to 50% in the control group (P < 0.05, not significant and not significant, respectively) |
| Notes | No significant differences between dropouts and those who continued to receive care. Funding and ethics reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Mounier-Veh. 1998

|  |  |
| --- | --- |
| Methods | Parallel, study duration 12 weeks, follow up at 12 weeks |
| Participants | 103 participants with treated and uncontrolled hypertension, mean age 54 years, 27% women. Setting: primary care, France |
| Interventions | Simplification of dosage regimen: Amlodipine 5mg once daily vs nifedipine 20mg twice daily |
| Outcomes | Electronic monitoring: 92.5% adherent in the intervention group compared to 74.8% among the controls (P < 0.001). net reduction in systolic blood pressure 0.8 mm Hg and 1.1 mm Hg net increase in diastolic blood pressure (not statistically significant, no exact P value reported) |
| Notes | Treatment allocation according to 'enrolment order' and 'randomisation list', study compares two different drugs. Ethics reported. No imbalance between groups at baseline. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | Insufficient details |
| Blinding (performance bias and detection bias) outcome assessors |  | Insufficient details |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Nessman 1980

|  |  |
| --- | --- |
| Methods | Parallel, study duration eight weeks, follow up at six months |
| Participants | 52 non-adherent participants with treated but uncontrolled hypertension, 75% white, 2% female, mean age 55 years. Setting: hospital outpatients, USA |
| Interventions | Intervention to change behaviour (self determination): nurse and psychologist teaching self-determination vs nurse and protocol-run clinic (control)well defined |
| Outcomes | Pill count: Intervention group compliant for 4.6 out of seven week vs 3.3 weeks in the control group (P < 0.001). Reduction in systolic blood pressure 6 mmHg (P < 0.05). |
| Notes | Only 10% of eligible patients took part in the study which may have led to self-selection. No imbalance between groups at baseline. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Non blinding insured |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Ogedegbe 2008

|  |  |
| --- | --- |
| Methods | Parallel RCT, 12months study duration, follow up occur after 3 months the done every three months: 3, 6, 9, 12 months. Power calculation done. They 173 expected to be recruited |
| Participants | 190 hypertensive African-American patients; with no significant differences between groups at baseline; mean age was 54 years, 88% were female, 17% were married, 77 % had high school or college education, 50% full time employed. Setting: 2 primary community centres, New York, USA. |
| Interventions | Intervention to change behaviour (motivational interviewing (MINT)); received UC and 4 sessions of (MINT ) which included behavioural counselling about medication adherence, patients was the basic element of these sessions to facilitate initiation and maintenance of behaviour change, vs usual care who didn't receive MINT counselling. MINT done by research assistant. |
| Outcomes | MEMS  - Adherence rate was higher for the MINT group compared to UC ( 60%vs, 47%, respectively , P= 0.054) with between group difference of 13% ( 95% CI, -0.2-27%). with ITT analysis MINT provided steady maintenance of medication adherence over 12 months 57%, compared to a significant decline noted in UC group 43%, P = 0.027).  - In the SBP and DBP the difference between group was -6.1 mm Hg (P =0.065) and -1,4 mmHg (P =0.464). |
| Notes | Poor adherence taking less than 80% of prescribed doses. Ethical approval and source of fund were reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computerized random number generator |
| Allocation concealment (selection bias) |  | Sealed envelope |
| Blinding (performance bias and detection bias) outcome assessors |  | Blinding ensured for clinical staff who measured BP and adherence |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Missing data have been imputed with appropriate analysis ITT. reasons of loss of follow up were reported |
| Selective reporting (reporting bias) |  | Not all of the study's pre-specified secondary outcomes reported (self efficacy, intrinsic motivation. |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised |

### Park 1996

|  |  |
| --- | --- |
| Methods | Parallel, four months follow up |
| Participants | 64 participants, mainly white with treated hypertension, 50% women, mean age 60 years. Setting: two chain pharmacies, US |
| Interventions | Intervention to change behaviour: pharmacy-based counselling |
| Outcomes | Pill count:  Mean adherence 86.6% in the intervention group compared to 89.1% in the control group (not statistically significant, no exact P value reported) |
| Notes | Small sample size, method of randomisation unclear. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Non blinding ensured |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Pierce 1984

|  |  |
| --- | --- |
| Methods | Factorial trial, six months follow up |
| Participants | 115 participants with uncontrolled hypertension, mean age 57 years, 60% women. Setting: one general practice clinic, Western Australia |
| Interventions | Complex/ combined intervention: three groups Self monitoring of blood pressure and health education alone and in combination vs usual care(not defined well) |
| Outcomes | Pill count and self report: Self-monitoring and education: 26% good adherers' vs 24% in the control group (not significant, no exact P value reported), self-monitoring only: 30% vs 24% (not significant, no exact P value reported), education only: 28% vs 24% (not significant, no exact P value reported). Blood pressure: education: 83% had blood pressure reduction vs 67% among controls (P < 0.05, effect size unclear), self monitoring: 74% vs 78% (not significant, no exact P value reported, effect size unclear), both education and self monitoring combined: 74% vs 78%, no exact P value reported, effect size unclear) |
| Notes | Randomisation procedure prone to bias. Reporting of outcomes inadequate. Funding reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computer generated |
| Allocation concealment (selection bias) |  | Concealment ensured |
| Blinding (performance bias and detection bias) outcome assessors |  | Blinding ensured |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Pladevall 2010

|  |  |
| --- | --- |
| Methods | Multicentre cluster RCT, 5 years duration, and follow up every 6 months. The mean follow up duration is 39 months. Power calculation done. NS differences in demographical characteristics between groups at baseline. |
| Participants | Estimated 264 patients/ group, included: 489 patients in CG and 446 patients in IG. All characteristics were similar with exception that baseline DBP, heart rate, and self reported medication non adherence were significantly higher among IG. Setting: Spain. |
| Interventions | Complex/ combined intervention: IG: Counted pill, designated a family member support to adherence behaviour by using motivational interviewing and provided educational information to patients. CG: received their standard care. |
| Outcomes | MEMS:  1- IG were less likely to have uncontrolled SBP (odd ratio 0.62 (95% CI 0.50-0.78) and more likely to be adherent (odd ratio 1.91 (95% CI: 1.19-3.05) than CG at 6 months.  2- After 5 years of follow up, 153 patients had at least 1 of the composite cardiovascular events: 67 (16%) in the IG and 86 (19%) in the CG (ns). |
| Notes | Non adherence defined as measured adherence <80%. Source of funding, ethical approval, ITT, and reasons of lost of follow-up were reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Ensured |
| Allocation concealment (selection bias) |  | Ensured |
| Blinding (performance bias and detection bias) outcome assessors |  | Insufficient details |
| Blinding (performance bias and detection bias) Data analysts |  | Insufficient details |
| Incomplete outcome data (attrition bias) |  | ITT and reason for loss of follow-up reported. |
| Selective reporting (reporting bias) |  | Insufficient details |
| Other bias |  | Bias related to cluster design |

### Rehder 1980

|  |  |
| --- | --- |
| Methods | Factorial, study duration three months, follow up at six months |
| Participants | 150 participants with treated hypertension, 92% black, 75% women, mean age 50 years. Setting: hospital outpatients, USA |
| Interventions | Complex/ combined intervention: (four groups) counselling with special medication container and special medication container only vs usual medication vials (well defined) |
| Outcomes | Pill count: 99% (counselling and container), 94% (container only) and 90% (counselling only) versus 88% among the controls, not statistically significant (no exact P value reported). |
| Notes | High dropout rate and small sample size for a factorial trial. Funding reported, imbalance reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Rinfret 2009

|  |  |
| --- | --- |
| Methods | RCT prospective open label blinded endpoints, power calculation done. 12 months study duration. Both groups are similar in demographical characteristics at baseline. |
| Participants | 250 hypertensive patients expected to be recruited, 223 (111 in intervention and 112 in control group) patients randomised. Mean age was 56 years, 45.7 female, and 66% newly diagnosed hypertension. Setting: 8 primary setting, Canada |
| Interventions | Complex/ combined intervention:  Intervention group: provided with an educational booklet, digital home BP monitor, log book and telephone linked IT management support program. control group received their normal care and educational material |
| Outcomes | MMAS and pharmacy refill:  - BP control in intervention group greater than control for both SBP (-11.9 vs-7.1 mmHg P <0.001), DBP (-6.6 vs -4.5 mm Hg P =0.007).  - Adherence improved 95% compare to 91% (P = 0.07). |
| Notes | Ethical approval and source of funding were reported. They used ITT and LOCF. Reasons for lost of follow up reported and documented. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Central randomisation |
| Allocation concealment (selection bias) |  | Insufficient details |
| Blinding (performance bias and detection bias) outcome assessors |  | Ensured |
| Blinding (performance bias and detection bias) Data analysts |  | Ensured |
| Incomplete outcome data (attrition bias) |  | Used ITT and LOCF |
| Selective reporting (reporting bias) |  | Insufficient details |
| Other bias |  | No bias related to design or early stopping |

### Rudd 2004

|  |  |
| --- | --- |
| Methods | Parallel RCT, study duration 6months, follow up done at 3 and 6 months. |
| Participants | 150 hypertensive patients; both groups had similar characteristics at baseline of study except for higher rate of and dyslipidemia for usual care group; mean of age was 59.5 year, 53% were female, 70% were married, 74% were white, 29% had college degree, 50.5% were full time employed. Setting: primary clinics in California in USA |
| Interventions | Intervention to change behaviours (nurse counselling): nurse care manger provide care for management of hypertension for INTervention group ; through counselling, phone follow up contacts with patients, modification of drugs. versus usual care who received the routine with no attempt was made to alter the frequency of office visits or any other aspect of doctor patient interactions |
| Outcomes | Electronic drug event monitor:  - The adherence rate for INT patients was 80.5% \_+ 23.0% . For UC patients was 69.2%\_+ 31.15, P = 0.03).  -  SBP fell by 14.2 mm Hg (95%CI-18.2 to -10) in INT group and by 5.7 mm Hg (95% CI -10.2 TO -1.3) in the UC P<.01  - DBP fell by 6.5 mm Hg in INT group (95% CI -8.8 to - 4.1) and 3.4 mmHg in the UC group (CI -5.3 to -1.5 P<.05).  - 97% in INT group had one or more changes in drugs therapy compared to 43% of UC, and 70 % of INT group received 2 or more drugs versus 46 % of UC. |
| Notes | Ethical approval, and source of fund were reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computer generated |
| Allocation concealment (selection bias) |  | no description |
| Blinding (performance bias and detection bias) outcome assessors |  | The blinding of the assessors of BP and adherence rate was ensured |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient information about missing data imputation. reasons for loss of follow up were reported |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping. |

### Sackett 1975

|  |  |
| --- | --- |
| Methods | Factorial, study duration not reported, follow-up at six months |
| Participants | 230 male steel workers. Setting: work site, Canada |
| Interventions | Complex/combined intervention: Doctor-led work site care, educational programme, both interventions vs neither intervention (control well defined) |
| Outcomes | Pill count: 54% of those receiving augmented convenience adherent compared to 51% receiving usual care (not statistically significant) 50% adherent in education group compared to 56% among controls (not statistically significant). Net increase of the percentage of participants with controlled BP (DBP less than 90 mmHg) of 4% for physician-led work site care and five% (physician-led work site care plus education), not statistically significant. |
| Notes | No power calculation as such, but important effect size reported a priori. Not reported imbalance at baseline. Funding reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) out come assessors |  | Blinding ensured |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Santschi 2008

|  |  |
| --- | --- |
| Methods | A cluster RCT, 12 months duration, follow up done at 2,4,6 and 12 months |
| Participants | 68 uncontrolled hypertensive patients, baseline characteristics were not similar between groups; mean of age for INT group was 61.4 years , for UC 71.2 years; 24 %of UC were smokers, while 18% for INT; INT group had higher obesity than UC (50%, 38%). Setting: 4 networks of community based pharmacists and general practitioners, and outpatient clinics in Switzerland |
| Interventions | Intervention to support behaviour (reminder):  Patients in the INT group received one of their antihypertensive drugs in MEMS vs UC group who received their antihypertensive treatment as usual from their community pharmacist without MEMS. |
| Outcomes | MEMS  -  SBP significantly decreased in INT group (143.4 (SE:3.9) mm Hg compared to UC ( 154.3 (2.7) mmHg P < 0.05) . DBP difference between groups was not significant. But the difference was decreased with time.  -The target BP was higher in the INT group compared to the UC group (P < 0.05). At 4 months, 38% in the INT group reached the target BP vs. 12% in the UC group (P < 0.05), and 21% vs. 9% at 12 months but not significant,  - For INT group over 4 times follow up the adherence was very high with median taking adherence of 96.0% ( range; 78.8-100). |
| Notes | Adherence > 80%. Reported source of fund, and ethical approval. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient information |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Open randomised |
| Blinding (performance bias and detection bias) Data analysts |  | Open randomised |
| Incomplete outcome data (attrition bias) |  | Used last observation carried forward with missing data reasons for loss of follow up reported. They claimed they used ITT but the figure did not show that. |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | Selection bias |

### Saunders 1991

|  |  |
| --- | --- |
| Methods | Parallel, study duration six months, follow up at six months |
| Participants | 224 participants newly diagnosed or infrequently attending, black, 73% women, about 65% aged 40 to 59 years in two intervention groups. Setting: Soweto, South Africa. |
| Interventions | Complex/combined intervention: Written reminders, patient-held records, home visits vs usual care (not defined well) |
| Outcomes | Pill count: 31% (newly diagnosed) and 68% (infrequent attenders) adherent in the intervention group vs 15% (newly diagnosed) and 37% (infrequent attenders) among the controls (P = 0.19 and 0.009 respectively). Reduction in BP 7 mm Hg diastolic (not significant) for newly diagnosed participants and net increase in diastolic BP 4.3 mm Hg among infrequent attenders (not statistically significant, no exact P value reported) |
| Notes | Dropouts were lower in the intervention groups. Similar in baseline, funding reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | They reported that |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Blinding ensured |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Schneider 2008

|  |  |
| --- | --- |
| Methods | Parallel RCT, 12 months duration; follow up at 6 and 12 months. |
| Participants | 85 patients with essential hypertension, with no significant differences between groups; mean of age was 71.95. Setting: primary centres in Ohio and Arizona, USA |
| Interventions | Intervention to support behaviour (reminder) Pill calendar:  patient assigned to receive Lisinopril in dose blister packaging which allowing patients to see if the dose had been taken each day, it had information if a dose is missed vs traditional bottles of loose tablets |
| Outcomes | Medication refill (daily doses adherence package)  -The percentage of on time refills and Medication possession ratio was significantly higher for the study group than the control (P =0.01) (P =0.04) respectively. The mean MPR for the study group being 6.2% higher than the control group.  - DBP was 2.6 mm Hg lower at 6 months and 5.7 mm Hg lower at 12 months for the study group than the control (ns)  - NO significant differences between the 2 groups in any of the long term outcome measures (angina, MI, renal impairment, emergency department visit, hospitalisation) |
| Notes | Ethical approval and funding reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient information |
| Allocation concealment (selection bias) |  | Insufficient details |
| Blinding (performance bias and detection bias) outcome assessors |  | Blinding insured |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient information |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping . |

### Schroeder 2005

|  |  |
| --- | --- |
| Methods | Parallel RCT. with 12 months duration and 6 months follow up. Power calculation done they expected to be recruited 330 patients. |
| Participants | 245 uncontrolled hypertensive patients; no significant differences between group at baseline, mean age was 68 years, 44% were female, 9.5% were smokers, 16.65% were diabetic. Setting: 21 general practices in Bristol, UK |
| Interventions | Intervention to change behaviour (nurses consultation):  nurses provide consultation, counselling and sessions for patients in order to encourage them to talk about hypertension drugs related problems vs CG who received standard care delivered at their respective practices (well defined) |
| Outcomes | MEMS  -IN both group the baseline timing compliance was high (90.8+\_15.6%) (94.5+\_7.6%).  -intervention had not had effect on timing compliance at follow up (CI -5.1-3.1).  - in both group there was no difference at follow up in SBP (-2.7 mm Hg; 95%CI-7.2 to 1,8) and DBP (0.2mm Hg; 95% CI-1.9 to 2.3). |
| Notes | Source of fund, ethical approval were reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computer generated |
| Allocation concealment (selection bias) |  | Insufficient information |
| Blinding (performance bias and detection bias) outcome assessors |  | Open RCT |
| Blinding (performance bias and detection bias) Data analysts |  | Open RCT |
| Incomplete outcome data (attrition bias) |  | Missing data was imputed with appropriate analysis ITT and reasons for loss of follow up were reported |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping. |

### Sclar 1991

|  |  |
| --- | --- |
| Methods | Parallel, study duration six months, follow up at six months |
| Participants | 344 previously treated and 109 newly diagnosed hypertensive participants, mean age 57 years. Setting: hospital outpatients, USA |
| Interventions | Complex/ combined intervention: Prescription refill pack containing drugs and educational material vs usual supply of drugs |
| Outcomes | Pill count: 34% (newly diagnosed) and 41% (established hypertensives) higher medication possession rates in the intervention groups compared to controls (P <0.05 for both groups). Reduction in blood pressure not reported. |
| Notes | No drop-outs reported despite uneven number randomised. No imbalance at baseline, funding reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No description |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Skaer 1993

|  |  |
| --- | --- |
| Methods | Factorial, study duration 12 months |
| Participants | 304 participants, previously untreated for mild to moderate hypertension, mean age 56 years, 46% women. Setting: pharmacy, USA |
| Interventions | Behavioural interventions to support (reminder) postal reminder: special unit dose reminder packaging and both combined vs usual care(not defined) |
| Outcomes | Prescription record: Increases in the 'medication possession ratio' of 8% (postal reminder), 11% (unit dose packaging) and 23% (both combined ) compared to usual care (P < 0.05 for all interventions) |
| Notes | Potential sources of bias not fully reported. Source of funding reported. No baseline imbalance between groups. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Random table |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Blinding ensured |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. Also no bias related to early stopping |

### Solomon 1998

|  |  |
| --- | --- |
| Methods | Parallel, six months follow up |
| Participants | 133 participants with treated hypertension, 64 % Caucasian, 28 % black, mean age 67 years. Setting: 10 departments of Veterans Affairs medical centres and one academic medical centre, USA |
| Interventions | Complex/combined intervention: patient-centred pharmaceutical care model by pharmacy residents vs usual care(well defined) |
| Outcomes | Pill count and self report: better compliance scores in intervention group (0.23) compared to controls (0.61, P < 0.05). Net blood pressure reduction 6.9 mm Hg systolic (P < 0.05) and minus 0.6 mm Hg diastolic (not statistically significant) |
| Notes | Only results from self-report of adherence reported. Likelihood of bias. No baseline imbalance between groups, ethics reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Open label |
| Blinding (performance bias and detection bias) Data analysts |  | Open label |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Sookaneknun 2004

|  |  |
| --- | --- |
| Methods | Randomised pre test, post test controlled study. 6 month study duration and follow up. Power calculation done the expected number to be recruited was 124/ group |
| Participants | 235 patients with controlled and uncontrolled BP. No significant difference between groups in demographics variables, men was 75 from 235, mean of age was 63.2 years. Setting: Two primary care unit and university community pharmacy in Thia. |
| Interventions | Complex/combined intervention: Pharmacists involvement in patient's care:pharmacists in the consultation interview discussed issues about hypertension and antihypertensive drugs related problems and they resolved and try to prevent it (e.g., assessed the patient's understanding of medication, counselled on  the use of their medication, assessed adherence and lifestyle habits, reviewed for adverse events) vs usual care. |
| Outcomes | Pill count and interview:  -The treatment group showed better adherence (P = 0.014) than control group at post test 70patients in treatment group and 60 patients in control considered adherent.  - Treatment group had significant reduction in both SBP and DBP than CG (P =0.037, 0.027, respectively) |
| Notes | Ethical approval, and source of fund were reported |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient information |
| Allocation concealment (selection bias) |  | In sufficient description details |
| Blinding (performance bias and detection bias) outcome assessors |  | In sufficient description details |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Missing data have been imputed with appropriate analysis ITT |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping. |

### Vivian 2002

|  |  |
| --- | --- |
| Methods | A prospective Parallel RCT, with 6 month duration and follow up. |
| Participants | 56 patients with essential hypertension, mean age was 64.75 years, all of them were male, 26% of control group were smokers, 41 of 53 patients were African American. Setting: Veterans Affairs Medical Centre in Philadelphia, Pennsylvania USA |
| Interventions | Complex/combined intervention: Pharmacists managed care intervention:Pharmacists monthly meet with patients to made appropriate changes on drugs, modify dosages, and provide drug counselling vs CG who received their usual standard care from their physicians.(not defined well) |
| Outcomes | Self report and pharmacy drug refill:  - 81% in INT group attained their BP goal of below 140/90mmHg, compared to 30% in CG (P <0.0001)  - No significant difference in compliance reported between(P > 0.25) or within (P > 0.07) the two groups at baseline or end of study.  - Mean changes in SBP from baseline for the intervention and control groups were -18.4 (95%CI-26.3,-10.5) and - 3.98 (95%CI-11.8,3.79) respectively (P = 0.01). the mean change in DBP -12.38(95%CI -16.49,-8.28)) and 2.54(95%CI, -149, 6.57) respectively with P = 0.001) |
| Notes | Non-compliance was defined as missing >3 doses of drug in 1 week, or having pharmacy records indicate failure to refill drugs within 2 weeks after the scheduled refill date.Ethical approval was reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | No blinding insured |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details but reasons for loss of follow up were reported |
| Selective reporting (reporting bias) |  | No description |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping. |

### Webb 1980

|  |  |
| --- | --- |
| Methods | Parallel three arm, study duration three months, follow up at 18 months |
| Participants | 123 participants with treated hypertension, black, 79% women, mean age 55 years. Setting: primary care, USA |
| Interventions | Patient education and intervention to change behaviour: Three groups: education or counselling vs usual care well defined. |
| Outcomes | Pill count: Differences in adherence scores minus 0.2 for education and plus 0.2 for counselling (P > 0.10). Net reduction in DBP 3.3 mm Hg for education and 2.3 mm Hg for counselling (P > 0.1, respectively). |
| Notes | Unclear on which outcome and treatment difference the power calculation was based on, unequal numbers due to drop-outs after randomisation but before start of intervention (no reasons given). Ethics reported, similar no imbalance |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Insufficient details |
| Allocation concealment (selection bias) |  | No description |
| Blinding (performance bias and detection bias) outcome assessors |  | Insufficient details |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

### Wetzels 2007

|  |  |
| --- | --- |
| Methods | RCT, 5 months duration follow up at 2 and 5 months, power calculation done; they number expected to be recruited164 in electronic 89 in usual care. |
| Participants | 258 hypertensive patients (90 in control, 168 in experimental) with uncontrolled BP. No significant difference between groups at baseline variables; 75 patients had age 56-65 years, 108 patients were male, 65 patients had middle education141 patients were unemployed, 153 patients were married. 21% were smokers. Setting: 43 family physicians, community, Netherlands |
| Interventions | Intervention to support behaviour (reminder): using MEMS, vs usual care with adjustment of drugs. |
| Outcomes | MEMS,  - At 5months, 50.6% of the patients in usual care group reached adequate BP control vs 53.7% in electronic monitoring group P =.73  - BP had not normalized but substantially decreased in 11.2%  vs 16.5%   of patients and average BP reduction was similar (10mmHg in SBP and 15mm Hg in DBP in both group.  -Adherence in MEMS group average 95.3%+\_10%, the adherence in control group (77 patients) for MEMS was 81 patients at baseline. No P value reported. |
| Notes | Source of fund, and ethical approval were reported. |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computer generated |
| Allocation concealment (selection bias) |  | Central allocation |
| Blinding (performance bias and detection bias) outcome assessors |  | In sufficient details |
| Blinding (performance bias and detection bias) Data analysts |  | No description |
| Incomplete outcome data (attrition bias) |  | They used appropriate analysis to deal with missing data ITT but the table didn't show that. reasons for loss of follow up were reported |
| Selective reporting (reporting bias) |  | No protocol |
| Other bias |  | No bias related to particular trial designs (e.g. carry-over in cross-over trials and recruitment bias in cluster -randomised trials) or related to early stopping . |

### Zarnke 1997

|  |  |
| --- | --- |
| Methods | Parallel, study duration eight weeks, follow-up at eight weeks |
| Participants | 31 participants with treated and controlled hypertension, 65% women, mean age 54 years. Setting: primary care and hospital outpatients, USA |
| Interventions | Intervention to support behaviour: Home blood pressure monitoring and self-measurement of blood pressure vs usual care (well defined) |
| Outcomes | Not clearly defined (pill count probably): 0.3 doses missed per subject per week in the intervention group compared to 0.4 in the control group (not statistically significant, no exact P-value reported). Net reduction in mean arterial blood pressure 2.9 mmHg (P = 0.039). |
| Notes | No power calculation but primary and secondary hypotheses stated. Funding and ethics were reported. Imbalance in term of mean BP at baseline |

#### Risk of bias table



|  |  |  |
| --- | --- | --- |
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) |  | Computer generated |
| Allocation concealment (selection bias) |  | Allocation concealed |
| Blinding (performance bias and detection bias) outcome assessors |  | Not reported |
| Blinding (performance bias and detection bias) Data analysts |  | Non blinding ensured |
| Incomplete outcome data (attrition bias) |  | Insufficient details |
| Selective reporting (reporting bias) |  | No description or protocol |
| Other bias |  | No bias related particular design as cross over and cluster randomised. also no bias related to early stopping |

## Characteristics of excluded studies



### 



|  |
| --- |
| Aramwit 2003 |
| |  |  | | --- | --- | | Reason for exclusion | Not RCT design |  Artinian 2001 |
| |  |  | | --- | --- | | Reason for exclusion | Not RCT design |  Binstock 1988 |
| |  |  | | --- | --- | | Reason for exclusion | No usual care control group |  Bobrie 2007 |
| |  |  | | --- | --- | | Reason for exclusion | Not RCT design |  Brunenberg 2007 |
| |  |  | | --- | --- | | Reason for exclusion | No adherence outcome |  Casebeer 1995 |
| |  |  | | --- | --- | | Reason for exclusion | Publication is a report of a study design only, not a study report. The study itself has to our knowledge not been published yet. |  Conen 2009 |
| |  |  | | --- | --- | | Reason for exclusion | No adherence outcome |  Cote 2003 |
| |  |  | | --- | --- | | Reason for exclusion | Not RCT design |  Deinzer 2006 |
| |  |  | | --- | --- | | Reason for exclusion | No adherence outcome |  Dejesus 2009 |
| |  |  | | --- | --- | | Reason for exclusion | Not directed to patients with hypertension |  Dennison 2007 |
| |  |  | | --- | --- | | Reason for exclusion | Intervention not directed at adherence |  Eisen 1990 |
| |  |  | | --- | --- | | Reason for exclusion | No contemporary control group |  Figar 2004 |
| |  |  | | --- | --- | | Reason for exclusion | No adherence outcome |  Figar 2006 |
| |  |  | | --- | --- | | Reason for exclusion | No adherence outcome |  Goldstein 2005 |
| |  |  | | --- | --- | | Reason for exclusion | Intervention not directed at adherence |  Gonzalez-Fern. 1990 |
| |  |  | | --- | --- | | Reason for exclusion | Hospital setting |  Guerra-Riccio 2004 |
| |  |  | | --- | --- | | Reason for exclusion | No adherence outcome |  Hagstrom 2004 |
| |  |  | | --- | --- | | Reason for exclusion | Not targeted hypertension groups of patients |  Halme 2005 |
| |  |  | | --- | --- | | Reason for exclusion | No adherence outcome |  Hayen 2010 |
| |  |  | | --- | --- | | Reason for exclusion | Not directed to adherence |  Koylan 2005 |
| |  |  | | --- | --- | | Reason for exclusion | Not RCT design |  Lee 2006 |
| |  |  | | --- | --- | | Reason for exclusion | Not Hypertension group of patients |  Marquez Contreras 2009 |
| |  |  | | --- | --- | | Reason for exclusion | No English copy |  Masso 2005 |
| |  |  | | --- | --- | | Reason for exclusion | Not RCT |  McKinstry 2006 |
| |  |  | | --- | --- | | Reason for exclusion | No adherence outcome |  McManus 2009 |
| |  |  | | --- | --- | | Reason for exclusion | No adherence outcome |  Morales Suarez-Var 2009 |
| |  |  | | --- | --- | | Reason for exclusion | Not directed to hypertensive patients |  Mori 2010 |
| |  |  | | --- | --- | | Reason for exclusion | Not RCT |  Morisky 2002 |
| |  |  | | --- | --- | | Reason for exclusion | Intervention not directed at adherence |  Park 2005 |
| |  |  | | --- | --- | | Reason for exclusion | Intervention not directed at adherence |  Powers 1982 |
| |  |  | | --- | --- | | Reason for exclusion | Unable to interpret results |  Qureshi 2007 |
| |  |  | | --- | --- | | Reason for exclusion | Intervention not directed to the patients |  Strogatz 1983 |
| |  |  | | --- | --- | | Reason for exclusion | No adherence outcome |  Takala 1979 |
| |  |  | | --- | --- | | Reason for exclusion | No adherence outcome |  Theunissen 2003 |
| |  |  | | --- | --- | | Reason for exclusion | It does not has intervention to enhance adherence |  Torres 2010 |
| |  |  | | --- | --- | | Reason for exclusion | No English copy |  Wizner 2009 |
| |  |  | | --- | --- | | Reason for exclusion | No English copy |  Zismer 1982 |
| |  |  | | --- | --- | | Reason for exclusion | No adherence outcome | |

## Characteristics of studies awaiting classification



### Gomez-Marcos 2006

|  |  |
| --- | --- |
| Methods | Experimental design |
| Participants | 838 hypertensive patients |
| Interventions | Received quality improvement intervention which consists of combined program comprising audit, feedback. Training sessions about hypertension. versus control group |
| Outcomes | Intervention group SBP/ DBP decreased 8.16/3.71mmhg. adherence also increased with P < 0.05 |
| Notes | No English version |

### Marquez-Contreras 2004

|  |  |
| --- | --- |
| Methods | Comparative controlled multicenter randomised cluster study. 6months duration. follow up at 1, 3, 6 months |
| Participants | 104 hypertensive patients. receiving mono-therapy for uncontrolled BP. 26 primary centres in Spain |
| Interventions | Intervention patients received messages and reminders to their mobile phones 2 day per week during 4 months versus control group who received their usual care. |
| Outcomes | Pills count,  The compliance rate was 85.1% in control group versus 85.75 in intervention group with mean compliance 90.2% |
| Notes | No English version |

### Marquez-Contreras 2009

|  |  |
| --- | --- |
| Methods | RCT |
| Participants | 450 uncontrolled hypertensive patients, age 62.4 years, |
| Interventions | Received twice educational magazine at home. versus control group |
| Outcomes | MEMS  The overall compliers in intervention was 83.2% versus 49.25 in control group with P =0.0001). correct time compliers was for INT 745 versus 42.6% in CG p=0.0001)  BP controlled was 81.6% versus 56.3% in CG. |
| Notes | No English version |

## Characteristics of ongoing studies



### Bennett 2009

|  |  |
| --- | --- |
| Study name | The effectiveness of health coaching, home blood pressure monitoring, and home-titration in controlling hypertension among low-income patients: protocol for a randomised controlled trial |
| Methods | RCT, 12months duration, follow up at 6 and 12 months |
| Participants | 300 Hypertensive patients with poorly controlled hypertension, low income in primary care clinic, California and San Francisco, USA |
| Interventions | Health education;  Providing health coaching via telephone about home BP monitoring, medication adherence and understanding, assistance with home titration of hypertension drugs. versus CG who received same calls but without assistance in titration of their hypertension drugs |
| Outcomes | SBP, DBP, Side effects, patient and provider satisfaction |
| Starting date | 2009 |
| Contact information | Heather Bennett. heather.bennet@ucsf.edu |
| Notes | No clear adherence outcome, still the results not published just the protocol. |

### Dolor 2009

|  |  |
| --- | --- |
| Study name | Hypertension Improvement Project (HIP): study protocol and implementation challenges, power calculation done; they expected to be recruited 340 patients. |
| Methods | Nested 2\*2RCT. duration 18 months, follow up at 6 and 18 months |
| Participants | 574 hypertensive patients. Mean age 60.5yrs, 61% were female, 93% with high school, 85% had adequate income, 37% were African American, 48% were not smokers. Setting: 8 primary care practice in DUKE, USA |
| Interventions | Behavioral intervention over 6months by trained interventionists, followed by 12 month home advisors phone contacts. versus control group who received a brief advice and brochures on lifestyle modification for control of BP by interventionists. |
| Outcomes | SBP, DBP, BP control. behavioural change  self report questionnaires. |
| Starting date |  |
| Contact information | Dolor: rawena.dolor@duke.edu |
| Notes |  |

### Haafkens 2009

|  |  |
| --- | --- |
| Study name | A cluster-randomised controlled trial evaluating the effect culturally-appropriate hypertension education among Afro-Surinames and Ghanian patients in Dutuch general practice: study protocol |
| Methods | A cluster RCT, |
| Participants | 152 patients; 76 in control group and 76 in intervention group. 4 primary care practice in Amesterdam, Netherlands |
| Interventions | Usual care received standard hypertension eduction. Intervention patients will received three culturally appropriate hypertension education, with materials to target life style support. |
| Outcomes | SBP, Adherence  self reported questionnaire |
| Starting date |  |
| Contact information | Joke A Haafkens: j.a.haafkens@amc.uva.nl |
| Notes |  |

### Lau 2010

|  |  |
| --- | --- |
| Study name | Evaluation of a community pharmacy-based intervention for improving patient adherence to anti-hypertensives: a randomised controlled trial |
| Methods | Multicentre prospective RCT |
| Participants | 56 pharmacies and 182 hypertensive patients for each group. in Australia |
| Interventions | Usual care group; pharmacist provided routine care versus pharmacist care group: the patient provided care from pharmacist who received training about the study and about the drug adherence enhancing. |
| Outcomes | BP, adherence/ self report questionnaire |
| Starting date |  |
| Contact information | Johnson.greorge@pharm.monash.edu.au |
| Notes |  |



Appendix 3, Authors permission to use and translate the research instruments

**A. BMQ Permission**From: Rob Horne [mailto:[rob.horne@pharmacy.ac.uk](mailto:rob.horne@pharmacy.ac.uk)]  
Sent: Friday, January 09, 2009 2:44 PM  
To: Gray Richard Prof (NAM)  
Cc: 'amy whitehead'  
Subject: RE: BMQ  
  
Hi Richard  
Thanks for your interest in the BMQ. Happy for you to use according to our standard conditions attached, which are designed to protect the integrity and IPR of the questionnaire. Please sign and return and then permission is automatic.  
  
I've also added information about the questionnaire. It's a bit complex and there are issues about whether you use the Specific, General or combined specific and general module.   
  
Hope this is OK for now  
BW  
Rob

**B. MMAS Permission**

**From:** Donald E. Morisky <dmorisky@ucla.edu>  
**To:** Fadwa halaiqa <fadwa\_halaiqa@yahoo.com>  
**Sent:** Thursday, June 11, 2009 15:27:03  
**Subject:** Re: Morisky scale  
  
Thank your Fadwa for your note re the use of the Morisky Medication Adherence Scale (MMAS).   We now have two versions of this scale, the previous MMAS-4 which is a simpler 4-item scale, mainly for use in the health care system, encouraging provider and patient interaction, assessment and consultation/reinforcement of positive adherence behaviors.  The new scale is the MMAS-8 which is mainly for research purposes, has a higher reliability (internal consistency) and equal concurrent and predictive validity.  I will send you the publication of each of these studies.  I will give you permission to use the scale in your doctoral, post graduate studies at the University of East Anglia, Norwich, UK, under the supervision of Professor Richard Gray.  I will waive any licensure fee for this copyrighted intellectual property, and only request that you adhere to the standard procedures in translating the scale (forward and backward translation by two independent linguistic experts), cite our work for all references to the MMAS and send me a report of your results.     
  
Please let me know which scale you prefer to use....  
  
Best wishes,  
  
Dmorisky

***Donald E. Morisky, Sc.D., M.S.P.H., Sc.M.   
Professor and Program Director, Predoctoral Training in the Social and Behavioural Determinants of HIV/AIDS Prevention  
Department of Community Health Sciences  
UCLA School of Public Health  
650 Charles E. Young Drive South  
Box 951772  
26-070 CHS  
Los Angeles, CA 90095-1772***

**Appendix 4, Adherence therapy manual (English version)**

http://eastanglia.academia.edu/RichardGray/Books/718181/Adherence\_therapy\_manual**Appendix 5, Invitation letter**

Dear participant

I am pleased to invite you to take a part in a study called “Adherence Therapy for People with Hypertension: A Randomised Controlled Trial”. That will be conducted over eleven weeks.

If you participate in the study you will be in one of two groups. One group will get their normal care and an additional brief adherence intervention; the other (control) group will receive just their normal care. Your blood pressure will be measured and the number of pills you take correctly will be measured by pills counting. Additionally your beliefs and attitudes about medications will be measured by questionnaire. Some of you may be asked to give your views about therapy at an interview with the researcher. All data will be used only for the purpose of study. Your privacy and confidentiality will be maintained.

Before you decide, please take time to read the patient information sheet. For further information you can directly contact the study researcher. It is entirely up to you to decide whether or not to take a part. If you do decide to take part, you will be asked to sign an informed consent form. You will be free to withdraw at any point without explaining any reason, after deciding to take a part. Your participation or non-participation will have no effect on services that you or any member of your family may receive from the health care providers.

**Sincerely**

**Researcher:** Fadwa N Alhalaiqa

PhD student, University of East Anglia

Telephone No 0096279735142 Email: [F.AL-Halaiqa@uea.ac.UK](mailto:F.AL-Halaiqa@uea.ac.UK)

Appendix 6, Information sheet

**Title of the project:** Adherence Therapy for People with Hypertension: A Randomised Controlled Trial

**Researcher**: Fadwa N Alhalaiqa

**Introduction:**

You are being invited to participate in a research study, before you decide you need to understand why this study is being done and what it would involve for you.

Please take time to read the following information carefully and if there is anything that is not clear or you would like further information please contact the researcher using the details provided below. Take your time to decide whither or not you wish to take part. If you agree to participate please complete the reply slip paper and send it back in the free post envelope provided.

**Why are we doing this research?**

The aim of this study is to evaluate the efficacy of adherence therapy AT (a 20 minutes consultation session by trained clinician over a series of seven weeks, talking about your drugs concerns) in a sample of people with hypertension in Jordan.

**Why have I been invited to take part?**

You have been invited to join our study because you have uncontrolled hypertension and your doctor has prescribed antihypertension medication for you. This project will involve 136 hypertensive patients taking medication.

**Do I have to take part?**

No. It is up to you. If you do, the researcher will ask you to sign a form giving your consent. You will be given a copy of this information sheet and your signed form to keep. You are free to stop taking part at any time during the research without giving a reason. If you decide to stop, this will not affect the care you receive.

**What will happen to me if I take part?**

If you take a part in this study, you will be put into groups and then compared. All patients have an equal chance to be either in the control (treatment as usual) or experimental group (AT). The assignment of patients for each group will be done by an independent clinical trials unit. Groups’ allocation is done by a computer which has no information about the individual. Patients in the control group will receive treatments as usual, which consists of medication, blood pressure measurements, laboratory investigation and other care depending on individual needs. In addition to treatments as usual, patients in the experimental group will get adherence therapy; seven sessions with a specially trained nurse to talk about your anti hypertension medication. Each weekly session will last around 20 minutes. Some of these sessions will be audio taped.

All patients (in both groups) will have their blood pressure measured by a qualified nurse who blind to intervention assignment; blood pressure will be measured two times, once before starting of the study, second after seven weeks. Your beliefs and attitudes about medications will be assessed by questionnaire at the start and the end of the study. Nurse who blind to intervention assignments will also count your pills at the end of the study. Some patients who got adherence therapy will be invited to participate in an interview with the researcher to discuss issues what they thought about the therapy. These interviews will happen after 11 weeks from the start of the study and will involve a separate visit to the clinic. They will last up to 30 minutes and be audio taped.

The data and computer files from the audio recorded therapy sessions and interviews will be kept securely in locked storage by the researcher for 20yrs. Patients will be expected to cover their own costs of transportation to the clinic; no additional funds are available to cover patient’s expenses.

**What are the possible risks if I take part in the research?**

We for see no additional risks for you if you take a part in the study

**Who can I complain to?**

In case you have a complaints or concern on your treatment by a member of staff or anything to do with the study, you should ask to speak to the researcher who will do their best to answer your questions (contact NO 00962797351342). If you remain unhappy and wish to complain formally, you can do this through ministry of health in Jordan compliant procedure and details can be obtained from the hospital.

**What are the possible benefits of taking part?**

We can not promise, but the information you get might help to enhance your adherence to antihypertension medication, control your blood pressure and enhance your beliefs and attitude towered your medication. The result for this study will help other hypertension patients to be stick to their medication.

**Will my taking part in this study be kept confidential?**

If you consent to take a part in the research you are free to express your idea regarding antihypertension medications. Your answer will not identify you in any way. All personal data will be kept in separate files from the remaining research data. The research data will be anonymised and only the researcher will hold the key to the codes. The researcher will not disclose identifiable information to anybody without your consent.

**Who is organizing and funding the research?**

No financial help will be provided for the patients to participate in this study.

**Who has reviewed the study?**

Before any research goes ahead it has to be checked by a Research Ethics Committee. They make sure that the research is safe and ethical. Your project has been checked by the University of East Anglia Research Ethics Committee and by ministry of health in Jordan

**Whom can I talk if I want more information?**

The researcher on the project is the person whom you can contact with all your questions, queries and with any problems that arise for you personally throughout the course of the study. We will let your care team know that you are participating in this study and therefore you can also contact them if you have any questions. If you are interested in participation please full the attached reply slip and send it through free post envelope provided.

**Thank you very much for taking your time to read this information sheet. I will contact you again to hear if you would like to participate in this project.**

**Contact details:**

**Fadwa Alhalaiqa**

**Email:** [F.AL-halaiqa@uea.ac.uk](mailto:F.AL-halaiqa@uea.ac.uk)

**Telephone ……………**

**Reply slip**

**Name of participant**: ……………………………………………………………………

**Contact details**:

Home address: …………………………………………………………………………….

Phone Number: ……………………………………………………………………………

E-mail address: ……………………………………………………………………………

**Appendix7, Consent form**

Study Number:

Patient Identification Number for this trial:

Title: Adherence Therapy for People with Hypertension: A Randomised Controlled Trial

Name of Researcher: Fadwa Naji Alhalaiqa please initial box

|  |  |  |
| --- | --- | --- |
| 1. | I confirm that I have been given a full explanation by the researcher, Fadwa Alhalaiqa and that I have read and understand the information sheet given to me which is attached, I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. |  |
| 2. | I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, and without my medical care or legal rights being affected. |  |
| 3. | I understand that the researcher wills maintain my confidentiality and privacy throughout the research process. Any comments that I make and are used in the research publications will not identify me in any way. All personal data will be kept in separate files from the remaining research data. The research data will be anonymised and only the researcher will hold the key to the codes. |  |
| 4. | The researcher will not disclose my information to anybody without my consent. |  |
| 5. | I agree to my doctor and the hospital team managing my hypertension being informed of my participation in the study. |  |
| 6. | I may be asked to participate in an interview regarding the intervention. I agree to this interview being audio taped and I understand the researcher will keep all computerized files 20 yrs in locked storage to maintain my confidentiality. |  |
| 7. | I will be allocated randomly to be in the control or experimental group, and I agree to this. |  |

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Patient Date Signature

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Name of Person Date Signature

Appendix 8 Demographical data form

Rater name………………………………………Date……………………………….

Clinic ……………………………………………

1. Age…………..years old
2. Gender
3. Male
4. Female
5. Nationality
6. Jordanian
7. Palestinian
8. Others Specify…………….
9. Level of education
10. Elementary school
11. High school
12. College
13. University/postgraduates studies
14. Living in Home situation
15. Alone
16. Spouse
17. Children
18. Others Specify …………….
19. Marital status
20. Married
21. Single
22. Widowed
23. Others Specify ……………..
24. Income/Month:
25. less than 200JD
26. 201-400JD
27. Above 400JD
28. Health Insurance:
29. Ministry of Health
30. Military Services
31. Private Insurance
32. Others Specify ……………..
33. Habitual life style:
34. Smoking

1-Yes Cigarettes /day……….

2-No

1. Exercise

1-Yes Specify……………………………

2-No

c- Dietary restriction

1-Yes Specify ………………………...

2-No

1. Occupation

1-Yes Specify …………………..

2-No

3-Retired

1. Current Anti-hypertension Medication Prescribed

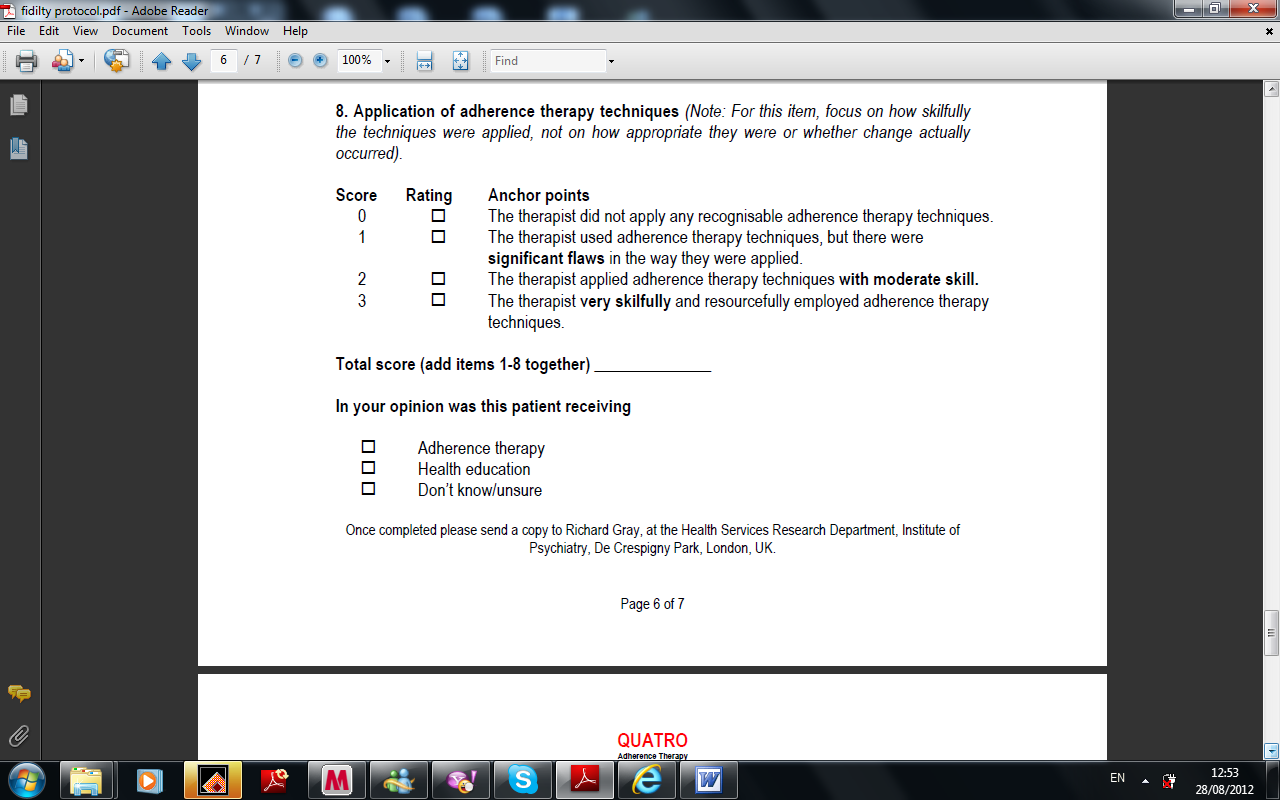
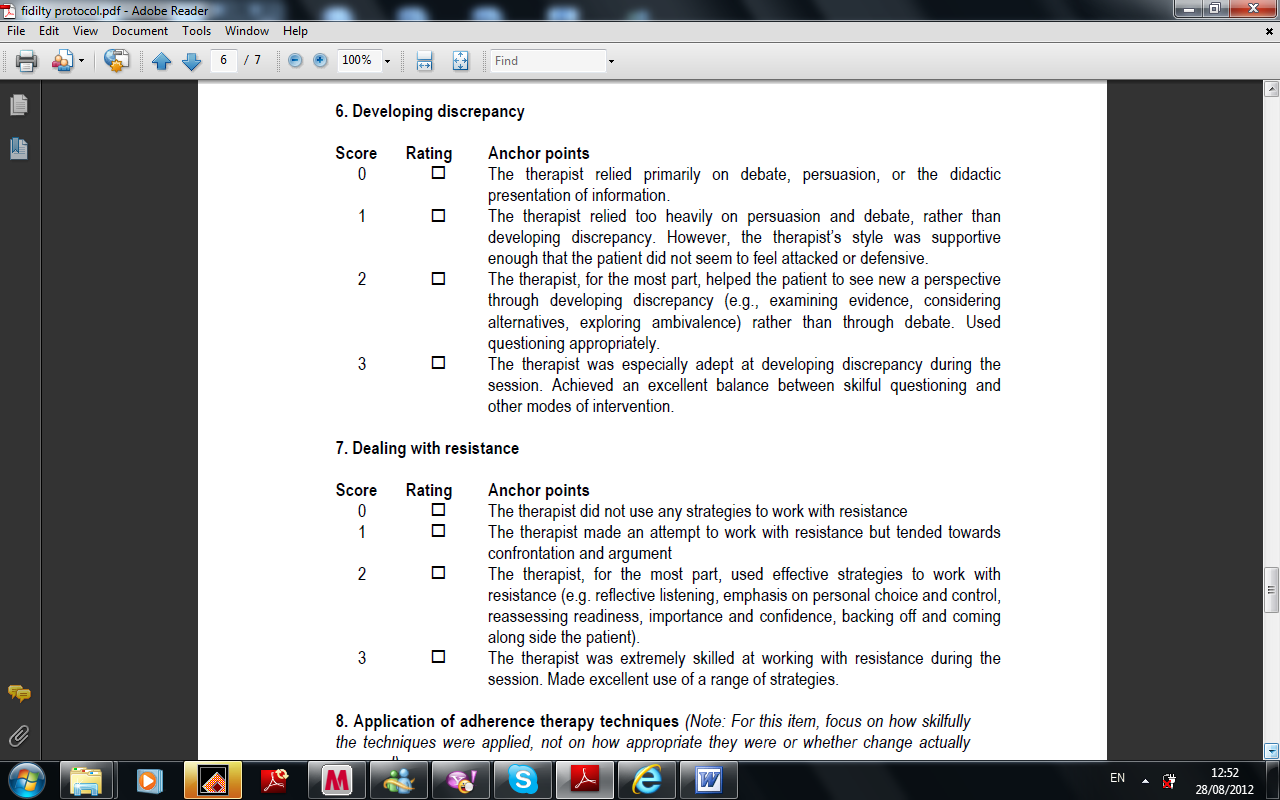
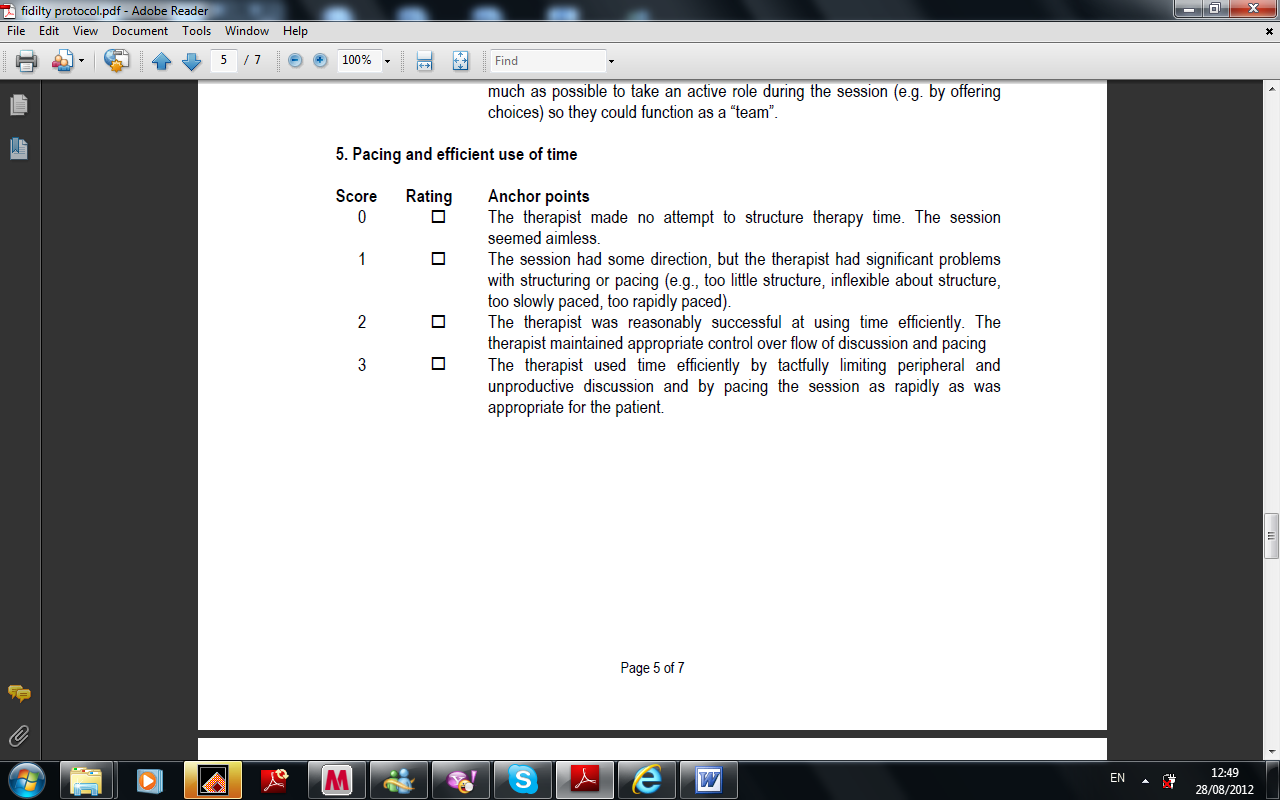
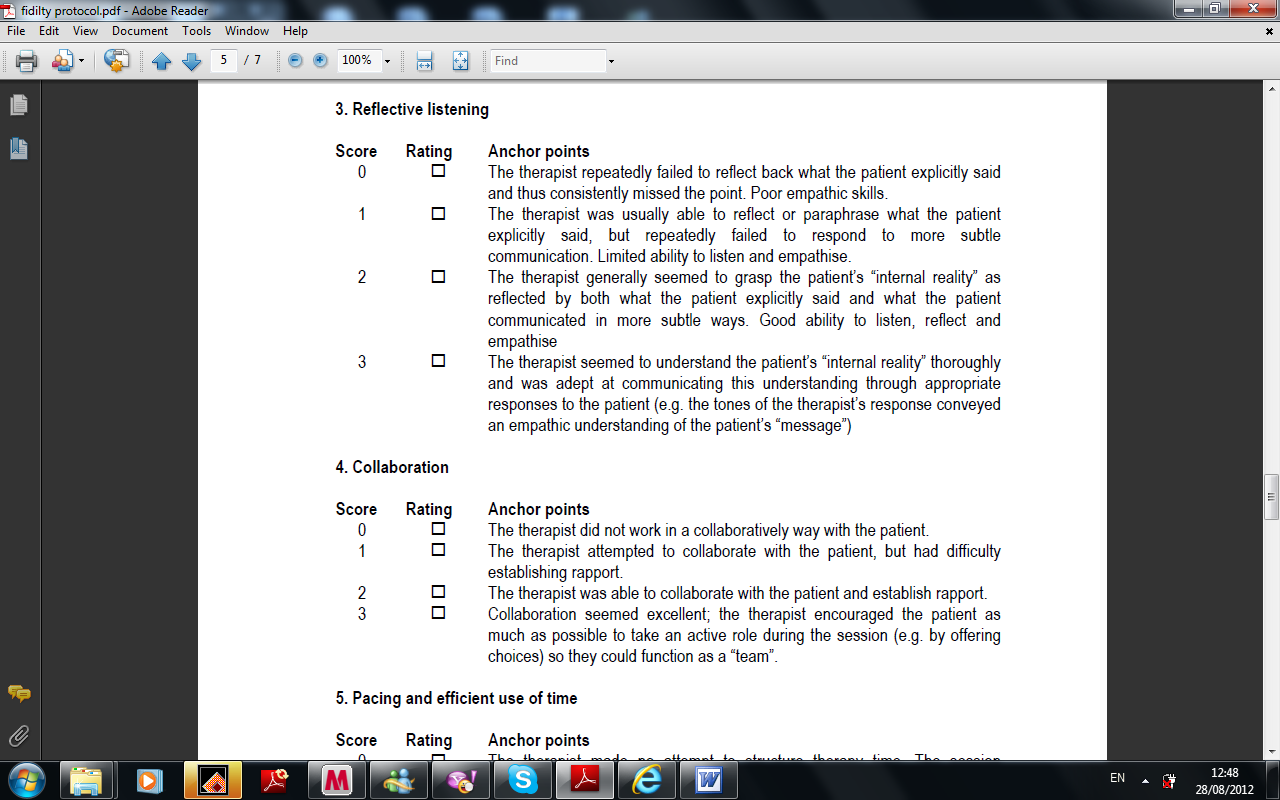
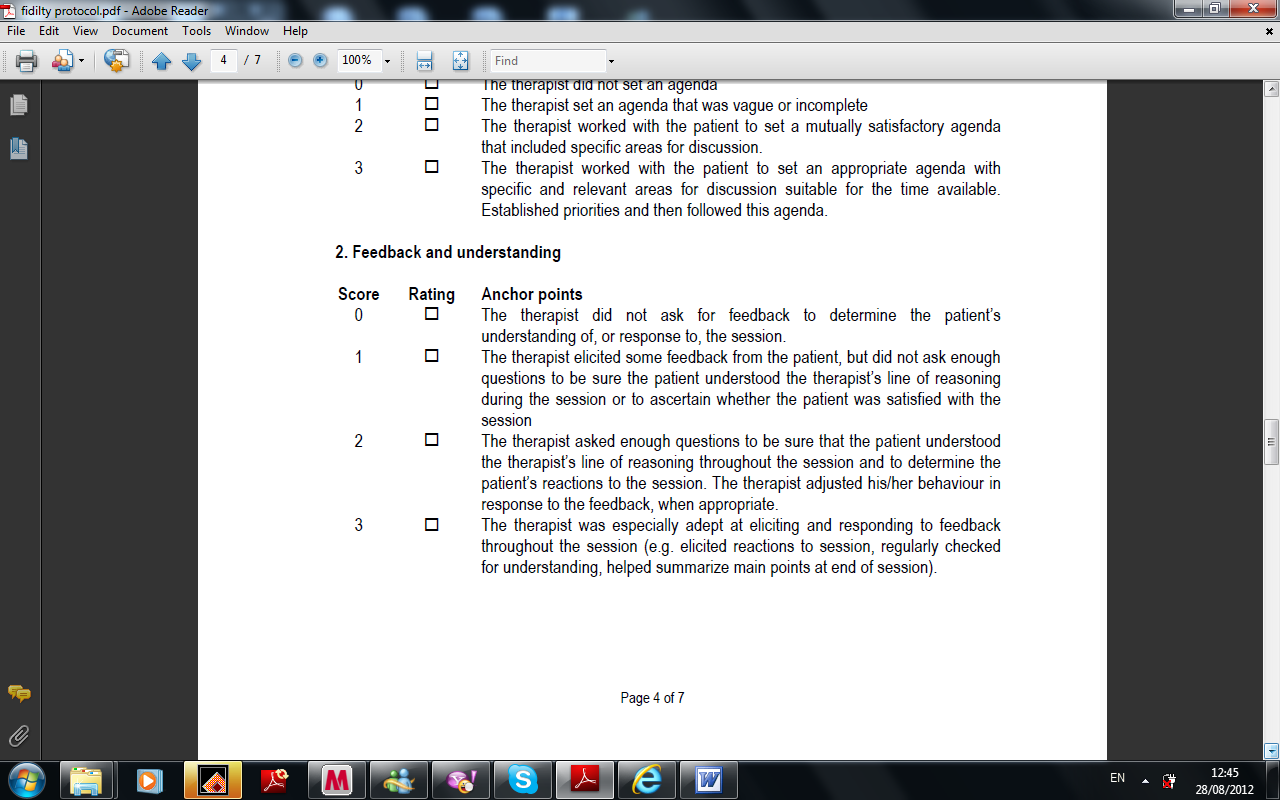
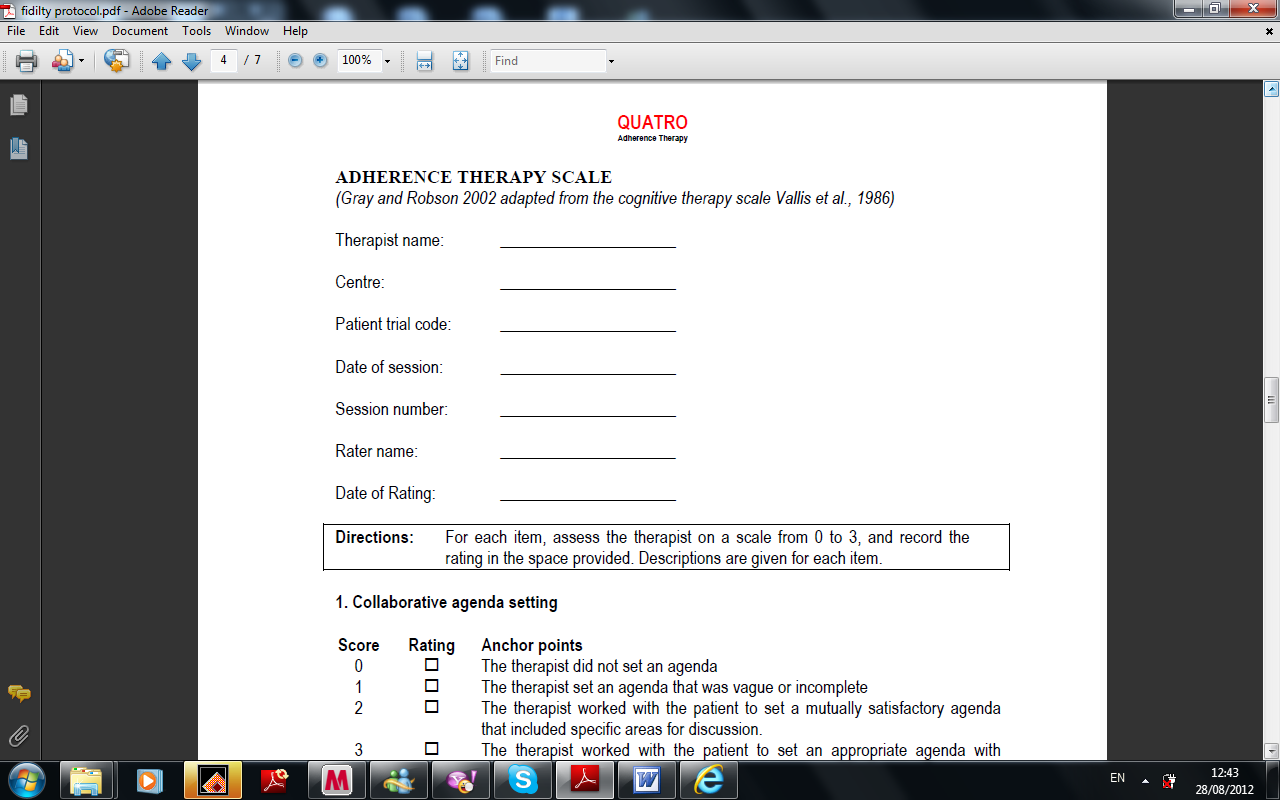
Drug name Dose

…………………………………………………………………………………………

…………………………………………………………………………………………

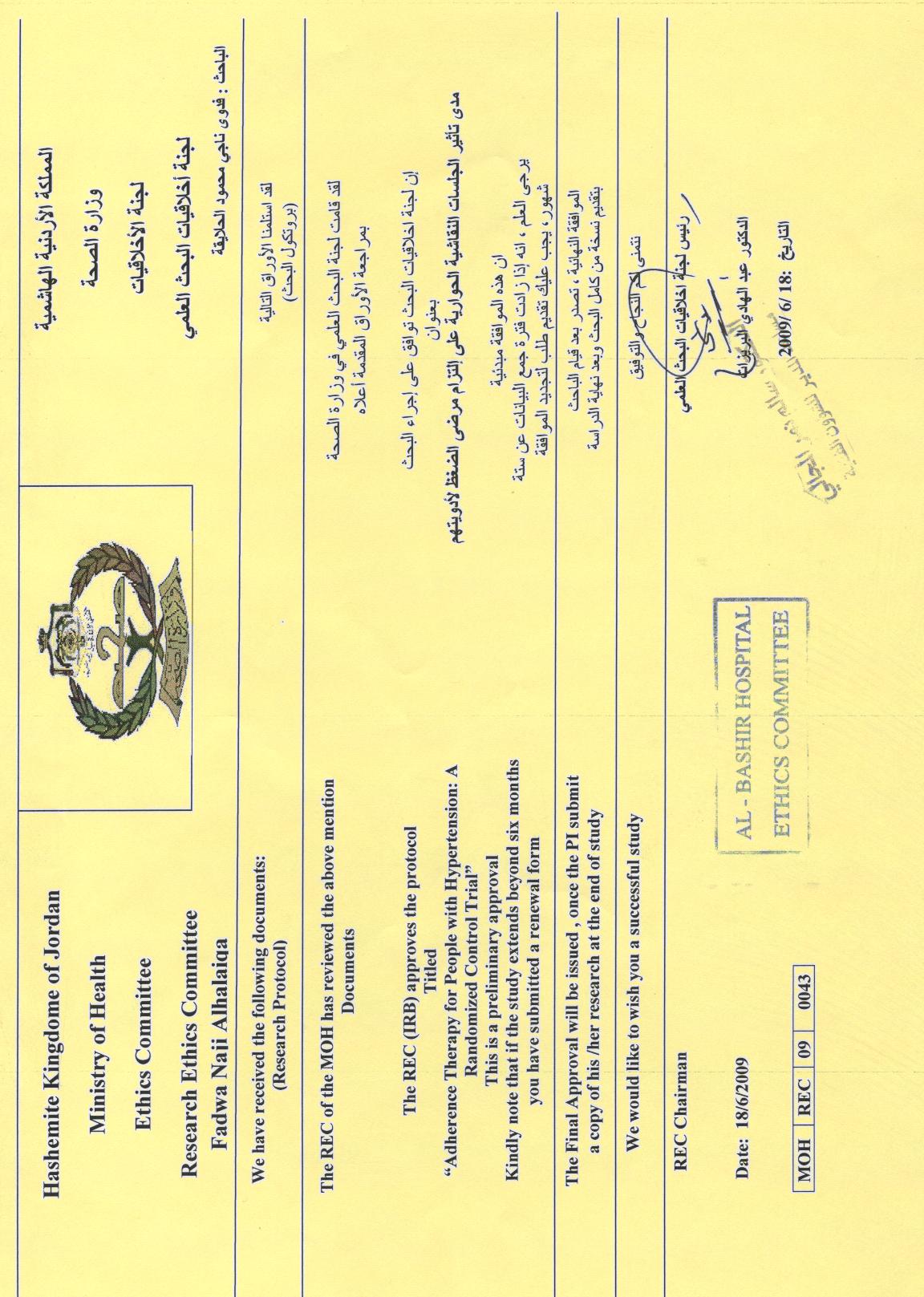
…………………………………………………………………………………………

**Appendix9 Treatment fidelity**



**Appendix 10, Ethical approval**

**a) Ministry of health Jordan**



**b) Ethical approval from University of East Anglia,**

|  |  |  |
| --- | --- | --- |
| Fadwa Al.Halaiqa |  | Research Office, Room 1.09  Chancellors Drive Annex  University of East Anglia  Norwich NR4 7TJ  United Kingdom  Email:[Jane.Carter@uea.ac.uk](mailto:Jane.Carter@uea.ac.uk)  Tel: +44 (0) 1603 591023  Fax: +44 (0) 1603 591132  Web:www.uea.ac.uk  Web: <http://www.uea.ac.uk> |
| 14 November 2018 |

Dear Fadwa,

Reference No: 2009034

Thank you for sending in your application documents. The Ethics chair has seen the approval letter from Jordan and as a result of this we are happy to accept this as ethical approval.

Yours sincerely,



Dr. Jane Carter

+44 (0) 1603 591023

Jane.Carter@uea.ac.uk

Appendix 11, Semi -structured interview questions to explore patient experience with adherence therapy

1. Describe what you thought about the adherence therapy?
2. How could the therapist’s communication affect on your uptake and satisfaction of the intervention?
3. Discuss the effect of session’s environment on your acceptance?
4. What are your expectations from the AT?
5. Is AT met your health expectations? How?
6. Did AT make it more or less likely you would take your medication? How?
7. Did you feel you got benefit from talking with the therapist about medication? How?
8. Which intervention you feel you got more benefit from it: problem solving, looking back, exploring ambivalence, looking forward, or talking about beliefs? How?
9. Discuss your recommendation that could be used to enhance patient adherence and satisfaction with adherence therapy?
10. What is your thought about time of AT in term of seven and weekly sessions is there a need to be less or more?

**Appendix 12, Journal of Human Hypertension**

See the following website:

http://www.nature.com/jhh/journal/vaop/ncurrent/full/jhh2010133a.html