



**Medication adherence in resistant hypertension:
An investigation of prevalence, psychological predictors
and patient perspectives**

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Declaration

I declare that this thesis has not been submitted as an exercise at this or any other University. I declare that this thesis is entirely my own work.

Signed: _____

Hannah Durand

Statement of Contribution

This thesis includes collaborative studies involving multiple authors. The candidate was responsible for the design, data collection, analysis and write-up of each of the three studies conducted and described within this thesis. The supervisory team, project team, Graduate Research Committee, and an expert advisory group advised and provided support in conducting the research. The specific contributions of each co-author on each published paper are described below.

The research project described within this thesis was carried out as part of a broader study examining patients with apparent-treatment resistant hypertension in general practice, led by Professor Andrew Murphy, Discipline of General Practice, National University of Ireland, Galway, and funded by the Health Research Board Patient-Oriented Research Award (Ref: HRA-POR-2014-615). This project produced two independent theses: (1) the current thesis; and (2) the thesis submitted by Dr Peter Hayes to the National University of Ireland, Galway in fulfilment of the requirements for the Degree of Doctor of Medicine.

Contributions of Co-Authors on Published Papers

Paper 1: Medication adherence among patients with apparent treatment-resistant hypertension: Systematic review and meta-analysis – Hannah Durand, Peter Hayes, Eimear C. Morrissey, John Newell, Monica Casey, Andrew W. Murphy, & Gerard J. Molloy

HD had overall responsibility for the study, including the design, study selection, data extraction, narrative and statistical analysis, and write-up of the study. PH, ECM, AWM and GJM each contributed to the screening and quality assessment of articles. PH contributed to the data extraction phase of the study. JN contributed to statistical aspects of the study. PH, MC, AWM and GJM reviewed and edited the manuscript. All authors read and approved the manuscript for publication.

Paper 2: Medication adherence for resistant hypertension: Assessing theoretical predictors of adherence using direct and indirect adherence measures – Hannah Durand, Peter Hayes, Brendan Harhen, Ann Conneely, David P. Finn, Monica Casey, Andrew W. Murphy, & Gerard J. Molloy

HD had overall responsibility for the study, including the design, statistical analysis, and write-up, and contributed to the data collection for the study. PH and MC contributed to the data collection for the study. BH, AC and DPF contributed to the biochemical analysis

and its interpretation. AWM and GJM oversaw the study. PH, MC, DPF, AWM and GJM reviewed and edited the manuscript. All authors read and approved the manuscript for publication.

Paper 3: A qualitative comparison of high and low adherers with apparent treatment-resistant hypertension – Hannah Durand, Monica Casey, Liam G. Glynn, Peter Hayes, Andrew W. Murphy, & Gerard J. Molloy

HD had overall responsibility for the study, including the design, data collection, analysis, and write-up of the study. MC contributed to the data collection for the study. MC, LGG, PH, AWM and GJM all contributed to the data analysis. AWM and GJM oversaw the study. All authors reviewed and edited the manuscript and approved the manuscript for publication.

List of Works

Below is a list of publications and conference presentations that have stemmed from work relating to this thesis.

Publications

- Durand, H.**, Casey, M., Glynn, L. G., Hayes, P., Murphy, A. W., & Molloy, G. J. (under review). A qualitative comparison of high and low adherers with apparent treatment-resistant hypertension. *Psychology, Health & Medicine*.
- Durand, H.**, Hayes, P., Harhen, B., Conneely, A., Finn, D. P., Casey, M., Murphy, A. W., & Molloy, G. J. (2018). Medication adherence for resistant hypertension: Assessing theoretical predictors of adherence using direct and indirect adherence measures. *British Journal of Health Psychology*, 23(4), 949-966. <https://doi.org/10.1111/bjhp.12332>
- Durand, H.**, Hayes, P., Morrissey, E. C., Newell, J., Casey, M., Murphy, A. W., & Molloy, G. J. (2017). Medication adherence among patients with apparent treatment-resistant hypertension: Systematic review and meta-analysis. *Journal of Hypertension*, 35(12), 2346-2357. <https://doi.org/10.1097/HJH.0000000000001502>
- Hayes, P., Casey, M., Glynn, L. G., Molloy, G. J., **Durand, H.**, O'Brien, E., . . . Murphy, A. W. (under review). Apparent treatment resistant hypertension in Irish general practice: The feasibility and impact of urine toxicological analysis combined with ambulatory blood pressure monitoring. *British Journal of General Practice*.
- Hayes, P., Casey, M., Glynn, L. G., Molloy, G. J., **Durand, H.**, O'Brien, E., . . . Murphy, A. W. (2018). Prevalence of treatment-resistant hypertension after considering pseudo-resistance and morbidity: A cross-sectional study in Irish primary care. *British Journal of General Practice*, 68(671), e394-e400. <https://doi.org/10.3399/bjgp18X696221>
- Hayes, P., Kieley, H., Casey, M., Glynn, L., Molloy, G. J., **Durand, H.**, Newell, J., & Murphy, A. W. (2018). Prognosis of patients with apparent treatment resistant hypertension – A feasibility study. *BMC Pilot and Feasibility Studies*, 4(43). <https://doi.org/10.1186/s40814-018-0232-5>
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Conference Presentations

- Durand, H.**, Casey, M., Hayes, P., Murphy, A., & Molloy, G. (2018). *Exactly what it says on the tin? A qualitative study on medication adherence for resistant hypertension in primary care*. Paper presented at the 15th International Congress of Behavioral Medicine, Santiago, Chile.
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development. Symposium conducted at the 32nd Annual Conference of the European Health Psychology Society, Galway, Ireland.

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Molloy, G. J., **Durand, H.**, Morrissey, E., Hayes, P., Casey, M., & Murphy, A. W. (2016). *Medication non-adherence and apparent-treatment resistant hypertension: A meta-analysis of prevalence*. Paper presented at the 14th International Congress of Behavioral Medicine, Melbourne, Australia.

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Durand, H., Morrissey, E., Hayes, P., Casey, M., Murphy, A., & Molloy, G. (2016). *Medication non-adherence among patients with apparent treatment-resistant hypertension: A systematic review protocol*. Poster presented at the 3rd Annual Conference of the Psychological Society of Ireland Early Graduate Group, Dublin, Ireland.

Additional Publications

Below is a list of additional publications produced by the candidate between 2015 – 2018, during the course of the PhD project.

Durand, H., Birnie, K. A., Noel, M., Vervoort, T., Goubert, L., Boerner, K. E., Chambers, C. T., & Caes, L. (2017). State versus trait: Validating state assessment of child and parental catastrophic thinking about children's acute pain. *The Journal of Pain, 18*(4), 385-395. <https://doi.org/10.1016/j.jpain.2016.11.012>

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disability regarding chronic low back pain by general practitioners in Ireland. *PloS One*, 13(3), e0194387. <https://doi.org/10.1371/journal.pone.0194387>

- Dwyer, C. P., McKenna-Plumley, P. E., **Durand, H.**, Gormley, E. M., Slattery, B. W., Harney, O. M., MacNeela, P., & McGuire, B. E. (2017). Factors influencing the application of a biopsychosocial perspective in clinical judgement of chronic pain: Interactive Management with medical students. *Pain Physician*, 20, E951-E960.
- Morrissey, E. C., **Durand, H.**, Nieuwlaat, R., Navarro, T., Haynes, R. B., Walsh, J. C., & Molloy, G. J. (2016). Effectiveness and content analysis of interventions to enhance medication adherence in hypertension: A systematic review and meta-analysis protocol. *BMC Systematic Reviews*, 5(1), 96. <https://doi.org/10.1186/s13643-016-0278-5>
- Morrissey, E. C., **Durand, H.**, Nieuwlaat, R., Navarro, T., Haynes, R. B., Walsh, J. C., & Molloy, G. J. (2017). Effectiveness and content analysis of interventions to enhance medication adherence and blood pressure control in hypertension: A systematic review and meta-analysis. *Psychology & Health*, 32(10), 1195-1232. <https://doi.org/10.1080/08870446.2016.1273356>

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Abstract

Background

Resistant hypertension is a chronic condition in which the arterial blood pressure remains persistently above goal despite concurrent treatment with three or more antihypertensive agents of different classes. It appears relatively common in clinical practice, despite the established effectiveness of antihypertensive medications. Clinical factors such as inadequate dosing of antihypertensive medications, white coat hypertension (the phenomenon in which blood pressure is higher in clinical settings versus other settings), improper blood pressure measurement, and poor adherence to antihypertensive treatment all preclude a diagnosis of resistant hypertension. Poor adherence is considered the most common cause of pseudo-resistance to treatment among patients with apparent treatment-resistant hypertension and can result in unnecessary treatment escalation and referral to specialist hypertension clinics at significant cost to the patient and the healthcare system. Despite forming a core component of the definition and diagnosis of resistant hypertension, the extent, predictors and patient perspectives of non-adherence have not been extensively examined for this group.

Aim

The aim of this research is to examine the extent, theoretical predictors, and patient perspectives of non-adherence to antihypertensive medications for apparent treatment-resistant hypertension in primary care.

Methods

This research comprised: (1) a systematic review and meta-analysis to examine the extent of medication non-adherence in the published literature, and the study-level predictors thereof; (2) a quantitative cross-sectional study to examine the extent of poor adherence among a large sample of patients with apparent treatment-resistant hypertension receiving treatment in primary care using multiple diverse adherence measures, as well as the predictive value of theoretical constructs drawn from the Common-Sense Model of Self-Regulation (i.e., treatment-favourable beliefs, coherence of beliefs resulting from experience with treatment, and medication-taking habit strength); and (3) a qualitative comparison of high and low adherers to delineate factors associated with good and poor adherence using thematic analysis.

Findings

(1) The systematic review and meta-analysis revealed that approximately one-third of patients classed as having apparent treatment-resistant hypertension in the published literature may be more appropriately classed as pseudo-resistant due to poor adherence. Subgroup analysis further revealed that adherence estimates were dependent on the type of adherence assessment method used, with the highest non-adherence observed for physical tests for medications in bodily fluids. There was a small but significant difference in adherence estimates across study settings, with lowest non-adherence estimates observed in primary care settings, suggesting that a proportion of patients may be prematurely referred for specialist treatment without adequate assessment of adherence in primary care. (2) The cross-sectional quantitative study indicated that, even among a single sample of participants, the measure used to assess adherence has a considerable impact on the adherence estimates obtained. Habit strength was demonstrated to be the strongest predictor of adherence behaviour across all analyses. Treatment-related beliefs and coherence of beliefs did not predict adherence, even for patients with relatively weak habits. Treatment burden was also not associated with adherence or habit strength for this sample. (3) The qualitative comparison of high and low adherers identified that illness- and treatment-related beliefs, coherence of beliefs, and medication-taking habits are all important factors in determining whether a patient will adhere to treatment. Most patients described the important role of the general practitioner in promoting good adherence, but highlighted system-related factors as potentially diminishing people's confidence in their care. Overall differences between high and low adherers were subtly nuanced, highlighting the challenges for healthcare practitioners in clearly identifying poor adherence and potential determinants.

Conclusion

The findings of this research provide important new insights into adherence among patients with apparent treatment-resistant hypertension. The quantification of the problem of non-adherence and identification of methodological limitations in the existing literature, quantitative examination of theoretical predictors of adherence, and qualitative investigation into characteristics of high and low adherers with apparent treatment-resistant hypertension together contribute to the evidence base for the development of targeted behavioural interventions to promote antihypertensive adherence in primary care.

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List of Abbreviations

ABPM	Ambulatory blood pressure monitor
ACE	Angiotensin-converting enzyme
AHA	American Heart Association
aTRH	Apparent treatment-resistant hypertension
BP	Blood pressure
CI	Confidence interval
COREQ	Consolidated Criteria for Reporting Qualitative Research
CSM	Common-Sense Model of Self-Regulation
DBP	Diastolic blood pressure
DOT	Directly observed therapy
EM	Expectation Maximisation
ESC	European Society of Cardiology
ESH	European Society of Hypertension
GMS	General Medical Services
GP	General practitioner
GRIPP2-SF	Guidance for Reporting Involvement of Patients and the Public 2 – Short Form
HPLC-MS/MS	High-performance liquid chromatography coupled to mass spectrometry
ICPC	International Classification of Primary Care
LC-MS	Liquid chromatography-mass spectrometry
MAR	Missing at Random
MARS	Medication Adherence Rating Scale
MCAR	Missing Completely at Random
MEMS	Medication Event Monitoring System
MMAS	Morisky Medication Adherence Scale
mmHg	Millimetre of mercury
MNAR	Missing Not at Random
MPR	Medication possession ratio

PPI	Public and patient involvement
PPP-R	Public and Patient Partnership in Research
PRISMA	Preferred Reporting Items for Systematic-Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RH	Resistant hypertension
TILDA	The Irish Longitudinal Study on Ageing
SBP	Systolic blood pressure
WestREN	Western Research and Education Network
WHO	World Health Organization

“Keep a watch...on the faults of the patients, which often make them lie about the taking of things prescribed. For through not taking disagreeable drinks, purgative or other, they sometimes die.”

Hippocrates, Decorum

1. Introduction: The Problem of Medication Non-Adherence among Patients with Apparent Treatment-Resistant Hypertension

Chapter Overview

In this chapter, the background to this research will be described. An introduction to important aspects of the study will be presented, such as information related to resistant hypertension; information related to non-adherence to medication; and the relevance of medication non-adherence for patients with resistant hypertension. The rationale for the current research will then be made and the outline for this thesis will be presented.

Hypertension

Hypertension is a chronic condition in which the blood pressure (BP) in the arteries is persistently elevated. This condition affects approximately 40% of adults worldwide (Poulter, Prabhakaran, & Caulfield, 2015; World Health Organization [WHO], 2011). In the context of Ireland, the Irish Longitudinal Study on Ageing (TILDA) has estimated that 63.7% of people aged over 50 years suffer from the disease (C. M. Murphy et al., 2016). It is a major risk factor for coronary artery disease, stroke, heart failure, peripheral vascular disease, vision loss, and chronic kidney disease. According to the WHO (2008), hypertension is responsible for at least 45% of deaths due to heart disease, and 51% of deaths due to stroke. In sum, complications of hypertension account for 9.4 million deaths worldwide every year (Campbell et al., 2015; Lim et al., 2012).

BP is expressed by two measurements, the systolic and diastolic pressures, which are the maximum and minimum pressures, respectively. Normal BP at rest is within the range of 100–140 millimetres of mercury (mmHg) systolic and 60–90 mmHg diastolic. For most adults, high BP is present if the resting BP is persistently at or above 140/90 mmHg. This goal may be relaxed to 150/90 mmHg in patients greater than 60 years of age (James et al., 2014). For individuals with certain conditions, such as atherosclerotic cardiovascular disease or proteinuric chronic kidney disease, a lower goal BP (i.e., <130/80 mmHg) may be used (James et al., 2014).

Hypertension can be effectively treated with lifestyle changes and medication. Lifestyle changes such as losing weight, decreasing sodium intake, increasing physical activity, and adopting a healthy diet can significantly decrease the risk of health complications associated with hypertension (Eckel et al., 2013). Indeed, there is enduring evidence that health-related behaviour may be causally linked to the development of

cardiovascular diseases (World Health Organization, 2007). In cases where lifestyle changes alone are not sufficient, medication is used. Several classes of medications, collectively referred to as antihypertensive medications, are available for treating hypertension. There is considerable evidence for the efficacy of pharmacological treatments for reducing morbidity and mortality from cardiovascular disease (Musini, Tejani, Bassett, & Wright, 2009; Wright & Musini, 2009). However, despite the established efficacy of antihypertensive treatments, among treated hypertensive patients there lies a cohort at the upper end of the cardiovascular risk spectrum; that is, patients whose hypertension is resistant to treatment.

Resistant Hypertension

Definition. Resistant hypertension is defined as BP that remains uncontrolled despite concurrent treatment using three antihypertensive medications of different classes (Calhoun et al., 2008; Mancia et al., 2013). Ideally regimens will include one diuretic, and all agents should be prescribed at optimal dose amounts. Patients who require four or more antihypertensive medications to achieve BP control are also considered resistant to treatment. Although arbitrary regarding the number of medications required, resistant hypertension is thus defined to identify patients who may have reversible causes of hypertension and/or patients who, because of persistently high BP, may benefit from special diagnostic and therapeutic considerations (Calhoun et al., 2008).

Operational definitions of resistant hypertension used in the published literature are heterogeneous. Owing to these varying definitions of treatment resistance, it has been difficult to compare findings between studies among patients with resistant hypertension to date (Myat, Redwood, Qureshi, Spertus, & Williams, 2012). Myat et al. (2012) have called for consensus between national and international professional bodies on a universal definition of resistant hypertension to allow robust comparisons between future studies. Although there has been a greater consensus between professional bodies in more recent scientific and clinical statements (Calhoun et al., 2008; Mancia et al., 2013), this remains an important consideration when interpreting research findings regarding resistant hypertension.

Aetiology and pathogenesis. In most cases, the pathogenesis of resistant hypertension is uncertain (Yaxley & Thambar, 2015). Cross-sectional and outcome studies have identified characteristics associated with resistant hypertension, but underlying mechanisms of treatment resistance, principally potential genetic mechanisms, have not been investigated (Calhoun et al., 2008). Resistant hypertension can occur secondary to other

medical conditions, most often chronic kidney disease or primary hyperaldosteronism, but also renovascular disease and obstructive sleep apnoea (Logan et al., 2001; Viera, 2012). In the absence of a secondary cause, the condition is most likely multifactorial. Common clinical characteristics of patients with resistant hypertension include obesity, diabetes, chronic kidney disease, black ethnicity, female sex (Epstein, 2007), older age, and arterial stiffness resulting from uncontrolled BP over time (Pickering, 2007). Low potassium and target organ damage, including albuminuria, retinopathy and left ventricular hypertrophy, have also been associated with the disease (Muxfeldt, Bloch, Nogueira Ada, & Salles, 2005).

Patient behaviour can also contribute to the development of resistant hypertension (Park & Campese, 2007; Tobe & Lewanczuk, 2009). This includes ingesting agents that interfere with antihypertensive medications, such as nonsteroidal anti-inflammatory agents, which block prostaglandins and induce sodium retention. Common cold remedies and decongestants may also interfere with BP control, as they often contain agents that stimulate the sympathetic nervous system. Oral contraceptive hormones may also slightly raise BP in certain women. Other lifestyle factors, especially excessive sodium intake, can impact on the efficacy of common antihypertensive medications, particularly diuretics, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers. Excessive alcohol consumption, illicit drug use, obesity and a sedentary lifestyle may also necessitate increased antihypertensive therapy to achieve BP control (Park & Campese, 2007; Tobe & Lewanczuk, 2009).

Prognosis. The prognosis of resistant hypertension is unknown, but cardio- and cerebrovascular risk is undeniably increased as patients often have a history of long-standing, severe hypertension complicated by multiple other cardiovascular risk factors such as those discussed above (Calhoun et al., 2008). Some research suggests that patients with resistant hypertension are at a fourfold greater risk of cardiovascular events relative to hypertensive patients who achieve their BP targets (Pierdomenico et al., 2005; Tobe & Lewanczuk, 2009). Longitudinal research by Daugherty et al. (2012) suggests that patients with resistant hypertension are almost 50% more likely to have a cardiovascular event over 3.8 years of follow-up.

Prevalence and incidence. A recent cohort study conducted in the UK suggests that the prevalence of resistant hypertension has plateaued and decreased in recent years, consistent with a decrease in incidence from 2004 onwards (Sinnott, Smeeth, Williamson, &

Douglas, 2017). Despite this, resistant hypertension still appears relatively common in clinical practice (Sinnott et al., 2017; Vongpatanasin, 2014). Given the complexity involved in confirming treatment resistance (Kaplan, 2005), the true prevalence of this condition is uncertain. The reported prevalence of resistant hypertension varies widely depending on measures taken to exclude those with pseudo-resistance, as well as variable interpretations of its definition (Ferro, 2017). Two recent meta-analyses of prevalence studies suggest that 10–14% of treated hypertensive patients may be classed as having resistant hypertension (Achelrod et al., 2014; Noubiap et al., 2018). However, most studies included in these reviews were incapable of ruling out pseudo-resistance caused by measurement error, white coat effects, sub-optimal dosing, or poor medication adherence. It has been argued that simply by following professional guidelines for both diagnosis and treatment (e.g., Calhoun et al., 2008; Padwal et al., 2009; Mancia et al., 2013) resistant hypertension should become less prevalent, and its causes more easily identified and treated. Indeed, P. Hayes et al. (2018) demonstrate that, when best practice guidelines for the assessment of true resistant hypertension are followed (i.e., all antihypertensive agents are adequately dosed, 24-hour ambulatory BP monitoring is employed to rule out white coat hypertension [the phenomenon in which patients exhibit a BP level above the normal range in a clinical setting only], appropriately adjusted BP cut-off levels for patients who are elderly or who suffer from chronic kidney disease or diabetes are used, and medication adherence is assessed), resistant hypertension accounts for only 3.3% of treated hypertensive patients in primary care.

Diagnosis. Uncontrolled hypertension does not necessarily imply resistance to treatment. Patients who lack BP control secondary to poor adherence and/or an inadequate treatment regimen, as well as those who exhibit white coat hypertension, cannot be classed as truly resistant to treatment. Until these factors have been examined, patients who meet the basic criteria for resistant hypertension are described as having ‘apparent treatment-resistant hypertension’ (aTRH). Patients whose uncontrolled BP is demonstrated to be due to any one of these factors are instead classed as having pseudo-resistant hypertension (Calhoun & Grassi, 2017).

A diagnosis of true resistant hypertension should not be made before ensuring that BP has been measured accurately and that readings are reflective of true BP. Improper BP measurement (e.g., using an inappropriately sized cuff, or white coat hypertension) can result in misdiagnosis of resistant hypertension. It has been estimated that up to 50% of apparent cases of resistant hypertension may be due to improper or inaccurate BP measurement

(Padwal et al., 2009). Therefore, it is recommended that alternative means of BP measurement, such as home or ambulatory BP monitoring, should be utilised to minimise measurement error, and thereby identify patients whose office BP readings do not reflect their true BP, either due to masked hypertension or a white coat effect (O'Brien et al., 2005).

An inadequate medication regimen also precludes a diagnosis of true resistant hypertension. Physicians must consider whether the antihypertensive medications prescribed: (1) are appropriate for the patient (e.g., ACE inhibitors and beta-blockers may not be as efficacious in patients of African origin); (2) are too short-acting (e.g., some antihypertensive medications have a short half-life and need to be dosed multiple times per day); (3) are appropriately combined (e.g., beta-blockers combined with ACE inhibitors may not give an additive antihypertensive effect); (4) include a diuretic as part of the regimen; (5) are sufficiently dosed and clinically validated antihypertensive doses are being used (Tobe & Lewanczuk, 2009). If BP goals are not being met, an adjustment of the treatment regimen or an increase in dosage may be required (James et al., 2014).

Perhaps the most challenging behavioural cause of aTRH for healthcare practitioners is patient non-adherence to medication. Simply put, patients cannot be classed as resistant to a treatment they are not taking. Medication adherence, particularly as it pertains to resistant hypertension, is discussed in detail below.

Medication Adherence

“Drugs don't work in patients who don't take them.”

This quote, attributed to former US Surgeon General C. Everett Koop (Osterberg & Blaschke, 2005), tackles a difficult truth in healthcare worldwide: that is, many patients do not take the medications they need to successfully treat their conditions. Medication adherence is defined as the process by which patients take their medication as prescribed (Vrijens et al., 2012). Non-adherence can take many forms: the advice given to patients by their healthcare professionals to cure or control disease may be misunderstood, carried out incorrectly, forgotten, or even completely ignored (Martin, Williams, Haskard, & DiMatteo, 2005). Dubbed “the key mediator between medical practice and patient outcomes” (Kravitz & Melnikow, 2004, p. 197), non-adherence to medication is ubiquitous, and a major cause of poor healthcare outcomes and high healthcare costs. Among patients with chronic illness, it is often reported that approximately 50% do not take medications as prescribed (Lee, Grace, & Taylor, 2006; Sabaté, 2003).

Non-adherence compromises health outcomes in many ways but is most obvious when patients fail to take medications that likely would effectively manage their illnesses. Poor adherence to medication contributes significantly to increased morbidity and mortality, with estimates indicating that approximately 9% of all cases of cardiovascular disease (CVD) and 13 per 100,000 CVD deaths per year in Europe alone may be due to non-adherence (Chowdhury et al., 2013). Non-adherence also has indirect effects on patient outcomes. For example, if a physician erroneously believes a patient has taken their medications as prescribed, they may make inappropriate changes to the regimen, which can result in further complications; thus, not only do non-adherent patients fail to benefit from effective medication, they also risk being harmed by inappropriate prescribing and unnecessary treatment intensification (Martin et al., 2005; Pittman et al., 2012).

The economic consequences of medication non-adherence are considerable. Costs of non-adherence are both personal and economic, with serious knock-on effects in terms of increased demands for healthcare resources should patients' health deteriorate as a result of not taking prescribed medication (NICE, 2009). Non-adherence is estimated to cost European governments €125 billion annually; and costs arising from complications of poor adherence represent 14% of total healthcare expenditure in the United Kingdom's National Health Service (European Federation of Pharmaceutical Industries and Associations, 2013). Non-adherence also presents an economic challenge for industry; as of 2015, non-adherence equates to an estimated global revenue loss of \$637 billion to the pharmaceutical industry each year (T. Moore, Chawla, & Firlik, 2016).

Medication adherence is a multifaceted issue and a dynamic process that changes over time. According to Vrijens et al. (2012), it consists of three components: initiation, implementation, and discontinuation. Initiation occurs when a patient takes the first dose of a prescribed medication. Discontinuation occurs when the patient stops taking the prescribed medication, for any reason. Implementation is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose. Persistence is the length of time between initiation and the last dose, which immediately precedes discontinuation. Problems with medication adherence are characterised by two major patterns: non-persistence, and good persistence but poor implementation (primarily missed doses and drug holidays). These are not necessarily independent; for example, suboptimal implementation may lead to poor BP control, which in turn can lead to non-persistence

(Blaschke et al., 2012). Identification of a patient's non-adherence pattern is crucial, as the intervention strategy will depend on the type of pattern.

Medication Adherence for Resistant Hypertension

Awareness of non-adherence in the treatment of hypertension has increased in recent years; however, relatively little progress has been made to combat the issue. Although pharmacological antihypertensive therapy has a positive safety and tolerability profile and reduces the risk of stroke by approximately 30% and myocardial infarction by approximately 15% (Law, Morris, & Wald, 2009), evidence suggests that as many as 50% to 80% of patients treated for hypertension are non-adherent to their medication regimen (Costa, 1996; Cramer, Benedict, Muszbek, Keskinaslan, & Khan, 2008; Elliott, 2008). Although poor adherence to antihypertensive therapy is associated with increased risk of cardio- and cerebrovascular events (Corrao et al., 2011), approximately half of patients prescribed an antihypertensive drug will discontinue its use within 1 year (Vrijens et al., 2008). This is particularly important in understanding and intervening in patients who appear to have resistant hypertension.

Though there is extensive evidence available regarding adherence among the general hypertensive population, the literature on adherence among those who may be considered resistant is limited. Resistant hypertension presents unique specific challenges to adherence in addition to those faced by patients with hypertension that is controlled by two or fewer antihypertensive agents. As an asymptomatic chronic condition requiring daily adherence to a multi-medication regimen, it presents significant challenges to patients and healthcare practitioners alike. Physicians frequently underestimate patient non-adherence for hypertension (Meddings et al., 2012), which can lead to unnecessary treatment intensification and diagnostic testing, ultimately resulting in increased treatment burden for patients, practitioners and the healthcare system (May et al., 2014).

Given that resistant hypertension is defined in terms of the number of medications prescribed, and that a patient cannot be deemed resistant to a treatment he or she is not taking, assessment of medication adherence for patients with aTRH is vital to ensure patients receive the appropriate care. Medication non-adherence may be responsible for a significant proportion of aTRH cases; in fact, some have argued that poor adherence is the most common cause of aTRH (Jung et al., 2013; Vrijens et al., 2017). Several reviews examining resistant hypertension have been published in recent years (e.g., Berra et al., 2016; Hyman & Pavlik,

2015), each reporting highly variable estimates of non-adherence; however, these have not been systematic in their examination of the literature, documenting neither their search strategy nor selection criteria. Therefore, the extent of the problem of medication non-adherence among patients with aTRH is unknown.

Achieving satisfactory adherence may have a far greater impact than any other effort to improve antihypertensive treatments (Vrijens et al., 2017). A recent meta-analysis revealed that interventions to improve medication adherence for hypertension have a modest main effect on reducing BP, suggesting that behavioural adherence interventions have the potential to reduce BP by a clinically significant magnitude in terms of cardiovascular risk reduction (Morrissey, Durand, et al., 2017). Using a probabilistic prevalence-based model, over a 10-year period, Mennini et al. (2015) estimated that a total saving of €332 million could be achieved by increasing adherence to antihypertensive therapy to 70% in five European countries (Italy, Germany, France, Spain, and England). Furthermore, it is estimated that approximately 8% of the global total health expenditure could be avoided from the responsible use of medicines and resulting improvements in adherence (Aitken & Gorokhovich, 2012).

Barriers to Adherence

Poor adherence to medical treatment severely compromises patient outcomes and increases patient mortality (Chowdhury et al., 2013). In order to improve medication adherence, the multifactorial causes of non-adherence must be understood. Medication non-adherence is a complex and highly individualised behaviour, influenced by a combination of socio-economic, patient-, treatment-, system-, and illness-related factors. Over 200 factors involved in non-adherence have been identified (Horne & Weinman, 2002); however, predictors of non-adherence are generally not well described, and thus it is difficult to draw systematic conclusions on potential barriers based on the current literature (Jin, Sklar, Min Sen Oh, & Chuen Li, 2008). Some of the most pertinent factors associated with medication adherence for (resistant) hypertension will be discussed below.

Patient-related factors.

Socio-demographic characteristics.

Age. There is mixed evidence regarding the role of age in predicting medication adherence. The literature suggesting a negative effect of younger age on adherence is relatively consistent (Jin et al., 2008). For elderly people, some studies suggest that older age

is associated with better medication adherence (Krousel-Wood, Thomas, Muntner, & Morisky, 2004); however, some studies found conflicting results, such that advancing age affects adherence among elderly people in the opposite direction (Balbay, Annakkaya, Arbak, Bilgin, & Erbas, 2005; Benner et al., 2002). Elderly patients may have additional problems that affect adherence, such as problems with vision, hearing and memory. Additionally, they may have more difficulties in following medical instructions due to cognitive impairment or other physical difficulties, such as having problems with swallowing tablets, opening medication containers, handling small tablets, distinguishing colours or identifying markings on medicines (Cooper et al., 2005). On the contrary, older adults may also be more concerned about their health than younger patients, such that older patients' non-adherence is unintentional in many cases; therefore, if they can get the necessary support from healthcare providers or family members, they may be more likely to be adherent (Jin et al., 2008).

Gender. The evidence regarding the relationship between gender and adherence is similarly mixed, with some studies suggesting that female patients are more adherent (Choi-Kwon et al., 2005; Fodor et al., 2005), others that males are more adherent (Caspard, Chan, & Walker, 2005), and others that there is no relationship between gender and medication adherence (Mathes, Jaschinski, & Pieper, 2014; Vik, Maxwell, & Hogan, 2004).

Educational attainment. Several studies indicate that patients with higher educational level might have higher adherence (Mathes et al., 2014). Intuitively, it may be expected that patients with higher educational level should have better knowledge about their disease and therapy and therefore be more adherent. However, even highly educated patients may not understand their conditions or believe in the benefits of being adherent to their medication regimen (DiMatteo, 1995). There is some evidence to suggest that patients with lower education levels have better adherence (Senior, Marteau, Weinman, & Genetic Risk Assessment for FH Trial (GRAFT) Study Group, 2004), perhaps because patients with lower educational attainment may place more trust in physicians' advice.

Psychological factors. A range of specific stand-alone psychological factors that have been linked to medication adherence is described in this section. Later in the chapter, broader theoretical frameworks that have been applied in this literature are presented.

Beliefs about the illness and therapy. Perceptions about illness, perceived illness burden, and beliefs about medication have been demonstrated to significantly predict medication adherence; having a more threatening view of illness is associated with higher

adherence, which is in turn associated with lower perceived illness burden (Rajpura & Nayak, 2014). Having a negative attitude towards treatment (e.g., depression, anxiety, fears or anger about the illness) is viewed as a strong predictor of poor adherence (Jin et al., 2008). Beliefs about medicines have been associated with adherence, such that higher adherence is associated with stronger perceived necessity of treatment and fewer concerns about treatment (Crayton et al., 2017; Horne, Chapman, et al., 2013). Concerns about the benefits of medication appear to play a more significant role in the prediction of adherence than perceived risks associated with their use (Rajpura & Nayak, 2014). The necessity-concerns differential, an important aspect of the Beliefs about Medicines framework, posits that patients implicitly weigh the costs against the benefits when deciding whether to adhere to a medication regimen and that personal beliefs about the necessity of the medication are balanced against concerns about the potential adverse effects of taking it (Horne & Weinman, 1999). Interestingly, recent research using polynomial regression analysis has suggested that patients with ambivalent beliefs (i.e., strong concerns and strong necessity beliefs) are less adherent than those exhibiting indifference (i.e., weak concerns and weak necessity beliefs; Phillips, Diefenbach, Kronish, Negron, & Horowitz, 2014), suggesting that the interplay between these factors is more complex than has been previously understood. Therefore, whether an individual is ambivalent as opposed to indifferent may have predictive value beyond simply weighing the strength of necessity beliefs against the strength of concern beliefs.

Health literacy and disease-related knowledge. Health literacy is the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions. Patients with low health literacy have less knowledge about how to manage their illness compared with patients who have adequate health literacy. This lack of knowledge can take several forms: some patients lack understanding of the role their medication plays in the treatment (Ponnusankar et al., 2004); others lack knowledge about the disease and consequences of poor adherence (Alm-Roijer et al., 2004; Gascón et al., 2004); and some may erroneously believe that the need for medication is intermittent (Bender & Bender, 2005; Vic et al., 2004). Patients with low health literacy and inadequate disease-related knowledge are theoretically more likely to be non-adherent to their medication; however, the research evidence is varied (Berkman, Sheridan, Donahue, Halpern, & Crotty, 2011; Crayton et al., 2017; DeWalt, Berkman, Sheridan, Lohr,

& Pignone, 2004; Gazmararian et al., 2006; Gellad, Grenard, & Marcum, 2011; Kripalani, Gatti, & Jacobson, 2010; Ngoh, 2009).

Patient-prescriber relationship. A healthy patient-prescriber relationship, analogous to 'therapeutic alliance' in psychotherapy, is based on a patient's trust in the prescriber and empathy from the prescriber towards the patient. Studies have shown that adherence is good when physicians are emotionally supportive, reassuring and respectful, and treat patients as equal partners in managing their health (P. J. Moore et al., 2004). Spending too little time with patients may threaten their motivation for adhering to therapy (Gascón et al., 2004; P. J. Moore et al., 2004). Similarly, poor communication with healthcare providers is also likely to have a negative impact on adherence (Martin, Williams, Haskard, & DiMatteo, 2005). In addition, having multiple healthcare providers prescribing medications may decrease patients' confidence in the prescribed treatment (Vlasnik et al., 2005). Patient satisfaction and participation in the patient-prescriber relationship can be understood through the lens of attachment theory, which has important implications for health-related behaviours that involve on-going interactions with physicians. Attachment theory (Ainsworth, 1973, 1991; Bowlby, 1969) proposes that individuals internalise early experiences with caregivers and form internal working models that determine for the individual whether he or she is worthy of care (view of self) and whether others can be trusted to provide care (view of others). These models influence the individual's interactions with others, and their interpretations of these, into adulthood (Bowlby, 1969). In the context of adherence, research suggests that individuals with a secure attachment style are more adherent (M. A. Moon, 2002), and that those with anxious-preoccupied, fearful-avoidant or dismissive-avoidant attachment styles are less adherent (Bennett, Fuertes, Keitel, & Phillips, 2011; Ciechanowski, Katon, Russo, & Walker, 2001).

Depression. Patients with depression have many risk factors that could contribute to non-adherence, such as fatigue, lack of motivation, social withdrawal, feelings of hopelessness, cognitive changes, and expectations about the benefits or harms of treatment. Patients with depression may also have more difficulty with patient-provider communication and less satisfaction with their care (Piette, Richardson, & Valenstein, 2004). A meta-analytic review by DiMatteo, Lepper, and Croghan (2000) revealed that depressed patients are three times more likely than non-depressed patients to be non-adherent to physicians' advice. A more recent review by Grenard et al. (2011) found similar results among patients in the

United States; the estimated odds of a depressed patient being non-adherent were 1.76 times the odds of a non-depressed patient, across 31 studies and 18,245 participants.

Personality. Personality traits, as conceptualised in the five-factor model of personality (McCrae & Costa, 2003), have been widely examined with regard to medication adherence. Conscientiousness, the trait of being careful, vigilant, and goal-oriented, is the personality trait most frequently associated with high adherence to prescribed medication. A recent meta-analysis concluded that greater conscientiousness is associated with better medication adherence and that the magnitude of this association is comparable to other better-established psychological predictors of poor adherence such as depression (Molloy, O'Carroll, & Ferguson, 2014). Traits Neuroticism and Agreeableness have also been implicated in relation to medication adherence; such that those who are high in neuroticism and/or low in agreeableness are less likely to adhere to their medications (Axelsson, Brink, Lundgren, & Lötvall, 2011).

Cognitive function. Cognitive function includes all cerebral activities that lead to knowledge, including all means and mechanisms of acquiring information, encompassing reasoning, memory, attention, and language. Deficits in several components of cognitive function, including executive function, working memory, episodic memory, information processing speed, language, attention and mental flexibility, have been associated with poor medication adherence (Alosco et al., 2012; Hinkin et al., 2002; Insel, Morrow, Brewer, & Figueredo, 2006; Stilley, Bender, Dunbar-Jacob, Sereika, & Ryan, 2010). Even very mild cognitive impairment can have a detrimental and significant impact on medication adherence in elderly people living independently in the community (T. L. Hayes, Larimer, Adami, & Kaye, 2009). Despite the potential breadth of this area of research, relatively speaking, relations between specific domains of cognitive function and adherence are not well studied and often poorly described (Stilley, Sereika, Muldoon, Ryan, & Dunbar-Jacob, 2004).

Prospective memory. Prospective memory is defined as a psychological process that enables humans to execute previously formed intentions at an appropriate future point in time (Harris & Wilkins, 1982; McDaniel & Einstein, 2007). Simply stated, prospective memory describes an individual's ability to remember to do something at a later time. Somewhat of a misnomer, prospective memory is based on several different cognitive functions (e.g., goal formation, planning, task management, attentional control mechanisms) and not necessarily confined to memory alone (St. Pierre, Hofinger, & Simon, 2011). Deficits in prospective memory have been demonstrated to increase the risk of suboptimal medication adherence

across various clinical populations, age groups, types of prospective memory tasks, and study designs (Zogg, Woods, Saucedo, Wiebe, & Simoni, 2012). Conversely, lapses in prospective memory may lead to patients taking more than the prescribed dose of a medication, having forgotten whether they had taken their daily dose and taking another as a result (Khan et al., 2014). Prospective memory failure, colloquially described as ‘forgetfulness’, is also one of the reasons for non-adherence most commonly cited by patients (Abughosh et al., 2016; Holt, Rung, Leon, Firestein, & Krousel-Wood, 2014; Khan, Shah, & Hameed, 2014) and health workers (Allen, Brownstein, Satsangi, & Escoffery, 2016).

Causal learning from experiential feedback. Insights from cognitive psychology have led to the recent conceptualisation of medication adherence as a causal-learning process, such that a patient learns whether a medication is effective, necessary and tolerable from personal experience with taking the medication (Rottman, Marcum, Thorpe, & Gellad, 2017). Receiving feedback through action is theoretically important for adherence; without feedback that a medication produces the expected results, the individual may re-evaluate the cause, identity, control, timeline, and/or consequences of the health threat, as well as the necessity and consequences of the treatment (Phillips et al., 2016; Phillips et al., 2013). Although this is an emerging area of inquiry, recent empirical work suggests that experiential feedback may better predict intentional non-adherence than unintentional non-adherence (Phillips et al., 2013), and that experiential feedback is no more predictive of adherence for symptomatic than asymptomatic conditions (Phillips et al., 2016). However, further investigation and improved measurement of experiential feedback are needed.

Conclusion and integration. While these psychological factors are presented as independent sub-categories in the preceding text, it is worth acknowledging the wide range of complex relationships that exist between these factors. More comprehensive theoretical models that attempt to integrate multiple variables into descriptive, predictive or explanatory models are presented later in this chapter.

Social and economic factors.

Cost and income. Cost is a crucial issue in patient adherence, particularly for patients with chronic disease as the treatment period could be life-long. Co-payments and higher medication costs are associated with poorer adherence (Mathes et al., 2014). Cost and income are interrelated; healthcare cost may not be as large a burden if the patient has a relatively high income. Even patients who qualify for the provision of state or insurance-funded

medication may be affected by cost-related barriers such as supplementary prescription charges, particularly those who are prescribed a multi-medication regimen. Treatment escalation is one of the main reasons for increased treatment cost, particularly with regard to hypertension; poor adherence leads to treatment failure, disease progression and more complex treatments, which can in turn result in even poorer adherence (Vrijens et al., 2017).

Scarcity. Another interesting socioeconomic consideration closely linked to cost, income and education is the idea of scarcity. There is some evidence to suggest that simply having less (e.g., money or time) can modify the way in which people allocate attention, causing them to engage more deeply in some problems while neglecting others (Shah, Mullainathan, & Shafir, 2012). With regard to medication adherence, this re-allocation of attention may result in patients neglecting to collect their medication due to the immediate financial cost without consideration of potential future consequences for their health. Scarcity is not limited to financial resources; time is another essential resource for which scarcity can have adverse behavioural implications. For example, if certain medications need to be taken at particular times, with food or away from food, *et cetera*, adhering to a medication routine can impose time constraints on an individual's activities (capability constraints), thus increasing the risk of non-adherence for those for whom time is scarce (Strazdins et al., 2011). The health consequences of a coalescence of low income, time scarcity, and distance from services have been demonstrated for other health behaviours (e.g. Takahashi, Wiebe, & Rodriguez, 2001); however, more research examining this interaction specifically for medication adherence is needed.

Social support. Relationships between medication adherence and practical, emotional, and unidimensional social support; family cohesiveness and conflict; marital status; and living arrangement have been identified. Among these, practical support appears to be the strongest predictor of adherence (DiMatteo, 2004a; Molloy, Perkins-Porras, Bhattacharyya, Strike, & Steptoe, 2008). Patients who have emotional support and practical help from family, friends or healthcare providers are more likely to adhere to treatment (T. A. Miller & DiMatteo, 2013). DiMatteo (2004a) also found that adherence is almost twice as high in patients from cohesive families and 1.5 times lower in patients from families in conflict. Being married and living with another person (for adults) may increase adherence modestly (DiMatteo, 2004a). Social support can help patients in reducing negative attitudes to treatment, having motivation and remembering to implement the treatment.

System-related factors. Healthcare system-related factors affecting adherence primarily involve availability and accessibility. Poor accessibility to healthcare (Ponnusankar et al., 2004), long waiting time for clinic visits (Balkrishnan et al., 2003; Lawson et al., 2005; P. J. Moore et al., 2004; Wai et al., 2005), difficulty in getting prescriptions filled (Vlasnik et al., 2005), and unsatisfactory clinic visits (Gascón et al., 2004; Lawson et al., 2005; Spikmans et al., 2003) all contribute to poor adherence.

Illness-related factors.

Illness severity. No consistent evidence demonstrates that patients with greater disease severity based on clinical evaluation are more adherent to medication than healthier patients (Jin et al., 2008). Rather than actual disease severity, perceived health status may have a greater influence on adherence. Patients expecting poor health outcomes may be more motivated to adhere to treatment provided they consider the medication to be effective (Jin et al., 2008).

Symptom severity. A critical feature of hypertension is that it is asymptomatic. Patients with asymptomatic or oligosymptomatic conditions are more likely to have poor adherence; the lack of symptoms equates to a lack of physical cues (e.g., aches and pains) to action, thus increasing the chances of patients forgetting to take their medication (Insel, Einstein, Morrow, Koerner, & Hepworth, 2016). Furthermore, as described in the preceding section on causal learning and experiential feedback, maintaining the behaviour of taking medication daily is more difficult when patients do not receive salient feedback that the behaviour is producing benefits (Rothman, Sheeran, & Wood, 2009; Rottman et al., 2017).

Treatment-related factors.

Duration of treatment. Acute illnesses are associated with better adherence than chronic illnesses (Gascón et al., 2004). A longer duration of treatment may also jeopardise medication adherence, as longer duration may compromise patient's beliefs about the efficacy of the medication (Ghods & Nasrollahzadeh, 2003; Jin et al., 2008). However, the evidence for the role of treatment duration in predicting adherence is inconsistent (Mathes et al., 2014).

Pill burden and regimen complexity. Pill burden refers to the number of pills that a patient takes on a regular basis, along with all associated efforts that increase with that number (e.g., storing, organising, consuming, and understanding the various medications in the regimen). Pill burden for hypertension tends to result from free combinations of

antihypertensive medications and makes the daily routine of medication-taking complex, which can be a barrier to optimal adherence (Gerbino & Shoheiber, 2007). By definition, patients with aTRH are prescribed multiple antihypertensive medications, thereby increasing pill burden and so their risk for poor adherence (Ingersoll & Cohen, 2008). There is consistent evidence demonstrating the negative effect of regimen complexity on adherence (Mathes et al., 2014). Recent debate around the use of polypills (i.e., pills that combine multiple active pharmaceutical ingredients) has emphasised that polypills improve adherence, are generally well tolerated, and reduce risk factor levels for cardiovascular disease (A. K. Gupta, Arshad, & Poulter, 2010; Munger, 2010; Sherrill, Halpern, Khan, Zhang, & Panjabi, 2011; Webster et al., 2016); however, between-study heterogeneity limits the certainty of the effect on risk factors, and the implementation of polypills into clinical practice remains a challenge (Coca et al., 2017; Huffman, Xavier, & Perel, 2017; Webster, Castellano, & Onuma, 2017). Re-packing of medication has also been used to improve adherence where pill burden is an issue (Dupclay et al., 2012). Pill burden may also be reduced through ‘de-prescribing’ medications, following analysis of costs and benefits of continued use (Hilmer, Gnjjidic, & Le Couteur, 2012). Prescribing long-acting active ingredients over short-acting ones, provided there are no contraindications or potential for drug interactions, may also reduce pill burden (e.g., if prescribing an ACE inhibitor, selecting lisinopril, which is dosed once a day, over captopril, which may be dosed 2–3 times per day; Giles et al., 1989).

Adverse effects. Evidence that adverse side-effects of medication have a negative impact on adherence is quite consistent (Grant, Devita, Singer, & Meigs, 2003; Iihara et al., 2004; Ponnusankar et al., 2004; O’Donoghue, 2004). The influence of side-effects on adherence may be explained in terms of physical discomfort, scepticism about the efficacy of the medication, and decreasing trust in physicians as a result of the adverse effects experienced from taking the prescribed treatment (Jin et al., 2008). Evidence also suggests that adherence may be associated with an individual’s perceived sensitivity to the effects of medicines. Patients’ personal judgements of how much medicine is needed to deliver benefit or to avoid potential adverse effects may influence decisions about how much medication to take as well how long to persist with treatment (Horne, Faasse, et al., 2013).

Quantifying Adherence

Medication non-adherence may be measured directly or indirectly. Direct measures of non-adherence detect the presence of a drug in a person’s body using assays for the drug, its metabolites, or other markers in urine, blood, or other bodily fluids, or involve direct

observation of patients swallowing their medication followed by monitoring of its effects on BP (i.e., directly observed therapy [DOT]). Indirect methods measure non-adherence behaviourally by means of electronic drug monitoring (e.g., using a Medication Event Monitoring System [MEMS]), pill counts, prescription refill records, medication possession ratios (MPR), proportion of days covered (PDC) calculations, medical record review, clinician assessment, or self-report questionnaires. An overview of some of the most commonly used measures of adherence is presented in Table 1.1.

Table 1.1.

Methods for Assessing Medication Adherence

Method	Direct/indirect	Advantages	Disadvantages
Directly observed therapy	Direct	Verified ingestion of medication	Impractical in an outpatient setting Invasive
Drug level in biologic fluids (e.g., blood, urine, plasma)	Direct	Can confirm recent ingestion of medication	Data limited to recent use Pharmacokinetic variations Invasive Expensive
Electronic monitoring (ingestible sensors)	Direct	Can confirm ingestion of medication	Invasive Expensive Potential for adverse device-related effects
Electronic monitoring (inhalation or injection detection)	Direct	Can confirm ingestion of medication Can identify unintentional non-adherence due to poor technique	Expensive Accuracy is instrument-dependent
Electronic monitoring (pill containers or electronically chipped packaging)	Indirect	Precise data on regimen adherence	Expensive Inconvenient Cannot confirm ingestion
Interview	Indirect	Easy to use Inexpensive	Influenced by question construction and interviewer's skill Prone to desirability and recall biases

Patient-kept diary	Indirect	Only self-report method with regimen data	Potential for overestimation Patient must return diary
Pill count	Indirect	Easy to use Inexpensive	No data on regimen adherence Patient may forget or alter unused portion
Prescription record review, electronic	Indirect	Non-invasive Longitudinal data Large populations	Knowledge of database required Validity of variables Cannot confirm ingestion
Prescription record review, manual	Indirect	Non-invasive	Limited to specific location Cannot confirm ingestion
Self-report questionnaire	Indirect	Easy to administer (onsite, mail, phone) Empirically validated May explain patient behaviour	Lack of continuous data Accuracy is instrument-dependent Prone to desirability and recall biases

Each of these measures has its own strengths and limitations. Direct measures using bodily fluids are increasingly used in research but remain infrequently used in clinical settings due to their cost and inability to provide feedback at the point of care (Voils, Hoyle, Thorpe, Maciejewski, & Yancy, 2011). Although they can confirm that the medication has been ingested, direct measures often provide only a single snapshot of adherence behaviour. Furthermore, depending on the time of day the dose was ingested, certain medications (e.g. calcium-channel blockers) may be undetectable by the time the blood or urine sample is provided. DOT, which involves observed swallowing of medication which, if followed by a reduction in a clinical marker (e.g., BP) is indicative of non-adherence for patients previously

classified as being resistant to pharmacotherapy, is arguably an alternative direct measure of adherence; however, it is impractical and costly in terms of healthcare resources. Electronic monitoring using devices such as MEMS, which records the date and time when the package is opened to remove medication, has the advantage of being a dynamic measure; however, MEMS cannot prove ingestion or rule out intentional non-adherence. Pharmacy refill data, pill counts and MPR are similarly limited. The self-report method, despite being criticised for its risk of bias, has unique advantages over other methods, including being brief, inexpensive, applicable in various settings, and able to provide immediate feedback (Voils et al., 2011). Furthermore, depending on the scale used, self-reports offer the opportunity to detect underlying issues contributing to non-adherence, and to differentiate between intentional and unintentional non-adherence. Other systems in development for monitoring adherence include ingestible sensor systems combined with wireless observed therapy (Belknap et al., 2013) and electronically chipped packaging.

There is no one gold standard method of measuring adherence. In addition to the trade-offs between measures in terms of validity and reliability, inherent differences between the initiation, discontinuation and implementation components of adherence preclude a single, quantitatively useful parameter to cover all three (Vrijens et al., 2012). Hence, a combination of methods is widely recommended (A. K. Gupta et al., 2010; Lam & Fresco, 2015; Vrijens et al., 2017). Despite this, in a meta-analytic review of adherence research over 50 years, only 9.8% of studies used more than one adherence measurement method, with a trend for more recent research to be *less* likely to use multiple methods (DiMatteo, 2004b). In almost fifteen years since this review was published, there has been little improvement with regard to this major methodological limitation.

There is no consensual standard for what constitutes acceptable adherence (Osterberg & Blaschke, 2005). Adherence outcomes are frequently reported as dichotomous variables (i.e., adherent versus non-adherent); however, adherence can vary along a continuum from 0 to 100% or more, since patients may sometimes take more than the prescribed doses of their medicines (Khan et al., 2014; Pullar, Kumar, Tindall, & Feely, 1989; Rudd et al., 1988; Spilker, 1991). Much of the research considers greater than 80% adherence to be acceptable; however, this may not be clinically valid for certain populations with serious life-threatening conditions and/or patients prescribed less ‘forgiving’ medications that need to be taken more reliably in order to be effective (Lowy et al., 2011; Osterberg, Urquhart, & Blaschke, 2010; Vrijens et al., 2017).

Theoretical Perspectives on Medication Adherence

As discussed earlier in the chapter, individual social and psychological factors that pertain to medication adherence do not operate in isolation; indeed, there are considerable complex interrelations between these factors with regard to the management of chronic illness. Health psychology theory has provided several useful, empirically validated models for understanding and explaining adherence behaviour. The theoretical frameworks that underpin this thesis will be discussed in detail below.

Social cognition models. The term ‘social cognition models’ refers to a group of similar theories that specify a number of cognitive and affective factors, such as beliefs and attitudes, as the proximal determinants of behaviour. These models provide a useful approach to understanding health behaviour by describing the important social cognitive variables involved in predicting such behaviours (Armitage & Conner, 2000). Although social cognition models do not deny that behaviour is influenced by many other factors (e.g., social structural, cultural, and personality factors), they assume that the effects of these are largely or completely mediated by the factors specified in the model. This is sometimes referred to as the ‘sufficiency hypothesis’ (Sniehotta, Penseau & Araújo-Soares, 2014). The factors included in these models are assumed to be more amenable to change than other factors (e.g., personality; Conner & Norman, 2005); thus, social cognition models are particularly useful for the development of interventions to modify health behaviours.

Social cognition models of health beliefs and behavioural intentions include the Theory of Reasoned Action (Ajzen & Fishbein, 1980) and the Theory of Planned Behaviour (Ajzen, 1991), the Health Belief Model (Rosenstock, Strecher, & Becker, 1988), self-efficacy theory (Bandura, 1982), and Protection Motivation Theory (Rogers, 1975). These models suggest that the perceived (1) severity of a health threat, (2) susceptibility to the threat, (3) ability to perform a treatment, and (4) treatment efficacy predict whether an individual will engage in a treatment behaviour. These models have been extensively used in health research; however, they are limited by their exclusive focus on beliefs at the initial phases of treatment-behaviour development (e.g., Halm, Mora, & Leventhal, 2006).

Common-Sense Model of Self-Regulation (CSM). The CSM (H. Leventhal, Brissette, & Leventhal, 2003; H. Leventhal, Diefenbach, & Leventhal, 1992) is a theoretical framework that has been extensively used to explain the primarily reflective or deliberative processes by which individuals formulate illness- and treatment-related beliefs and

behavioural action plans for addressing illness. The CSM incorporates elements of other social cognition models pertaining to health but is specific to an illness, experienced symptoms of that illness, and the individual patient. The CSM posits that individuals create cognitive and emotional representations of their illness based on concrete and abstract sources of information available to them to make sense of and manage the problem (Hagger, Koch, Chatzisarantis, & Orbell, 2017; Hagger & Orbell, 2003). The interpretation of this information forms the first step in the process of seeking help, engaging in a coping strategy or adopting an illness management routine (Bishop & Converse, 1986). Information from multiple sources (e.g., personal experience as well as the opinions and discourses of significant others, health professionals and media sources) contributes to an individual ‘making sense of’ or forming a representation of their condition. A schematic representation of the CSM is depicted in Figure 1.1.

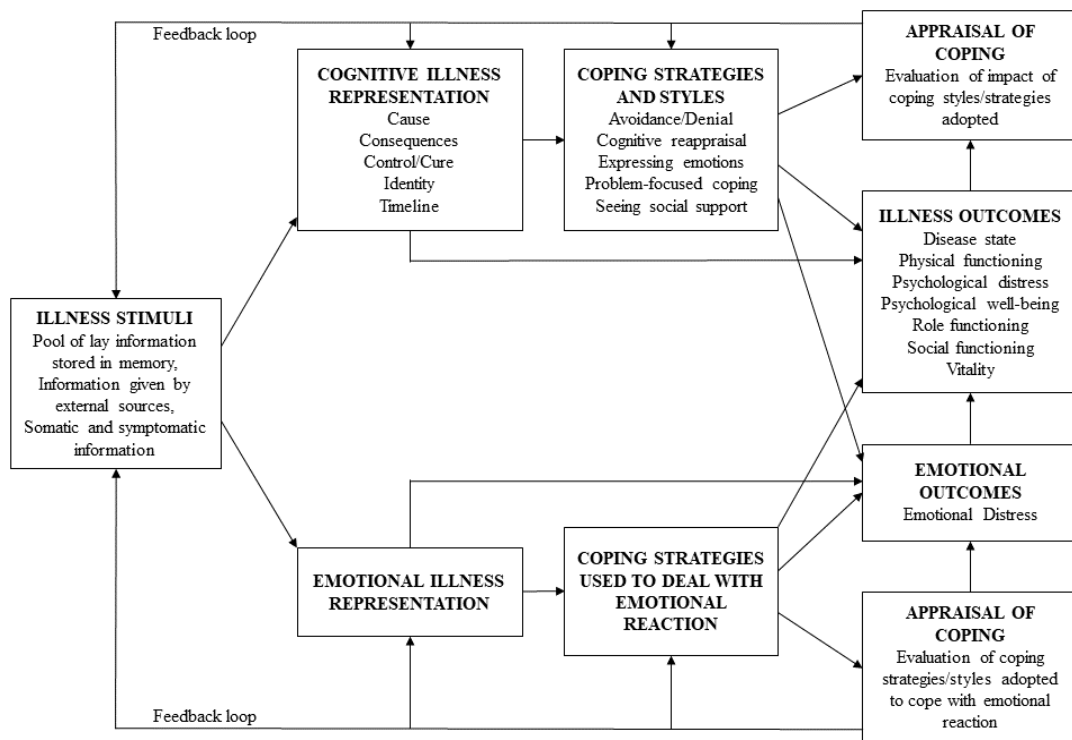


Figure 1.1. Schematic representation of H. Leventhal et al.’s (1980) Common Sense Model of Illness Representations. Adapted from Hagger and Orbell (2003).

Central to CSM are five constructs that form the elements of an individual’s illness representations: (1) identity (labelling of a condition and the experience of symptoms the patient believes are linked to this label), (2) causes, (3) perceived consequences (e.g., disability and death, or social, monetary, or health-related consequences of the illness and

treatment), (4) timeline (perceived chronicity of the illness e.g., acute, chronic, episodic), and (5) controllability/cure (the perception that various factors, e.g., patient or physician behaviour, influence the disease and its course). The CSM posits that these constructs affect how a patient will behave in response to a health threat, including their adherence to a prescribed treatment for the illness.

The CSM and its individual constructs have been examined with regard to a number of different illnesses, including hypertension, and have been found to predict disease management behaviours such as medication adherence (Hagger et al., 2017; Hagger & Orbell, 2003; Jones, Smith, & Llewellyn, 2016). Illness perceptions, specifically controllability/cure representations, and medication beliefs have been demonstrated to account for 1% (Hagger & Orbell, 2003; Hagger et al., 2017) and 77–81% (Horne et al., 2013) of variance in adherence behaviour respectively. Although the CSM has been widely used to predict adherence behaviour for chronic conditions, the effect sizes are relatively small and between-study heterogeneity is considerably high (Aujla et al., 2016; Brandes, & Mullan, 2014; Doyle & Mullan, 2017). Therefore, some have argued that the CSM is not the most appropriate model to use in predictive studies of adherence (Brandes & Mullan, 2014). This may be in part because existing studies that attempt to validate the CSM do not adequately comprise other important factors involved in adherence to medication in the long-term (i.e., consistent and repeated behaviour) beyond beliefs and intentions. Exclusive focus on health beliefs and other behaviour-initiation factors may not be sufficient for assessment of adherence behaviour in the long-term, because the mechanisms of behaviour repetition are theoretically distinct from those of behaviour initiation (Rothman, 2000).

Habit. Reflective factors such as those described in the CSM may better predict intentional non-adherence (i.e., skipping a dose, decreasing or increasing a dose) than unintentional non-adherence (i.e., forgetting; Phillips, Leventhal, & Leventhal, 2013). With repetition in stable contexts, behaviour can shift to automatic repetition through habitual action (Rothman, Sheeran, & Wood, 2009). Habitual action does not require reflection or deliberation on the reasons for doing a behaviour, because habits are automatically triggered by conditioned contextual cues (Gardner, 2015; Wood & Neal, 2007; e.g., a person may automatically take their medication after brushing their teeth in the morning and evening). For patients with chronic conditions who have been taking medications over an extended period of time, reflective factors such as beliefs and intentions have been shown to be less predictive of adherence than behavioural habit strength in a maintenance stage (e.g., Danner,

Aarts, & de Vries, 2008; Phillips, Leventhal, & Burns, 2017; Phillips et al., 2016; Phillips et al., 2013). Hence, proponents of the CSM have argued for further delineation of the automatic versus reflective processes within the CSM (Phillips et al., 2016; Phillips et al., 2017).

What is a habit? Several definitions of habit exist in the literature (e.g., Gardner et al., 2012; Gardner et al., 2011; Nilsen et al., 2008; Nilsen et al., 2012; Ouellette & Wood, 1998; van t'Riet et al., 2011; Verplanken & Wood, 2006; Wood & Neal, 2009); a majority of these have explicitly defined habit as either a type of behaviour or a tendency towards behaviour (Gardner, 2015). According to Gardner (2015), these conceptualisations are problematic in similar ways; both result in tautological arguments for how habit predicts behaviour (e.g., '*habitual behaviour is caused by habitual behaviour,*' or, '*an individual tends to perform a behaviour because they have a tendency to perform the behaviour,*') and lack explanatory value. In contrast, definitions that conceptualise habit as a form of automaticity avoid this by identifying habit as a cognitive mechanism independent of behaviour (Gardner, 2015). However, these definitions are also flawed; such reasoning implies that a behavioural response is an inevitable outcome of encounters with associated cues; whereas empirical evidence has demonstrated that habits can be inhibited given sufficient willpower and self-regulatory resources (Neal, Wood, & Drolet, 2013).

A more useful and logically sound definition of habit has been proposed by Gardner (2015), which views habit as "*a process by which a stimulus automatically generates an impulse towards action, based on learned stimulus-response associations*" (pp. 280; see also West & Brown, 2013). This conceptualisation of habit is novel in two respects. First, it characterises habit as a process by which action is cued, which minimises conceptual issues that arise from portraying habit as behaviour, automaticity or any other distinct component of the wider process. It also incorporates the cue-dependence, automaticity and conditioned stimulus-response associations that characterise and distinguish habitual action from other forms of automatic behaviour (Gardner et al., 2012; Lally et al., 2010; Orbell & Verplanken, 2010; Wood & Neal, 2009). Second, depicting the 'response' to habit cues as an impulse (i.e., high-level schematic representations of action which, if insufficiently opposed, trigger execution of action; e.g., Michie & West, 2013) allows for the possibility that habitual tendencies may, once activated, be overridden prior to translation into action.

The role of habit in long-term medication adherence. Focusing exclusively on health beliefs and other behaviour-initiation factors, such as those described in the CSM, is

suboptimal for assessing long-term medication adherence: because (1) the mechanisms of behavioural repetition are likely to differ from those of behaviour initiation (Rothman, 2000), and (2) beliefs and intentions have been demonstrated to be more predictive of behaviour in the short-term than in the long-term (Sheeran, 2002; Verplanken, 2006). Habit theory may help to bridge the gap between beliefs and long-term behaviour maintenance. Habits are theoretically important for long-term adherence; they do not tax cognitive and self-regulatory resources, are not subject to tempting behavioural alternatives, and are the default behaviour (Danner, Aarts, & de Vries, 2008). For patients to be adherent to long-term treatment, they need to develop automatic routines, or habits, for the required behaviour. Habit development can free up cognitive capacity to address new and changing health-related circumstances and tasks. Repeated, long-term tasks, such as taking medication for a chronic condition, are most efficiently and economically delegated to routines that do not require attention. In the long-term, if a behaviour is habitual, beliefs and intentions formed through conscious decision-making lose predictive power of the behaviour (Honkanen, Olsen, & Verplanken, 2005; Sheeran, 2002).

Habits are triggered automatically and by everyday environmental cues (Wood & Neal, 2007). The theoretical importance of habits for adherence behaviours has been acknowledged (Reach, 2004), but the focus of habit research has been on the early stages of habit development – both its mechanisms and interventions to automate behaviour with contextual cues (Gollwitzer, 1999; H. Leventhal, 1970). Despite its utility for adherence, habit theory has not been applied to the same extent to the assessment of existing, or long-term, adherence routines. Instead, habit strength is primarily tested as a moderator of the relationship between behavioural intentions and adherence behaviour (Phillips, 2011; Sheeran, 2002).

Integrating the CSM and Habit Theory to Predict Long-Term Adherence

Unlike many other health belief models, the CSM is not limited to beliefs at only the initial phases of treatment-behaviour development (e.g., Halm, Mora, & Leventhal, 2006). Despite this, beliefs at behaviour initiation have been the primary focus of existing research on the CSM (Phillips, 2011). Furthermore, given that focusing only on health beliefs and other behaviour-initiation factors is suboptimal for the assessment of long-term adherence for reasons described above, recent work has endeavoured to extend theories of health beliefs to include additional theoretical constructs that are relevant for behaviour development beyond the initiation phase. Phillips et al. (2011; 2016; 2013) theorise that (1) CSM ‘coherence’ (i.e.,

a certainty in one's beliefs regarding the illness and treatment resulting from direct, personal experience that the treatment does what it is supposed/expected to do) and (2) habit strength both add considerably to prediction of long-term adherence behaviour development after patients' health beliefs are taken into account.

While the majority of empirical research guided by the CSM has focused on beliefs, the theoretical framework involves processes that go beyond specific beliefs. The CSM posits that patients form cognitive representation of the illness and its treatment, respond to address the health threat (i.e., cognitively, behaviourally, or both), evaluate feedback from their response, and integrate that feedback into their cognitive representation (beliefs) of the illness and treatment. If performing the treatment provides the patient with evidence that the treatment is working, and thereby also confirms the individual's treatment-favourable beliefs, then the individual's CSM becomes 'coherent.' This is similar to the processes posited in social cognitive learning theory (Bandura, 1977) in that carrying out the treatment behaviour is motivated by its consequence (e.g., receipt of reward or punishment). If the behaviour is rewarded (e.g., symptoms are alleviated, BP is reduced, etc.), then they are theoretically motivated to repeat that behaviour. However, Phillips (2011) posits that experiential feedback from behavioural performance will not only motivate behavioural repetition, but also functions to "cohere" the individual's cognitive representation of the illness and treatment, which may in turn motivate multiple health behaviours, not just the behaviour that was tested. Research on symptom interpretation (e.g., Cameron et al., 2005; Gonzalez et al., 2007) provides empirical support for this hypothesis. Symptoms can function as evidence for or against the efficacy of treatment and/or illness representations, and this evidence predicts treatment adherence (Siegel, Schrimshaw, & Dean, 1999; Leventhal & Prohaska, 1986). In sum, coherence regards the action(s) a person takes to address an illness and how the usefulness of that action is either supported or negated by its outcome.

In order for a patient to engage in a potentially life-long treatment behaviour for a chronic condition, that patient needs to develop automatic routines/habits for that behaviour. The value of behaviour routinisation for freeing up the mental capacity to address novel and challenging circumstances, as discussed above, has long been recognised (Verplanken, 2006). Behaviours and tasks that are repeated in the long-term are most efficiently and economically delegated to automatic routines that do not require attention. In the long-term, if a behaviour becomes habitual, beliefs and conscious intentions lose predictive power of the behaviour

(Honkanen, Olsen, & Verplanken, 2005; Sheeran, 2002). Despite this, there has been limited integration of habit theory into the assessment of existing adherence routines (Phillips, 2011).

A key aim of this thesis is to replicate and extend the work of Phillips and colleagues (2013; 2016), which integrates habit theory and common-sense self-regulation theory to improve medication adherence assessment. This general theoretical framework of long-term behaviour development places these constructs (i.e., health beliefs, coherence, and habit strength) into a timeline, or progression, of habit development. According to this framework, once an individual becomes aware of a health threat, they will engage in a *belief formation* process; when they have an idea of what treatment may work to address the health threat, they will then test the treatment in a the *behavioural testing* process; feedback from the treatment behaviour will provide evidence as to the veracity of the health beliefs, which, if favourable, will result in coherence, thereby increasing the likelihood that the individual will repeat the behaviour; finally, *behavioural repetition* over time is theorised to occur, leading to behaviour routinisation and maintenance of long-term adherence behaviour. Using this proposed theoretical framework, Phillips et al. (2013) found that habit strength was the strongest predictor of objective and self-reported medication adherence, and more recently attempted to extend the CSM to include automatic behavioural repetition, or habit strength, as a treatment adherence factor (Phillips, Cohen, Burns, Abrams, & Renninger, 2016). When testing this extended model (see Figure 1.2), they found that medication and physical activity adherence were better predicted by automatic behavioural repetition than illness- or treatment-related beliefs and/or experiences among patients with Type II diabetes mellitus (Phillips et al., 2016). This extended model may be particularly useful for examining medication adherence for patients with aTRH. Therefore, the work presented in this thesis will attempt to replicate and extend Phillips' work in at least three important ways, including the following:

1. The proposed work will test the relationships between these variables in a new condition (i.e., resistant hypertension);
2. The studies will use multiple subjective and objective methods of assessing medication adherence in testing these relationships;
3. The studies will use multiple methodological approaches to understand non-adherence in aTRH.

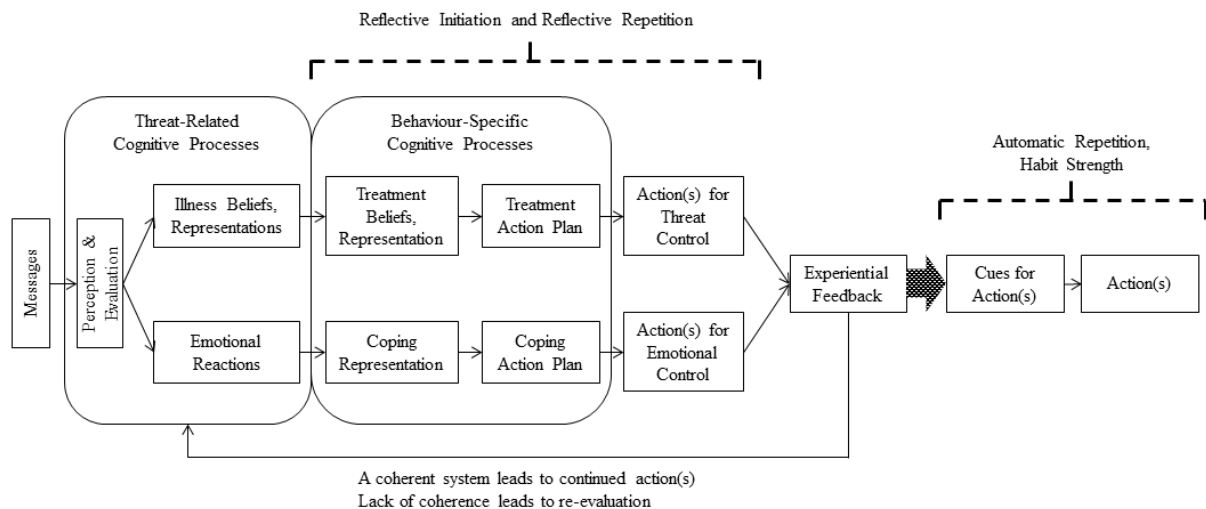


Figure 1.2. The CSM extended to include behavioural habit strength as an adherence factor important for long-term maintenance of treatment-related behaviour. Adapted from Phillips et al. (2016).

The Primary Care Context

The current research takes place within the context of an Irish primary care system. This has important implications for the research. Non-adherence to medications for the management of chronic conditions is a widespread problem in primary care. The annual cost of medicine wastage in primary care in the United Kingdom is estimated to be £300 million (€333 million), with £100–150 million (€111–166.50 million) identified as avoidable (Trueman et al., 2010). The same report also concluded that annual savings of over £100 million (€111 million) could be achieved if 80% of patients with hypertension were adherent to treatment.

General practitioners (GPs) are in a unique position to promote good adherence among their patients. Having the opportunity to get to know the patient as a person allows the physician to understand elements that are crucial to the patient's adherence (e.g., beliefs, attitudes, subjective norms, socio-cultural context, social supports, and emotional health challenges, particularly depression; Martin et al., 2005). Furthermore, where adherence data is available at the point of care, GPs have important unique opportunities for intervention before escalation of therapy and/or referral for specialist treatment. Indeed, a meta-analysis of the impact of different strategies to improve adherence and BP control found that collaboration with healthcare partners has the greatest impact (Glynn, Murphy, Smith, Schroeder, & Fahey, 2010).

Despite the potential opportunities to support adherence in primary care, non-adherence is not always effectively assessed. Operating under considerable time and financial pressures in busy primary care settings may preclude adequate adherence assessment. The difficulty of accurately assessing adherence in clinical practice is highlighted by Meddings et al. (2012); in their study, primary care providers recognised non-adherence for less than half of those patients who had significant gaps in their refill history. Additionally, patients' social desirability biases may prevent them from openly discussing adherence issues with their physicians. This highlights the need for adherence assessment methods that are both accurate and clinically valid.

Rationale

Just as the extent of resistant hypertension is unknown, so too is the proportion of aTRH cases that may be due to non-adherence to medication. The personal, social and economic consequences of this are considerable. Patients inappropriately classed as having resistant hypertension due to non-adherence are at elevated risk of cardio- and cerebrovascular events and may be unnecessarily referred for costly and invasive specialist treatment, leading to undue financial pressure on the healthcare system as well as causing patients and their families unnecessary emotional distress. Understanding the extent of the problem of non-adherence is essential to improve the effectiveness of antihypertensive medications and improve health outcomes. Using a systematic and statistically rigorous approach to synthesise the existing literature examining medication non-adherence for aTRH will contribute towards this goal.

Predictors of antihypertensive medication adherence have been extensively examined within the literature. However, these have not been examined specifically for patients with aTRH, whose condition is accompanied by unique specific barriers to adequate adherence. Using well-established theoretical frameworks to inform investigation of patient-level predictors of non-adherence for this population is necessary to provide a foundation of evidence upon which to build evidence-based behavioural interventions to improve adherence. Furthermore, basing this investigation in primary care will provide important insight into ways of improving adherence before unnecessary referral to specialist hypertension clinics.

Clinical decisions and research programmes depend on the reliable and valid measurement of adherence. Experts in the field of adherence research have called for more

thoughtful research on adherence (Bowen, Helmes, & Lease, 2001; DiMatteo, 2004b) with greater consideration of the methodological limitations that have impeded previous research, and more purposeful focused attention to the complex multiple measurement strategies that are necessary to address the reliability and validity limitations of adherence measurement. This research aims to use three diverse adherence measurement methods (i.e., self-report, prescription refill data, and biochemical urine analysis) to complement the strengths and weaknesses of each, ultimately producing a more useful and comprehensive estimate of non-adherence for this sample.

Quantitative methods provide essential information regarding the extent and precipitating factors of non-adherence behaviour. Despite the striking increase in research attention resistant hypertension has received in recent years, there has been no qualitative investigation among this group. Qualitative methods have the potential to help us better understand the complexities of adherence behaviour for patients whose health conditions necessitate multiple daily medications. This research will provide the first qualitative investigation into adherence behaviour for aTRH in primary care.

This research aims to fill these gaps in the research regarding medication adherence in aTRH by (1) systematically and statistically synthesising existing literature to estimate the extent and study-level predictors of non-adherence; (2) quantitatively assessing patient-level predictors of non-adherence for patients with aTRH in primary care; and (3) qualitatively investigating factors associated with good and poor adherence for this group.

Overall Aim

The overall aim of this research was to examine the extent, potential psychological determinants and patient perspectives of medication non-adherence for aTRH. The research questions and publications that arose for each study conducted in this research are outlined below.

Research Questions and Thesis Outline

- Study 1: What are the extent and study-level predictors of medication non-adherence for aTRH? (Paper 1)
 - **Durand, H.**, Hayes, P., Morrissey, E. C., Newell, J., Casey, M., Murphy, A. W., & Molloy, G. J. (2017). Medication adherence among patients with apparent treatment-resistant hypertension: Systematic review and meta-

analysis. *Journal of Hypertension*, 35(12), 2346-2357.

<https://doi.org/10.1097/HJH.0000000000001502>

- Study 2: What are the patient-level predictors of medication non-adherence for aTRH? (Paper 2)
 - **Durand, H.**, Hayes, P., Harhen, B., Conneely, A., Finn, D. P., Casey, M., Murphy, A. W., & Molloy, G. J. (2018). Medication adherence for resistant hypertension: Assessing theoretical predictors of adherence using direct and indirect adherence measures. *British Journal of Health Psychology*, 23(4), 949-966. <https://doi.org/10.1111/bjhp.12332>
- Study 3: What are the factors associated with good and poor adherence among patients with aTRH in primary care? (Paper 3)
 - **Durand, H.**, Casey, M., Glynn, L. G., Hayes, P., Murphy, A. W., & Molloy, G. J. (under review). A qualitative comparison of high and low adherers with apparent treatment-resistant hypertension. *Psychology, Health & Medicine*.

The methodology used to conduct this research is outlined in detail in the next chapter. A general discussion of the findings of the three studies, the limitations of the studies, and implications for future research and practice are presented in the final chapter of this thesis.

2. Methodology

Chapter Overview

The aim of this chapter is to outline the methodologies employed in this research. The aims of each individual study within the research will be presented. A description of the methods used to address the aim of each study will be provided with a discussion of the background and justification for their use. Finally, the ethical issues associated with this research will be addressed.

Aims and Objectives of This Research

The primary aim of this research was to examine the extent, potential predictors and patient perspectives of medication non-adherence for patients with aTRH in primary care. A secondary aim of this work was to provide a basis for the development of future interventions to address non-adherence in this population. Quantitative and qualitative methods were used to synthesise the existing literature, compare multiple adherence measures, test a predictive model of adherence, and qualitatively explore patient perspectives on adherence.

Approach to This Research

Three studies were carried out to address the aims of this research: Study 1, a systematic review and meta-analysis; Study 2, a quantitative cross-sectional study; and Study 3, a qualitative comparison of high and low adherers. Involving both quantitative and qualitative methodologies within the one programme of research is increasingly seen in health research (Dures, Rumsey, Morris, & Gleeson, 2010; Yardley & Bishop, 2015). The use of multiple methods in social and health science research has several advantages, for example, the capacity to answer complex research questions that single designs cannot adequately address; the ability to offset the weaknesses of either quantitative and qualitative methods alone; the chance to obtain a more complete and comprehensive understanding of the research problem; the ability to draw stronger inferences from research findings; and the opportunity to present a greater diversity of views within the research (Tashakkori & Creswell, 2007; Teddlie & Tashakkori, 2003). Quantitative and qualitative methods have traditionally been utilised separately, given the enduring belief that their underpinning epistemologies (i.e., the positivist epistemological perspective associated with quantitative methods, and the constructivist perspective associated with qualitative methods) are incompatible and their findings incomparable (Burke Johnson & Onwuegbuzie, 2004). The epistemology of pragmatism offers an alternative philosophical view that qualitative and

quantitative methods are distinct but commensurate; both methods are means of knowledge production that derive their value from the match between the method and the goals of the study (Burke Johnson & Onwuegbuzie, 2004; Cornish & Gillespie, 2009; Creswell & Plano Clark, 2007; Yardley & Bishop, 2015). At a practical level, pragmatism can be understood as choosing the most appropriate method for the research aim (Yardley & Bishop, 2015). By approaching the current research through the lens of pragmatism, the integrity of both quantitative and qualitative approaches is maintained while the quality and reliability of the research and its findings are ensured (Morse, 2003; Yardley, 2001).

Using multiple methods in this research addressed the limitations of the existing literature examining medication adherence for aTRH, particularly the lack of relevant research examining the extent, predictors, and patient perspectives of adherence behaviour for this group. Given the breadth of this enquiry, the use of both quantitative and qualitative methods underpinned by the philosophy of pragmatism was considered the most appropriate approach for this research. Within this research, Study 1 consisted of a systematic review and quantitative meta-analysis to examine the extent of medication non-adherence among patients with aTRH, as well as study-level predictors of non-adherence estimates in the existing literature. In Study 2, patient-level predictors of non-adherence were examined using a quantitative cross-sectional survey methodology guided by established psychological theory. Direct and indirect, objective and subjective measures of non-adherence were used. Finally, Study 3, a qualitative study informed by findings from Studies 1 and 2, was conducted to provide a more in-depth understanding of the quantitative findings and to explore patient perspectives on adhering to antihypertensive medications.

Study 1 – What is the Extent of Non-Adherence for aTRH?

Aims and objectives of Study 1. The aim of study 1 was to quantify the prevalence of medication non-adherence for aTRH in the existing literature and to statistically determine which study-level characteristics predict non-adherence estimates. The extent of medication non-adherence for aTRH was hitherto unknown; therefore, a systematic review and meta-analysis was conducted in Study 1.

Approach to Study 1. An explicit and systematic process was used in this study to obtain all relevant peer-reviewed published literature, to appraise the quality of the literature, and to produce a comprehensive and statistically robust estimate of the prevalence of medication non-adherence and its study-level predictors (A. X. Garg, Hackam, & Tonelli,

2008). A brief narrative synthesis was used to describe the overall state of the literature, and random effects meta-analysis was used to quantitatively analyse the data extracted from the studies included in the systematic review.

Procedure.

Search strategy. Electronic databases, PsycINFO, PubMed, Embase, Web of Science and CINAHL, were searched from database start to December 2015. These databases were selected as they were relevant to the topic of this review and commonly used in similar reviews. The search terms were selected based on a scoping search. Potential search terms, such as ‘refractory hypertension,’ were selected from relevant studies and their utility for returning studies related to the research question was tested to refine the search strategy. The candidate and the supervisory team agreed on the final search string to be used for the review. The following search string was ultimately used: ‘medication’ AND (‘adheren*’ OR ‘nonadheren*’ OR ‘non-adheren*’ OR ‘compliant*’ OR ‘noncompliant*’ OR ‘non-compliant*’) AND (‘resistant’ OR ‘uncontrolled’) AND ‘hypertension.’

Study selection. Studies published in English were included if they reported original research and if their study population consisted of patients with aTRH. Prevalence of medication non-adherence had to be reported as an outcome. Studies were excluded if they did not use an acceptable definition of resistant hypertension (i.e., less stringent than the accepted definition of uncontrolled BP despite concurrent treatment using three or more antihypertensive agents), were review or expert opinion articles, case studies, or contained secondary analyses on data already included in the review. Studies that utilised general hypertensive samples from which information relating to patients with aTRH could not be extrapolated were also excluded. Where dual or duplicate publication was identified, the paper with the most completely reported data was included. Intervention studies with appropriately reported baseline adherence data were also included.

All studies identified were transferred to an EndNote® database to be assessed for inclusion by two independent reviewers. Following the removal of duplicates, studies were excluded in step 1 if there was evidence in the title and/or abstract that they were not relevant. Full texts were read in step 2 to produce the final group of studies to be included in the review. In the case of disagreement between the two independent reviewers, a third reviewer with relevant expertise (i.e., methodological or clinical expertise required to make an informed decision) acted as an adjudicator. Authors were contacted when articles could not

be accessed in full text online. In all such cases, full-text articles were either provided by the authors or accessed via an Inter-Library Loan system.

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement guided the reporting of the inclusion and exclusion of studies in this systematic review. The PRISMA checklist and flowchart, presented in paper 1 (p. 59) of this thesis, facilitated transparency surrounding the decision-making processes in this study (Moher, Liberati, Tetzlaff, Altman, & The PRISMA Group, 2009).

Data extraction. A preliminary synthesis was conducted by tabulating the relevant data into a comprehensive data extraction table. The following data were extracted: author, publication year, country of publication, study setting, design, sample size, definition of resistant hypertension, number of medications, definition of non-adherence, proportion of non-adherent patients and factors associated with non-adherence, if reported. In studies where two separate assessments of adherence were used (e.g. de Souza et al., 2009), the proportion of non-adherent patients according to each individual measure was extracted; for the meta-analyses of adherence, an average of the individual adherence scores in each of these studies was used. The data extraction table is presented in paper 1 (pp. 60-70) of this thesis.

Quality and risk of bias assessment. The quality of the studies in this review was assessed to avoid or minimise the impact of a study that was not rigorously conducted on the findings and conclusions of this review (Hróbjartsson, Boutron, Turner, Altman, & Moher, 2013). Quality of each study in this review depended on whether its design, conduct, analysis and presentation were appropriate to answer the research question (Higgins et al., 2011).

Given the diversity of study designs included in this review, an assessment of the quality of studies was conducted with reference to criteria outlined by Sanderson, Tatt and Higgins (2011) in their review of quality and risk of bias assessment tools for observational studies. The summary results of the quality assessment are presented in paper 1 (p. 72) of this thesis, with detailed results presented in Appendix A. The findings of the quality assessment did not result in studies being excluded. The methodological limitations identified were deemed unlikely to have a significant impact on the outcome of interest for the review (i.e., the prevalence of non-adherence); as such, the role of each study in answering the research question was prioritised over the methodological issues identified (Gough, 2007; Hannes, 2011; Higgins et al., 2011).

Data synthesis. First, a brief narrative synthesis was used to describe the overall state of the literature. In particular, aspects of the literature that may influence interpretation of the study outcome were described. These included both clinical and methodological aspects of the studies.

Non-adherence estimates from each study were synthesised using a random-effects model. Random-effects meta-analysis was chosen for its ability to take into account the presence of unexplained heterogeneity between studies included in the meta-analysis (Borenstein, Hedges, Higgins, & Rothstein, 2009; Higgins, Thompson, & Spiegelhalter, 2009). A leave-one-out sensitivity analysis was conducted by iteratively removing one study at a time to ensure the findings were not driven by a single study. Subgroup analyses were conducted to detect moderator variables where evidence suggested a potential effect on non-adherence estimates. Further sensitivity analyses were conducted by (1) leaving out subgroups of studies that used adherence measures that may have been considered less reliable, and (2) leaving out subgroups with two or fewer studies.

Study 2 – What Predicts Non-Adherence for aTRH?

Aims and objectives of Study 2. The primary aim of Study 2 was to test the predictive value of the CSM extended to include coherence of beliefs from experience with treatment, medication-taking habit strength, and antihypertensive pill burden for long-term medication adherence for aTRH. Study 2 also evaluated the congruence between unique adherence measures; specifically, prescription refill records, self-report using empirically validated scales, and biochemical assay of urine using high-performance liquid chromatography coupled to mass spectrometry (HPLC-MS/MS).

Approach to Study 2. This study used a cross-sectional observational design to (1) assess associations among three unique adherence measures, (2) to examine the predictive value of treatment-related beliefs, coherence of beliefs, and habit strength, as specified in the CSM, for long-term medication adherence, and (3) examine the moderating role of pill burden on the relationship between habit strength and adherence.

Study 2 Hypotheses. In their original study, Phillips et al. (2013) tested three *a priori* hypotheses in a sample of patients with hypertension. Two of these related to adherence behaviour in general, and one specifically regarded intentional versus unintentional non-adherence. The current study examined these three hypotheses among a sample of patients

with aTRH, and an additional fourth hypothesis regarding the role of pill burden. The four hypotheses tested in this study are as follows:

Hypothesis 1 (H1): habit strength and CSM coherence will each account for incremental variance in patient adherence to that accounted for by patients' treatment-related beliefs, with habit strength accounting for the greatest amount of unique variance.

Hypothesis 2 (H2): patients' treatment-related beliefs and medication-taking habit strength will interact such that beliefs will predict adherence only for patients with weaker habits.

Hypothesis 3 (H3): habit strength will be more strongly related to unintentional non-adherence than to intentional non-adherence; conversely, CSM coherence and treatment-related beliefs will be more strongly associated with intentional non-adherence than with unintentional non-adherence.

Hypothesis 4 (H4): habit strength will be more strongly related to patient adherence for patients who are prescribed fewer medications.

Measures. The questionnaire tool (Appendix E) used in this study was designed to assess components of the CSM (i.e., treatment-related beliefs), coherence of CSM beliefs, habit strength, and medication adherence. Participants completed a battery of psychometric measures, wore an ABPM to measure their BP over a 24-hour period, and provided a urine sample to assess adherence. Additional clinical and demographic variables, including prescription refill records, were drawn from patient's medical records as specified in P. Hayes et al. (2018). Details of the individual measures used in Study 2 and the rationale for their selection are summarised below.

Adherence measures. The primary outcome in this study was adherence to antihypertensive medication, assessed using three types of adherence measurement: self-report using empirically validated psychometric scales; prescription refill records; and biochemical analysis of urine using HPLC-MS/MS. The choice of measures was based on a review of approaches used in previous literature (see results of Study 1). These individual measures were then statistically compiled to create a single composite measure of adherence. Details of each individual measure and the composite measure are described below.

Self-reports of adherence. Self-report measures have the unique advantage of being able to assess reasons for non-adherence, for example, unintentional non-adherence due to prospective memory failure, or intentional non-adherence due to negative beliefs about medications. Two scales were used to assess patients' self-reports of adherence: the Morisky Medication Adherence Scale (MMAS; Morisky, Ang, Krousel-Wood, & Ward, 2008) and the Medication Adherence Report Scale (MARS; Horne, 2004). The MMAS (Morisky et al., 2008) is an eight-item measure with seven yes/no items and with answer options ranging from 'always' to 'never' on a five-point scale. The MMAS has been extensively validated (Krousel-Wood et al., 2009; Morisky & DiMatteo, 2011). Conventional scoring was used to create a composite variable of the 8 MMAS items, with higher scores indicating better adherence. Internal consistency for the MMAS was .62 for the current sample. The MMAS was used with permission from its developer. The MARS (Horne, 2004) is a five-item measure with answer options ranging from 'always' to 'never' on a five-point scale, where higher scores indicated better adherence. Internal consistency for the MARS was .77 for the current sample.

Prescription refill records. Prescription refill records are advantageous due to the relative simplicity of assessing adherence for large samples over an extended period of time. Although it is a crude measure of actual adherence behaviour, with regard to those who do not collect prescriptions, one can be relatively certain that medications have *not* been taken. Prescription refill records were available for patients on the General Medical Services (GMS) scheme (a means-tested scheme providing free healthcare services and medication cover for eligible individuals in Ireland, e.g. those aged ≥ 70 years or on a reduced income) via Socrates[®] practice management software. A majority of patients were in receipt of quarterly scripts (i.e., prescriptions for medications to cover a three-month period) as opposed to monthly scripts, thus precluding the use of the typical $< 80\%$ cut-off for non-adherence (Karve et al., 2009). Therefore, using this measure, patients were considered adherent if they had collected $\geq 75\%$ of their printed scripts from the practice over the last 12 months (i.e., three quarterly scripts/nine monthly scripts).

Biochemical analysis of urine using HPLC-MS/MS. HPLC-MS/MS is an analytical chemistry technique that combines the physical separation capabilities of high-performance liquid chromatography (HPLC) with the mass analysis capabilities of mass spectrometry, thereby synergistically enhancing the individual capabilities of each technique (Niessen, 2006). HPLC-MS/MS provides a highly sensitive and specific detection of commonly-

prescribed antihypertensive medications (or their metabolites) in bodily fluids. Given its relative simplicity and low cost, as well as the objective nature of the analysis, it is a potentially useful diagnostic test for patients with apparent resistance to BP lowering treatment (P. Gupta et al., 2017; Patel et al., 2016). Procedural details of the HPLC-MS/MS are published as supplementary material to paper 2 and provided in Appendix F of this thesis.

Adherence composite. As each adherence measure has established construct validity but is also subject to varying kinds of measurement biases (Osterberg & Blaschke, 2005), a unit-weighted composite adherence score was calculated by standardising and summing scores from each individual adherence measure (Bobko, Roth, & Buster, 2007). Each component measure (i.e., self-report, prescription refill records, and bioassay) was given equal weight in calculating the composite adherence measure, given that the measures are theoretically related and each has its own valid strengths and limitations. All adherence values were standardised and analysis of internal consistency was carried out to establish that individual adherence items were sufficiently related to form a composite score. All individual measures were positively correlated and Cronbach's α remained stable when each item was iteratively removed, suggesting that all adherence measures could be reliably included in a composite measure. The scores for each component measure were converted to *Z*-scores and the sum of the standardised scores was calculated to produce a unit-weighted composite score. Internal consistency for the adherence composite was .76.

Adherence versus non-adherence. Patients were categorised as adherent or non-adherent for descriptive purposes using each of the measures described above. Using prescription refill records, patients were classed as non-adherent if they had collected less than 75% of their prescriptions from the GP clinic over the previous 12 months. For the urine assay measure, patients were classified as non-adherent if one or more of their prescribed (detectable) antihypertensive medications were not detected in their urine. The standard cut-off of six on the MMAS was used to denote non-adherence; this score has been utilised in previous research (e.g., Moran et al., 2017), and has established sensitivity and specificity for identifying poor adherers (Morisky et al., 2008). With regard to the MARS, an accepted cut-off score to denote non-adherence has not been established, as the MARS is more typically used to produce a continuous score representing the spectrum of adherence behaviour. In this instance, Receiver Operating Characteristic (ROC) analysis was employed to determine the most appropriate cut-off point for this measure. ROC analysis illustrates the diagnostic ability of a binary classifier system as its discrimination threshold is varied (Hanley & McNeil,

1982). Results revealed that 23 was the most appropriate cut-off to optimise sensitivity and specificity of the MARS to determine non-adherence for this sample. Inferential analyses (described below) were conducted using continuous adherence scores derived from the composite measure, the urine assay adherence ratio, and both self-report measures, and dichotomous adherence scores derived from the prescription refill records.

Treatment-related beliefs. Treatment-related beliefs were assessed using a combination of empirically validated self-report measures: the Illness Perceptions Questionnaire–Revised (IPQ–R) treatment control items (Moss-Morris et al., 2002); and the Beliefs about Medicines Questionnaire (BMQ; Horne et al., 1999). A composite variable (average) of treatment-specific health beliefs was used, consisting of the IPQ scale items, the BMQ Specific Necessity scale items, and reverse-scored BMQ Specific Concern scale items. This approach to measuring treatment-related beliefs is consistent with Phillips et al. (2013), wherein items were selected for their theoretical alignment with the core constructs and processes specified in the CSM. The IPQ–R and the BMQ are described in detail below.

IPQ–R treatment control items. The IPQ–R comprises five scales assessing the five dimensions underlying patients’ models of illness (H. Leventhal & Nerenz, 1985). For the purposes of this study, only the treatment control items were used. Beliefs about the extent to which hypertension can be controlled or cured were assessed using a 5-item 5-point Likert-type scale, ranging from strongly disagree to strongly agree. Total scores ranged from 5 to 25, with higher scores indicating stronger beliefs that the illness can be controlled or cured. Examples of items are ‘*My medication can control my hypertension*’ and ‘*There is very little that can be done to improve my hypertension*’. Internal consistency of the IPQ–R treatment control items is .80 (Moss-Morris et al., 2002); in the current study, internal consistency was .71.

BMQ. The BMQ comprises two scales: one assessing patients’ beliefs about the necessity of their medication for controlling their illness, and the other assessing concerns about potential adverse consequences of using it. Each scale has five core items assessing beliefs that have been shown to be common across a range of chronic illness groups. Examples of items from the necessity scale are ‘*My health, at present, depends on this medicine*’ and ‘*This medicine protects me from becoming worse*’. Examples of items from the concerns scale are ‘*I sometimes worry about the long-term effects of this medicine*’ and ‘*I sometimes worry about becoming too dependent on this medicine*’. Respondents indicate their

degree of agreement with each individual statement about medicines on a 5-point Likert-type scale (ranging from 1 – strongly disagree to 5 – strongly agree). Scores obtained for the individual items within each scale are summed to give a scale score. Scores on the BMQ Specific Necessity subscale represent how necessary patients believe their hypertension medication is for their health, with higher scores indicating a greater necessity. Scores on the BMQ Specific Concerns subscale represent how concerned patients are about their hypertension medication, with higher scores indicating greater concern. Cronbach’s alpha values range from .55–.86 and .63–.80 for the BMQ Specific Necessity and Concerns subscales, respectively. In the current study, Cronbach’s alpha values were .81 for the Necessity subscale and .70 for the Concerns subscale.

Composite beliefs measure. As per Phillips et al. (2013), a composite variable (average) of treatment-specific health beliefs was used, consisting of the IPQ–R treatment control beliefs items, the BMQ Specific Necessity scale items, and the reverse-scored BMQ Specific Concern scale items. This is a relatively novel approach that has undergone limited psychometric evaluation. As such, results regarding treatment-related beliefs as measured using this approach should be interpreted with caution until extensive formal validation has been conducted. That said, the composite variable used is both theoretically and empirically supported for the following reasons: first, both sets of items derive from the CSM and regard specifically conscious, treatment-related beliefs; and second, analysis of internal consistency indicated acceptable reliability of the composite measure ($\alpha = .67$), suggesting that these items measure the same latent construct. In order to ensure that using a composite treatment-related beliefs measure did not have a detrimental impact on the analyses, sensitivity analysis was conducted using each of the IPQ–R subscale total and the BMQ Specific Necessity and Concerns totals as independent predictor variables. This analysis indicated that results were similar for both approaches; therefore, the approach taken by Phillips et al. (2013) was retained.

CSM-coherence. CSM-coherence is not to be confused with the coherence construct measured by the IPQ–R, which is more simply a measure of general understanding of illness. An individual may have abstract knowledge of their illness without ever having experienced the veracity of their beliefs by receiving experiential evidence that the treatment works as it is expected to do and/or that they are capable of performing the treatment (experiential and procedural knowledge). Research suggests that symptoms can provide evidence for or against the efficacy of treatment and/or illness representations, and this evidence predicts treatment

adherence (i.e., symptom experience predicts non-adherence if interpreted as evidence that the treatment is not working; E. A. Leventhal & Prohaska, 1986; Siegel et al., 1999). The construct of CSM-coherence regards the actions a person takes to address an illness threat and how the usefulness of those actions is either supported or negated by their outcomes, which may include symptom-related evidence. Therefore, symptom interpretation is viewed as a sub-construct of CSM coherence, which has not yet been used in measures for adherence prediction. CSM-coherence was assessed in the current study using two survey items: ‘*Have you noticed the positive benefits of the hypertension medicine? Yes/No*’, and ‘*Have you experienced any solid (convincing) evidence that the hypertension medication does what it is supposed to do? No evidence/Some evidence/Solid evidence*’ (Phillips et al., 2013). These items were standardised and averaged to make a composite score for CSM-coherence, with higher scores indicating more coherent CSM beliefs. Internal consistency for the survey items is .63 (Phillips et al., 2013); for the current sample, internal consistency was .61

Habit strength. Medication-taking habit strength was assessed using the Self-Report Behavioural Automaticity Index (SR-BAI; Gardner, Abraham, Lally, & de Bruijn, 2012). The SR-BAI consists of four items drawn from the Self-Report Habit Index (Verplanken & Orbell, 2003) that were most confidently and consistently judged to capture behavioural automaticity. The SR-BAI has been demonstrated to be a reliable, valid and parsimonious self-report measure of habit (Gardner et al., 2012). Items are rated on a seven-point response scale ranging from ‘strongly disagree’ (=1) to ‘strongly agree’ (=7), with higher scores indicating stronger medication-taking habits. Internal consistency for the SR-BAI is .68–.89 (Gardner et al., 2012); for the current sample, internal consistency was .87.

Sample size. The sample size in this study was determined based on power analysis carried out using G*Power software (Faul, Erdfelder, Lang & Buchner, 2007; Faul, Erdfelder, Buchner, & Lang, 2009). Sample size calculations indicated that to carry out a hierarchical multiple regression to detect a medium ($f^2 = .15$) and small effect ($f^2 = .10$), with an alpha level of .05, 95% power and 3 predictor variables, would require minimum samples of 125 and 186 participants, respectively. A total sample of 204 participants was achieved for Study 2, ensuring the study was adequately powered to detect small effects.

Participants. A purposive clinic-based recruitment strategy was used. GP clinics from the University-affiliated research network WestREN (Western Research and Education Network; Kavanagh, O'Brien, Glynn, Vellinga, & Murphy, 2010) were first invited to

participate. Patient records from participating practices were then screened for the internationally accepted criteria for aTRH. Patients meeting these criteria (i.e., patients who were prescribed three or more antihypertensive medications for a period of at least three months who did not have a 24-hour ABPM recording on file or whose ABPM recording was indicative of uncontrolled BP, and patients who were prescribed four or more antihypertensive medications for a period of at least three months regardless of their recorded BP control status) were invited by postal letter to participate in the study. The invitation to participate is provided in Appendix C.

Procedure. The questionnaire tool was pilot tested with two members of the Health Research Board Primary Care Clinical Trials Network Ireland (HRB PC CTNI) Public and Patient Partnership in Research (PPP-R) group and changes were made based on their feedback. The feedback related to the length of the questionnaire and the clarity of response options for certain items. All participants in Study 2 were provided with detailed study information and completed consent forms (Appendices C and D). The questionnaires took approximately 30 minutes to complete. Ethical approval for this study was obtained from the Galway University Hospitals Clinical Research Ethics Committee at Merlin Park University Hospital.

Data screening.

Outliers and normality. Data were screened for univariate and multivariate normality. No extreme univariate outliers were identified in initial data screening. The test for Mahalanobis Distance (D^2 ; Field, 2009) indicated no multivariate outliers (i.e., cases with unusual combinations of values on more than one variable, such as extreme low and high values).

Missing data. Some missing data were observed in the dataset. Little's Missing Completely at Random (MCAR) Test (Little, 1988) was used to determine whether the data were MCAR (i.e., missing independently of other variables observed in the dataset; Scheffer, 2002). Little's Test was significant ($p < .001$); therefore, data were found to be not MCAR. Post-hoc chi-square tests and t -tests indicated that although there was a systematic relationship between the propensity of missing values and the *observed* data, no such relationship existed for the *missing* data; that is missingness on variable X was related to other measured variables in the dataset, but unrelated to the underlying values of X (Peugh & Enders, 2004). Therefore, data were tentatively deemed Missing at Random (MAR) as

opposed to Missing Not at Random (MNAR). Given that data were found to be MAR, and the percentage of missing data was less than 30% (Owen et al., 2007; Peugh & Enders, 2004), Expectation Maximisation (EM) methods were used to substitute missing values. Using EM, the available quantitative data were used to estimate the values each participant would have entered into the missing cells (Allison, 2003). EM is an effective technique that is often used to manage missing data. It is preferable over more traditional approaches to missing data management (e.g., listwise deletion or mean imputation) as it reduces the likelihood of scoring bias (Allison, 2001; Graham, 2009), and is acceptable when the percentage of missing data is minimal (Graham, 2009). Analyses were conducted both with and without the imputed data included to ensure that the imputation did not bias the data.

Statistical analysis. Hierarchical multiple regression was selected as the most appropriate statistical method for addressing the aims of this study. Prior to conducting the analysis, the relevant assumptions of hierarchical multiple regression were tested. As described above, the sample size was deemed adequate given the number of predictor variables to be included in the analyses. Furthermore, no significant univariate or multivariate outliers were identified. As is often seen in adherence data (Horne, Chapman, et al., 2013; Molloy, Messerli-Bürgy, et al., 2014), self-report and urine assay measures of adherence were significantly skewed; therefore, associations among predictor and criterion variables were examined using Spearman's rho correlations. No strong relationships between predictor variables were observed. Collinearity statistics (i.e., tolerance and variance inflation factor values) were all within accepted limits (i.e., $>.1$ and <5 , respectively). Therefore, the assumption of multicollinearity was deemed to have been met (Coakes & Ong, 2011; Hair, Black, Babin, & Anderson, 2010). Residual and scatter plots indicated the assumptions of normality, linearity and homoscedasticity were satisfied (Hair et al., 2010; Pallant, 2016). Note that although self-report and urine assay measures of adherence were significantly skewed, the composite adherence measure was approximately normally distributed.

Hierarchical linear regression was conducted for the composite measure of adherence and each continuous outcome (i.e., adherence measured by self-report and urine assay). Logistic regression was conducted for dichotomous outcome variables (i.e., adherence measured by prescription refill). As per Phillips et al. (2013), the treatment-related beliefs variable was entered in the first step of the regression, the CSM coherence variable was entered in the second step, and the habit strength variable was entered into the last step. For moderation analysis (i.e., the test of H2), the independent variable and moderator of interest

were mean-centred and entered together in the first step, and the interaction of the two variables (the product of the mean-centred variables) was entered in the second step of the regression.

Study 3 – What is the Patient Experience of Adherence for aTRH?

Aims and objectives of Study 3. The aim of Study 3 was to qualitatively compare high and low adherers with aTRH to identify factors associated with variation in adherence behaviour.

Approach to Study 3. Although there has been some qualitative research investigating adherence for patients with hypertension (e.g., Kronish, Leventhal, & Horowitz, 2012; Marshall, Wolfe, & McKeivitt, 2012; Najimi, Mostafavi, Sharifirad, & Golshiri, 2018; Saleem, Hassali, Shafie, & Atif, 2012), there is no qualitative research among patients with aTRH. Qualitative methods enable us to gain a richer understanding of this important topic. Given that adherence is central to the definition and diagnosis of resistant hypertension, it is essential to gather rich and meaningful data regarding how patients living with aTRH engage with treatment. This study used qualitative methods to broaden understanding of factors associated with good and poor adherence among patients with aTRH in primary care.

Public and patient involvement (PPI). INVOLVE, the UK's national advisory group to support active public involvement in the National Health Service, defines PPI in research as research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them. The aim of PPI in this study was to enhance the research quality and relevance by actively involving members of the public in deciding important aspects of how the study should be carried out.

Prior to study commencement, the HRB PC CTNI PPP-R group were consulted regarding important aspects of the study. The PPP-R group is an established group of patients, potential patients, carers and people who use health and social care services that represents the broad demographic profile of people living in Ireland in terms of age, nationality and gender. The group was established to work with research teams within the HRB PC CTNI to ensure that the voice and perspective of the public are used to shape and guide the research the network produces. The group had contributed to one other HRB PC CTNI-affiliated study prior to the current study.

The PPP-R group was consulted specifically regarding the protocol of the study and the interview topic guide. Although the group did not necessarily have resistant hypertension,

all members had experience with taking medication. A brainstorming session was held with group discussion facilitated by the candidate and two experienced PPI facilitators. During the session, the candidate presented the background to the research in lay language and, following a period where the group had the opportunity to ask questions, asked the group to discuss factors they believed were important in determining whether a patient would adhere to a long-term daily medication regimen for an asymptomatic chronic condition. Group discussion continued until no new factors were identified. The group was then asked to review the recruitment materials and consent form to ensure the language was clear and the appropriate information was included. Aspects of how the study should be carried out were also discussed with the group, such as the interview format (i.e., one-to-one interviews or focus groups), mode (i.e. telephone or face-to-face), and location (e.g., the participant's home, the GP clinic, the University, etc.). Amendments were subsequently made to the study protocol based on the group's recommendations. The interview topic guide was developed based on factors the group deemed relevant, as well as existing qualitative research on adherence for hypertension.

Participants. A subsample of patients with aTRH who participated in Study 2 was invited to participate in the qualitative interviews. Both patients who self-reported high and low adherence in Study 2 were invited to participate. Stratified purposeful sampling was used to illustrate characteristics of particular subgroups of interest (i.e., high and low adherers) and to facilitate comparisons between these two groups. All participants in Study 3 were provided with detailed study information and completed consent forms (Appendices I and J).

Setting. As per recommendations from the PPP-R group, participants had the opportunity to choose whether their interview took place via telephone or in a private room in the University. Conducting the interviews in the participants' homes was not presented as an option as the PPP-R group felt strongly that people may be uncomfortable about inviting the researcher into their homes. Issues of researcher safety were also discussed as reasons not to suggest participants' homes as a potential interview setting. The GP clinic was also excluded as a potential interview setting due to the difficulty in ensuring that a private room where the interview would not be interrupted could be made available. Allowing participants to choose their preferred interview mode was considered important to ensure participants were comfortable and not inconvenienced. All participants elected for their interviews to be conducted via telephone or in a private room in the University.

Recruitment. Given the relatively small proportion of patients who self-reported poor adherence in Study 2, participants were recruited purposively with the aim of recruiting as many low adherers as possible. Patients whose self-report adherence scores on the MARS were ≤ 23 were selected for the poorly adherent group. This cut-off was selected based on ROC analysis, as described above. These participants were age- and sex-matched with participants within the same practice who reported perfect adherence (i.e., a total score of 25 on the MARS). Both highly adherent and poorly adherent patients were invited via postal letter to participate in Study 3. Letters were sent from the patients' GP clinics by clinic staff to ensure that patient contact information was not removed from the practice by the research team in order to protect patient confidentiality and anonymity. Patients had been informed that they might potentially be contacted for a follow-up interview during Study 2 participation and that they were under no obligation to participate.

Sample size. There are no widely accepted formulae for calculating required sample sizes for qualitative studies as there are for quantitative studies. Therefore, the required sample size could not be determined in advance of this study (Starks & Brown Trinidad, 2007). Previous recommendations related to sample size in qualitative research have been inconsistent and essentially arbitrary (e.g., Creswell, 1998; Morse, 1994). Instead, the concept of saturation is typically used for achieving an appropriate sample size in qualitative studies (Glaser & Strauss, 1967). Sampling continued until saturation was achieved, meaning that collecting new data no longer resulted in the identification of new themes or insights (Morse, Barrett, Mayan, Olson & Spiers, 2008). Determining whether the achieved sample was adequate also depended on the scope of the study, time and resources available, the nature of the topic, and the depth and quality of information obtained from each participant (Morse, 2000; Morse & Singleton, 2001). The final sample size in this study was 14 participants (8 high adherers and 6 low adherers).

Data generation and analysis. Semi-structured interviews were conducted between October 2017 and January 2018. This approach was used because semi-structured interviews provided an appealing balance between structure and flexibility (Holloway & Fulbrook, 2001). The aim of this study to examine patients' perspectives on taking daily medications was already specified. As a result, unstructured interviews would not have been appropriate. Individual interviews were chosen as opposed to focus groups based on recommendations from the PPP-R group, who felt that patients may be less forthcoming about their medication-taking behaviours in a group context.

An interview topic guide of open-ended questions focusing on the individual's experience of taking multiple daily antihypertensive medications was used flexibly to guide the interviews. Participants were encouraged to lead the flow of the interview. Topics of interest were followed up using general nondirective prompts (e.g., "*Could you tell me more about that?*", "*What do you mean by that?*", etc.). Interviews were terminated when the researcher decided that all major topics had been discussed. Interviews varied in length from 23 minutes to 54 minutes. Interviews were audio recorded and transcribed verbatim. NVivo™ v.11 software was used to organise, manage and analyse the data.

Thematic analysis was selected as the primary analytic approach as it allowed a combination of both inductive and deductive methods to be used, in accordance with the pragmatic approach. Braun & Clarke's (2006) five-phase framework for thematic analysis was used to explore the data. Phase one, familiarisation, involved becoming familiar with the data through repeated and active reading (i.e., searching for meanings, patterns, etc.). Initial analyses were conducted during and after successive listening to the audio recordings and reading of the transcripts. The researcher transcribed a portion of the interviews to facilitate the familiarisation and interpretive processes (Bailey, 2008). Phase two, generation of codes, involved generating an initial list of ideas about the content of the data and producing an initial list of codes. Phase three, searching for themes, involved generating preliminary categories consisting of codes that were theoretically and/or conceptually linked. This phase began the re-focusing of the analysis at the broader level of the themes. Phase four, reviewing themes, involved exploring a refining a set of candidate themes. Dual criteria of internal homogeneity (how meaningfully the data within the themes fit together) and external heterogeneity (how clear a distinction there was between the themes) were used to refine the themes (Braun & Clarke, 2006; Patton, 1990). Phase five, defining themes, involved defining and naming the themes by 'identifying the essence of what each theme is about and determining what aspect of the data each theme captures' (Braun & Clarke, 2006, p. 22).

Reflexivity. Reflexivity is defined as an attitude of attending systematically to the context of knowledge construction, particularly to the effect of the researcher, at every step of the research process (Malterud, 2001). Although the perspective or position of the researcher shapes all types of research, reflexivity is considered particularly important in qualitative inquiry. Personal reflexivity was considered important in this study. As such, the researcher attempted to consider how personal life experiences, biases, attitudes and beliefs may have affected the research process (Howitt, 2010).

The current study was conducted with the awareness of the importance of reflecting on how the researcher might influence the interviews. The researcher had no personal experience of living with a chronic health condition or adhering to a long-term treatment regimen and therefore would not have the same sort of insight into the patient experience as the study participants. For this reason, engaging in PPI prior to the study outset was important to ensure that the perspective of people who had these experiences was represented in the interview questions as best as possible. The age-cohort difference between the researcher and participants may also have had an impact on the interview process (Underwood, Satterthwait, & Bartlett, 2010). Age difference may have affected the participants' level of openness within the interviews. Conversely, participants may not have given as detailed accounts in the interviews were they speaking to someone they believed had a similar experience to their own, as they may have presumed an innate knowledge of the topic at hand (Hamberg & Johansson, 1999).

Reflexivity was enhanced at the point of analysis by the research team coming together to review the data and coding techniques and discuss subsequent categories and themes into which the data were sorted (Richards, 2014). The research team for this study, in addition to the lead researcher (PhD candidate in health psychology), consisted of three GPs, a nurse with experience of carrying out research in primary care, and a health psychologist/behavioural scientist with expertise in the area of treatment adherence. This multidisciplinary approach to the thematic analysis enhanced the validity of the study results and ensured that the diverse perspectives of those involved in hypertension care were more adequately represented. This also increased the clinical utility of the study.

Quality and rigour. Considerations were made to ensure the study was carried out rigorously and that the data and analysis were of sufficient quality. Four broad principles for assessing the quality of qualitative research were used (Yardley, 2000): (1) sensitivity to context demonstrated through sensitivity to the social setting, existing theoretical and empirical literature, ethical considerations, and the data obtained from the participants; (2) commitment and rigor in the degree of attentiveness to the topic of interest, the researcher's own methodological competence and skill, and the participant during data collection; (3) transparency and coherence demonstrated through clearly describing all stages of research; and (4) impact and importance in the theoretical (enriching understanding), socio-cultural, and practical domains. These principles were considered and adhered to during the design and implementation of this research.

Ethical Considerations

Ethical considerations were guided by a framework for evaluating the ethics of clinical research studies based on major ethical codes, declarations and other documents relevant to research with human participants (Emanuel, Wendler, & Grady, 2000). Although this framework is typically applied in clinical research, it was essential that this research, which may be considered to pose significantly less potential harm to participants, was approached with the same objective and person-centred standards. According to this framework, the research must adhere to the following requirements:

- The research must add social or scientific **value** in terms of enhancements in health or knowledge.
- The research must demonstrate **scientific validity** by applying accepted scientific principles and rigorous methodological standards.
- The research must demonstrate **fair participant selection** guided by scientific objectives, not vulnerability or privilege, with equitable distribution of potential risks and benefits among vulnerable and privileged groups.
- The research must demonstrate **a favourable risk-benefit ratio** in terms of the risks and benefits to the participants as well as society.
- The research must be subject to **independent ethical review** by persons with the power to approve, amend or terminate it.
- The research participants must be **informed** about the research and provide **voluntary consent** to participate.
- The research must show **respect** to participants by protecting their privacy, allowing them the opportunity to withdraw, and monitoring their wellbeing.

Participants were recruited in Studies 2 and 3; therefore, ethical approval was sought and obtained for data collection in these studies from the relevant Research Ethics Committee (Galway University Hospitals Clinical Research Ethics Committee). The primary ethical concerns raised by these two studies related to informed consent, confidentiality and anonymity, fair participant selection, favourable risk-benefit ratio and respect for participants. The following section will outline how each of these ethical concerns was addressed in this research. The consent forms and participant information sheets for Study 2 and Study 3 are included in Appendices C, D, I, and J.

Informed consent. The purpose of procedures for obtaining informed consent in this research was to ensure that it was truly the decision of the individual to take part in the research or not and that the research was in line with the individual's values, interests and preferences (World Medical Association, 1997). As well as providing accurate information related to the purpose, methods, risks and benefits of participation, it was necessary to ensure that participants understood the information provided and had the opportunity to ask questions (Applebaum, Lidz, & Meisel, 1987).

As a population with a chronic condition attending GP clinics that form part of an active research network, members of the target population may have been contacted and recruited for numerous studies. This may have affected patients' willingness to participate in the research in a negative or positive manner. Informed, voluntary consent and adequate time to make the decision to participate were vital to facilitate potential participants to choose, independently, to take part in the research if it was of interest to them.

Information related to each study and to informed consent was clear, provided in more than one form (i.e., written and oral) in lay language. Potential participants in Studies 2 and 3 were provided with detailed information about the study, what their participation would involve, how their data would be treated, that their participation was voluntary, and that they could withdraw at any time.

Favourable risk-benefit ratio. The anticipated risk associated with participating in this research was minimal; however, in Studies 2 and 3, the experience of completing a questionnaire and participating in an interview study related to medication adherence, participants' beliefs about their hypertension and antihypertensive medications, and their health status may have caused some distress for some participants. It was estimated that the distress caused by completing the questionnaires and interviews that comprised these studies would be low. The contents of the questionnaire and the interview were clearly outlined at the clinical appointment and the outset of the interview, respectively. This information was provided before patients gave informed consent. Distress may have been minimised when participants were fully aware of the content of each of the studies prior to their participation.

Fair participant selection and respect for participants. Criteria to ensure fair participant selection and respect for research participants were closely linked in this research. This research set out to adhere to international best practice guidelines for the identification of resistant hypertension; therefore, the exclusion criteria applied in this research were largely

predetermined by clinical factors. In addition to the international guidelines for participant selection (Calhoun et al., 2008; Mancina et al., 2013), GP expertise was relied upon to ensure that all patients who were invited to participate were appropriately identified and selected. Patients with comorbid physical and/or psychological diagnoses were not excluded from this research (Weijer & Miller, 2004). Respect was shown to participants in this research by providing detailed and accurate information regarding each study, recruiting participants only following the receipt of the informed consent, implementing and maintaining procedures for anonymity and confidentiality, and providing participants with a report of the findings of the study via their GP in a timely manner (Emmanuel et al., 2000).

Confidentiality and anonymity. The process of data collection and procedures for securely managing the data of each participant were of particular importance in this research, given its clinical health focus and potential vulnerability of the population. Challenges to confidentiality were encountered in this research, for example, the small sample sizes and level of description used in Study 3 (Rinaldi Carpenter, 2006), and the use of questionnaire data from Study 2 to identify participants for Study 3. Confidentiality was preserved by using unique participant identification numbers during all phases of the research. Confidentiality and anonymity were maintained in Study 2 and Study 3 by storing the questionnaires and transcripts in a secure location and by using anonymised documents for storing participant information (Emmanuel et al., 2000). During the participant identification process for Study 3, patient identification numbers from Study 2 were used to ensure confidentiality and anonymity. The pre-identified list of identification numbers used in this process did not indicate which patients had reported poor adherence in Study 2. The identification numbers were used to retrieve patient addresses from within Socrates[®] practice management software for the purpose of inviting them to participate in Study 3. Postal invitations were delivered from the GP clinics to ensure that patient contact information was not removed from the clinics by the research team. Confidentiality was enhanced in Study 3 by using digital recording equipment so that encrypted audio files could be saved to a password-protected computer. Discomfort or distress may have been minimised or avoided when participants were confident in the knowledge that the information they provided could not be associated with them should they feel embarrassed or worried about their responses.

Summary of This Chapter

This chapter provided an overview of the study design and details of the methodological approach of each study included in this thesis. The aims of the three studies

described in this chapter were to quantify, predict and examine patient perspectives on medication adherence for aTRH in primary care in Ireland. A systematic review and meta-analysis, a cross-sectional questionnaire-based study and a qualitative interview study were conducted to address these aims. The main ethical considerations related to informed consent, confidentiality and anonymity, fair participant selection, favourable risk-benefit ratio and respect for participants. Measures to address these ethical issues included the provision of detailed participant information and sharing the findings of completed studies with participants.

3. Study 1: Medication adherence among patients with apparent treatment-resistant hypertension: Systematic review and meta-analysis

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Abstract

Objectives. Medication non-adherence is a known behavioural contributor to poor blood pressure control that puts patients with hypertension at elevated cardiovascular risk. Studies of medication adherence for apparent treatment-resistant hypertension (aTRH) vary significantly with respect to design, methods, and setting; and as a result, have produced highly variable figures describing the prevalence of non-adherence. This review aimed to describe the prevalence and potential moderators of medication non-adherence estimates for aTRH.

Methods. Systematic review and random effects meta-analysis.

Results. From an initial discovery of 921 studies, we identified 24 studies that measured medication adherence for patients with uncontrolled blood pressure despite being prescribed three or more antihypertensive medications of different classes. Using a random effects model, the pooled prevalence of non-adherence was 31.2% (95% CI [20.2, 44.7], $I^2 = 99.50$) with non-adherence rates ranging from 3.3–86.1%. The strongest contributor to variance in non-adherence rates was the method of adherence assessment used. Studies that

relied on self-report measures of adherence and/or pharmacy data reported lower levels of non-adherence than studies using more objective methods, such as liquid chromatography–mass spectrometry in single time point bioassays or directly observed therapy.

Conclusions. Findings indicate that medication non-adherence is a significant problem among aTRH patients. Identifying the most accurate and clinically feasible adherence assessment methods is necessary to reduce blood pressure and cardiovascular morbidity, facilitate early behavioural intervention, prevent unnecessary diagnostic testing, and limit sometimes unnecessary and expensive blood pressure lowering procedures.

Registration Number. CRD42016028121

Key Words. Medication Adherence; Hypertension; Resistant Hypertension; Systematic Review; Meta-Analysis

Introduction

Medication non-adherence is a known behavioural contributor to poor blood pressure (BP) control that puts patients with hypertension at elevated cardiovascular risk (Mazzaglia et al., 2009; Pittman, Tao, Chen, & Stettin, 2010). The term apparent treatment-resistant hypertension (aTRH) is used to describe patients who appear to have resistant hypertension, i.e. patients whose BP remains above goal despite concurrent use of three or more antihypertensive agents of different classes, one of which should ideally be a diuretic and all of which should be prescribed at optimal dose amounts, or patients whose BP is controlled but require four or more medications to do so (Calhoun et al., 2008; Mancia et al., 2013), and for whom causes of pseudo-resistance (i.e., non-adherence, the white-coat effect, measurement error) have not been excluded. aTRH is common among treated hypertensive patients, with prevalence estimates of >10% consistently reported (Achelrod, Wenzel, & Frey, 2014). Patients with aTRH are at increased cardiovascular risk relative to those whose BP is controlled by three or fewer medications, and 50% more likely to experience an adverse cardiovascular event than patients with controlled hypertension (Daugherty, Powers, Magid, Tavel, et al., 2012).

It is not certain what proportion of aTRH can be attributed to non-adherence to antihypertensive medications. Studies of medication adherence for aTRH vary significantly with respect to design, methods and setting; and as a result, have produced highly variable non-adherence estimates. Two recent narrative reviews have reported highly variable

estimates of non-adherence for aTRH (e.g., 23.0–66.0% [Berra et al., 2016]; 7.0–65.5% [Hyman & Pavlik, 2015]); however, these only report on three common studies, and do not report how or why individual studies were selected for review and therefore may provide an arbitrary selection of the available evidence. There has been no systematic investigation of the prevalence of non-adherence estimates for aTRH, or statistical moderators of these estimates. This review aimed to systematically determine the prevalence of medication non-adherence among patients with aTRH.

Methods

This systematic review and meta-analysis has been conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). The review is registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42016028121).

Search strategy. Electronic databases PsycINFO, PubMed, Embase, Web of Science and CINAHL were searched for research articles published from the start of the databases until December 2015. The following search string used: ‘medication’ AND (‘adheren*’ OR ‘nonadheren*’ OR ‘non-adheren*’ OR ‘complian*’ OR ‘noncomplian*’ OR ‘non-complian*’) AND (‘resistant’ OR ‘uncontrolled’) AND ‘hypertension’. References of selected articles and review articles were checked to identify additional relevant papers.

Inclusion and exclusion criteria. Articles were considered relevant if they reported original research and if their study population consisted of patients with aTRH. Prevalence of medication non-adherence had to be reported as an outcome. Papers were excluded if they were review or expert opinion articles, case studies, or contained secondary analyses on data already included in this review. Where dual or duplicate publication was identified, the paper with the most completely reported data was included. Intervention studies with appropriately reported baseline adherence data were also included.

Study selection. Titles and abstracts were screened for inclusion by two independent reviewers (HD and ECM). Full texts were also evaluated by two independent reviewers (HD and PH). In the case of disagreement between reviewers, a third reviewer acted as an adjudicator (AWM or GJM, depending on the nature of the expertise required to resolve the disagreement). Papers were retained if they contained studies exploring non-adherence to antihypertensive medication in aTRH, were published in English and were available in full-

text by January 2016. Owing to the varying definitions of treatment resistance (Myat, Redwood, Qureshi, Spertus, & Williams, 2012), the following common definitions were acceptable: (1) uncontrolled BP ($\geq 140/90$ mmHg) despite antihypertensive regimen of ≥ 3 medications of different classes (including one diuretic) or treatment with ≥ 4 antihypertensive agents of different classes irrespective of BP control status (definition of the American Heart Association [AHA; Calhoun et al., 2008], the European Society of Hypertension [ESH], and the European Society of Cardiology [ESC; Mancia et al., 2013]); (2) uncontrolled BP ($\geq 140/90$ mmHg) despite antihypertensive regimen of ≥ 3 medications of different classes; or (3) definitions deemed more stringent than 1 or 2.

Data extraction. From each included study two reviewers (HD and PH) independently extracted the following information: country of publication, study setting, design, sample size, definition of resistant hypertension, number of medications, definition of non-adherence, proportion of non-adherent subjects and factors associated with non-adherence, if reported. Several methods of measuring non-adherence have been reported; these were grouped into categories: (1) case note evaluation/physician interview; (2) self-report scale; (3) physical test (urine/blood); (4) pill count/prescription refill data; (5) medication possession ratio (MPR); (6) electronic monitors (MEMS); (7) directly observed therapy (DOT); or (8) combination of measures (e.g., self-report scale and physical test).

Quality and risk of bias assessment. Given the diversity of study designs included in this review, an assessment of the quality of studies was conducted with reference to criteria outlined by Sanderson, Tatt and Higgins (Sanderson, Tatt, & Higgins, 2007) in their review of quality and risk of bias assessment tools for observational studies.

Data synthesis and statistical analysis. Statistical analysis was conducted using the ‘metaprop’ function in R (R Core Team, 2013; G. Schwarzer, 2007). Results are presented in Forest plots. Non-adherence estimates were calculated by dividing the number of patients meeting each study’s definition of non-adherence out of the total number of enrolled patients. When only percentages were reported, they were converted into absolute numbers. Confidence intervals (95% CI) were calculated for each prevalence point estimate. A random-effects model (REM) was used to calculate a pooled summary estimate of non-adherence, as the assumptions of fixed-effects modelling were not deemed tenable in this context (Borenstein, Hedges, Higgins, & Rothstein, 2009). I^2 statistics were calculated to quantify the share of dispersion across the effects that is due to true heterogeneity rather than sampling error (Borenstein et al., 2009). Egger’s test was used to detect publication bias

(Egger, Smith, Schneider, & Minder, 1997). A leave-one-out sensitivity analysis was performed by iteratively removing one study at a time to confirm that findings were not driven by any single study. Subgroup analysis was applied to detect moderator variables where evidence suggests potential impact on non-adherence estimates, provided that necessary data were retrievable from the primary studies. Subgroup analyses examined: (1) type of adherence measure (categorised above); (2) study setting (primary care, general hospital or specialist hypertension referral clinic); and (3) definition of resistant hypertension (AHA/ESH/ESC versus ‘other’) as potential moderator variables (see Table 3.1).

Results

Description of studies.

Literature search. A PRISMA flow diagram outlining the systematic review process is provided (Figure 3.1). The initial literature search resulted in the identification of 921 unique papers, after 800 duplicates were removed. Of these, 891 were rejected after reviewing the abstracts. Of the remaining 30 articles, six were excluded in the full-text screening phase. Therefore 24 fully extracted primary studies were available for meta-analysis. One included article (Štrauch et al., 2013) described two distinct study populations (i.e., inpatients and outpatients). These were treated as separate observations in the meta-analysis. No additional papers that met our inclusion criteria were identified through a reference list search. See Table 3.1 for a summary of included articles.

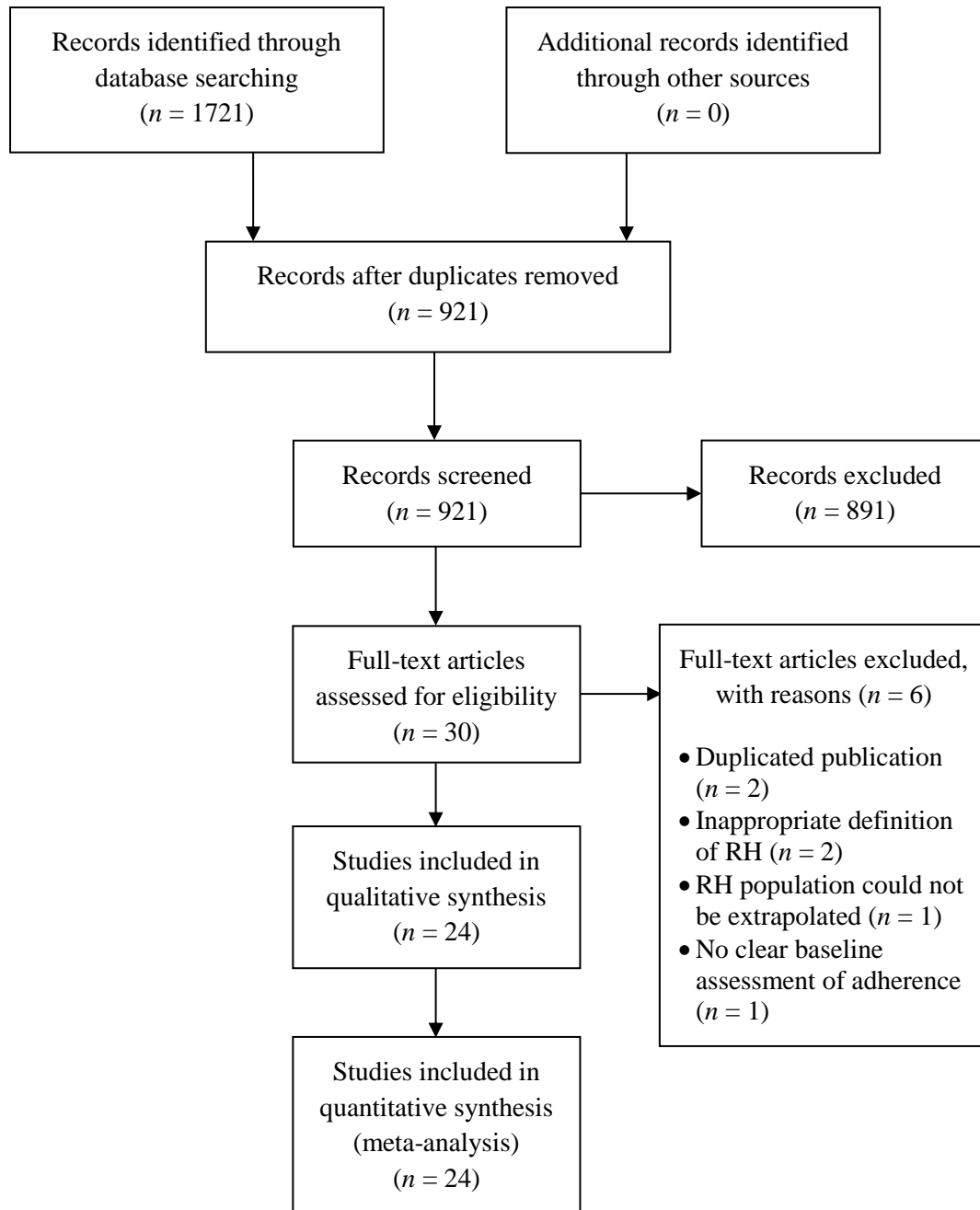


Figure 3.1. *PRISMA flow diagram.*

Table 3.1.

Summary of Articles Reporting on Medication Non-Adherence for Apparent Treatment-Resistant Hypertension

Author & year	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Non-adherence definition	N non-adherent (%)	Influencing factors
Beaussier et al., 2015	Prospective randomised parallel-group open-blinded endpoint trial	General hospital Paris, France	164	SBP ≥ 140 or DBP ≥ 90 on ≥ 3 meds incl. 1 diuretic	/	Combination: <ul style="list-style-type: none"> ▪ Physical test (plasma) ▪ Physical test (urine) ▪ Patient interview ▪ Pill count Sum of 4 items (max. score = 4)	Score <2	30 (18.3)	/

Author & year	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Non-adherence definition	N non-adherent (%)	Influencing factors
Brinker et al., 2014	Retrospective cohort	General hospital TX, USA	56	AHA/ESH/ESC	<ul style="list-style-type: none"> ▪ 5.3 ± 0.7 (non-adherent) ▪ 4.2 ± 0.4 (adherent) 	TDM	Levels of ≥ 1 medication below minimal detection limit	30 (53.6) <ul style="list-style-type: none"> ▪ Undetectable levels of ≥ 1 med: $n = 12$ (21.4) ▪ Undetectable levels of all meds: $n = 18$ (32.2) 	<ul style="list-style-type: none"> ▪ Younger age ▪ Higher DBP ▪ Higher heart rate
Bunker et al., 2011	Prospective cohort	Referral clinic London, UK	37	SBP ≥ 140 or DBP ≥ 90 on ≥ 3 meds incl. 1 diuretic	5 (3 – 7)	DOT	Clinically significant reduction in BP following witnessed drug taking	23 (62.2)	/
Burnier et al., 2001	Prospective cohort	General hospital Lausanne, Switzerland	41	SBP ≥ 140 or DBP ≥ 90 on ≥ 3 drugs on two consecutive clinic visits 1 month apart	/	MEMS	<80% days covered	3 (7.0)	/

Author & year	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Non-adherence definition	N non-adherent (%)	Influencing factors
Ceral et al., 2011	Retrospective cohort	Referral clinic, Prague, Czech Republic	84	SBP ≥ 150 or DBP ≥ 95 on ≥ 3 drugs	5.0 ± 1.2	Physical test (serum)	Levels of ≥ 1 medication below minimal detection limit	55 (65.5)	<ul style="list-style-type: none"> ▪ Younger age ▪ Higher BP ▪ Higher heart rate
Daughtery et al., 2012	Prospective cohort	Large population database (primary care) CA & CO, USA	3548	AHA/ESH/ESC	/	Pharmacy data	<80% days covered	1504 (42.4)	/
de Souza et al., 2009	Prospective cohort	Referral clinic Sao Paulo, Brazil	44	SBP ≥ 140 or DBP ≥ 90 on ≥ 3 meds incl. 1 diuretic on two consecutive clinic visits	5.4 ± 1.1	Combination: ▪ Pill count ▪ Self-report (MMAS-4)	<ul style="list-style-type: none"> ▪ <80% days covered ▪ Score <4 	<ul style="list-style-type: none"> ▪ Pill count: 16 (36.4) ▪ MMAS-4: 28 (63.6) 	/

Author & year	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Non-adherence definition	N non-adherent (%)	Influencing factors
Elmula et al., 2013		Referral clinic Oslo, Norway	18	SBP >140 on ≥ 3 meds incl. 1 diuretic at maximum or highest tolerated dose	5 (3 – 7)	DOT	Clinically significant reduction in BP following witnessed drug taking	3 (16.7)	/
Ewen et al., 2015a	Prospective cohort	General hospital Germany	27	SBP >140 on ≥ 3 meds incl. 1 diuretic at maximum or highest tolerated dose	5.0 \pm 1.6	Physical test (plasma and/or urine)	Levels of ≥ 1 medication below minimal detection limit	15 (55.6) <ul style="list-style-type: none"> ▪ Undetectable levels of ≥ 1 med: $n = 15$ (55.6) ▪ Undetectable levels of all meds: $n = 0$ 	No sig. differences

Author & year	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Non-adherence definition	N non-adherent (%)	Influencing factors
Ewen et al., 2015b	Prospective cohort	General hospital Germany	100	SBP >140 on ≥3 meds incl. 1 diuretic at maximum or highest tolerated dose	5.2 ± 1.4	Physical test (plasma and/or urine)	Levels of ≥1 medication below minimal detection limit	48 (48.0) <ul style="list-style-type: none"> ▪ Undetectable levels of ≥1 med: <i>n</i> = 46 (46.0) ▪ Undetectable levels of all meds: <i>n</i> = 2 (2.0) 	No sig. differences
Florczak et al., 2015	Prospective cohort	General hospital Warsaw, Poland	36	SBP >140 on ≥4 meds	5.3 ± 1.4	Physical test (serum)	Levels of ≥1 medication below minimal detection limit	31 (86.1) <ul style="list-style-type: none"> ▪ Undetectable levels of ≥1 med: <i>n</i> = 26 (72.2) ▪ Undetectable levels of all meds: <i>n</i> = 5 (13.9) 	/

Author & year	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Non-adherence definition	N non-adherent (%)	Influencing factors
J. P. Garg et al., 2005	Retrospective cohort	Referral clinic IL, USA	141	SBP ≥ 140 or DBP ≥ 90 on ≥ 3 meds	3.7 ± 0.9	MD interview	Physician determines the patient is non-adherent (not taking meds as prescribed or stopping meds without physician's direction)	23 (16.0)	/
Grigoryan et al., 2013	Prospective cohort	Primary care TX, USA	69	SBP ≥ 135 or DBP ≥ 85 ($\geq 125/75$ if diabetic) on ≥ 3 meds	/	MEMS	<80% days covered	20 (29.0)	/
Hameed et al., 2016	Retrospective cohort	Referral clinic Birmingham, UK	48	SBP ≥ 140 or DBP ≥ 90 on ≥ 3 meds	5 (4 – 5)	DOT	Clinically significant reduction in BP following witnessed drug taking	24 (50.0)	/

Author & year	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Non-adherence definition	N non-adherent (%)	Influencing factors
Irvin et al., 2012	Prospective cohort	Large population database (primary care) USA	2654	AHA/ESH/ESC	/	Self-report (MMAS-4)	Score ≥ 2	215 (8.1)	<ul style="list-style-type: none"> ▪ Black race ▪ Lower education ▪ Income < \$20,000 p/a ▪ Depressive symptoms ▪ History of CHD ▪ Comorbidities
Jung et al., 2013	Cross-sectional	Referral clinic Frankfurt, Germany	76	Office BP $\geq 140/90$ or ABPM $\geq 130/80$ on ≥ 4 meds	5 (IQR 4 – 6)	Physical test (urine)	Levels of ≥ 1 medication below minimal detection limit	40 (52.6) <ul style="list-style-type: none"> ▪ Undetectable levels of ≥ 1 med: $n = 28$ (36.8) ▪ Undetectable levels of all meds: $n = 12$ (15.8) 	<ul style="list-style-type: none"> ▪ Higher BP ▪ Higher heart rate

Author & year	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Non-adherence definition	N non-adherent (%)	Influencing factors
Massierer et al., 2012	Cross-sectional	Referral clinic Brazil	106	SBP \geq 140 or DBP \geq 90 on \geq 3 meds in right doses incl. 1 diuretic	/	Self-report (MMAS-4)	Score \geq 3	21 (19.8)	/
Pandey et al., 2015	Retrospective cohort	Referral clinic TX, USA	47	AHA/ESH/ESC	/	Combination: ▪ TDM ▪ MMAS-8	Levels of \geq 1 medication below minimal detection limit	24 (51.0)	▪ Younger age ▪ Female sex ▪ Higher heart rate
Porter et al., 2014	Pre-post intervention	Referral clinic NC, USA	60	SBP \geq 140 or DBP \geq 90 (\geq 130/80 if diabetic) on \geq 3 meds	3.8 \pm 1.2	MPR	<80% days covered	2 (3.3)	/

Author & year	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Non-adherence definition	N non-adherent (%)	Influencing factors
Rosa et al., 2014	Cross-sectional	Referral clinic Prague, Czech Republic	122	SBP ≥ 140 or DBP ≥ 90 on ≥ 3 meds in maximum doses incl. 1 diuretic	/	Physical test (blood)	Levels of ≥ 1 medication below minimal detection limit	27 (22.1) ▪ Undetectable levels of ≥ 1 med: $n = 10$ (8.2) ▪ Undetectable levels of all meds: $n = 17$ (13.9)	/
Sim et al., 2013	Prospective cohort	Large population database (primary care) CA, USA	60327	AHA/ESH/ESC	/	Pharmacy data	<80% days covered	4223 (7.0)	/

Author & year	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Non-adherence definition	N non-adherent (%)	Influencing factors
Strauch et al., 2013	Cross-sectional	Referral clinic Prague, Czech Republic	339 ▪ 176 inpatient ▪ 163 outpatient	AHA/ESH/ESC	▪ Inpatient: 2.5 ± 1.4 ▪ Outpatient: 5.2 ± 1.3	Physical test (blood)	Levels of ≥1 medication below minimal detection limit	Inpatient: ▪ Undetectable levels of ≥1 med: <i>n</i> = 18 (10.0) ▪ Undetectable levels of all meds: <i>n</i> = 16 (9.0) Outpatient: ▪ Undetectable levels of ≥1 med: <i>n</i> = 39 (24.0) ▪ Undetectable levels of all meds: <i>n</i> = 37 (23.0)	▪ Nonworking status ▪ Lower education ▪ Younger age
Velasco et al., 2015	Prospective cohort	Referral clinic TX, USA	78	AHA/ESH/ESC	4.4	TDM	Levels of ≥1 medication below minimal detection limit	43 (55.1)	▪ Younger age ▪ Higher DBP ▪ Higher heart rate ▪ Female sex

Author & year	Design	Setting	Sample	Definition of RH	Ave. no. of medications	Adherence measure	Non-adherence definition	N non-adherent (%)	Influencing factors
Yakovlevitch & Black, 1991	Retrospective cohort	Referral clinic	91	SBP \geq 140 or DBP \geq 90 on \geq 3 meds	/	MD interview	Patients admitted not taking medications according to the prescribed schedule and/or stopping medications without consulting a physician	9 (9.9)	/

Study characteristics. Twelve studies took place in Europe (Beaussier et al., 2015; Bunker, Callister, Chang, & Sever, 2011; Burnier, Schneider, Chioléro, Stubi, & Brunner, 2001; Ceral et al., 2011; Elmula et al., 2013; Ewen, Cremers, et al., 2015; Ewen, Meyer, et al., 2015; Florczak et al., 2015; Hameed, Tebbit, Jacques, Thomas, & Dasgupta, 2016; Jung et al., 2013; Rosa et al., 2014; Štrauch et al., 2013), ten in the US (Brinker et al., 2014; Daugherty, Powers, Magid, Masoudi, et al., 2012; J. P. Garg et al., 2005; Grigoryan, Pavlik, & Hyman, 2013; Irvin et al., 2012; Pandey et al., 2015; Porter, Taylor, Yabut, & Al-Achi, 2014; Sim et al., 2013; Velasco et al., 2015; Yakovlevitch & Black, 1991), and two elsewhere (de Souza et al., 2009; Massierer et al., 2012). The majority of studies were retrospective or cross-sectional cohort studies. Two RCTs and one pre-post intervention study were also included (Beaussier et al., 2015; Grigoryan et al., 2013; Porter et al., 2014).

Patient characteristics. The pooled participant sample was 68,313; however one study (Sim et al., 2013) accounted for over 60,000 of these. The number of patients included ranged from 18 (Elmula et al., 2013) to 60,327 (Sim et al., 2013). Mean age and sex distribution were similar across studies; however these were inconsistently reported. BP measurements, both systolic (SBP) and diastolic (DBP), were also inconsistently reported; those studies that did report these figures often broke BP down by subgroups or time points. The medications assessed were often not reported; those that were reported varied between studies.

Quality and risk of bias. A summary of the critical appraisal is presented in Figure 3.2. Egger's test for publication bias was significant ($Z = 7.28$, $df = 23$, $p = .02$).

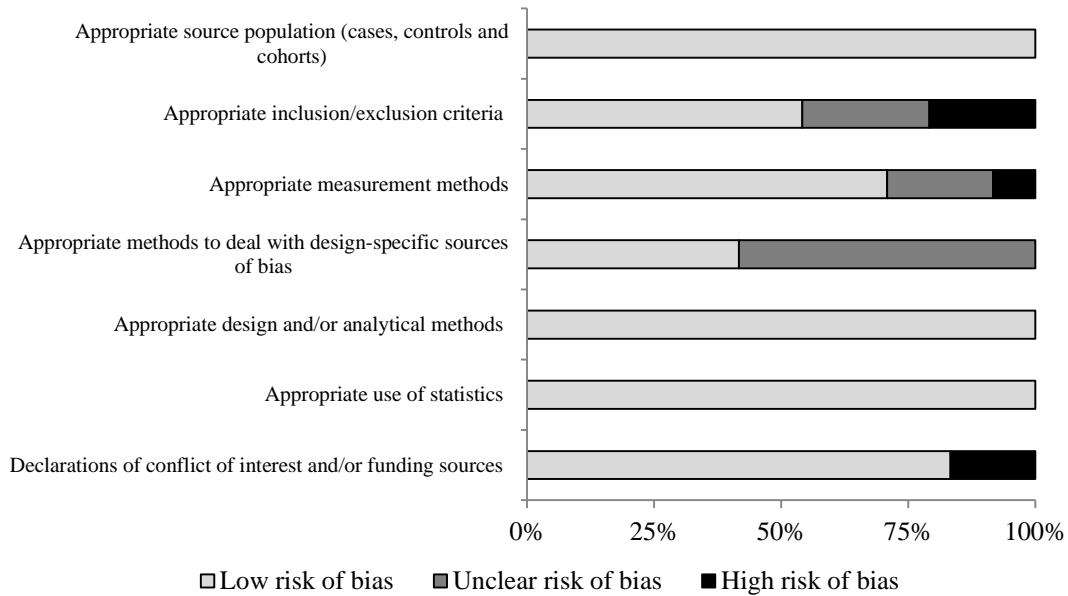


Figure 3.2. Risk of bias graph.

Summary of the evidence. Overall the studies included varied considerably with respect to design, methods, and setting. Of particular interest, the definitions of resistant hypertension and adherence varied significantly. Details of antihypertensive regimens are generally not reported, even for studies that use physical tests of urine or blood to measure adherence. Patients were often not reported to be on optimal hypertensive therapy, and the methodology of drug dosage assessment is typically not reported. For physical tests, timing of sampling after drug intake is not clearly defined. Furthermore, influence of preanalytical factors (procedures that occur prior to sample analysis that may produce erroneous results, e.g. patient identification, physical sample collection, sample preparation and handling, etc.) and pharmacokinetics on the level of drugs detected were not discussed. For the majority of studies, patient consent for adherence assessment was not adequately explained. No study provided information about patient agreement with the medication regimen. No study distinguished between under- and over-use of medications.

Prevalence of non-adherence. The prevalence of non-adherence varied between the studies, ranging from 3.3% (Porter et al., 2014) to 86.1% (Florczak et al., 2015). The lowest estimate of non-adherence was measured by MPR; the highest was measured using a physical test of urine.

The pooled prevalence of non-adherence was 31.2%, 95% CI [20.2, 44.7], with the REM. This analysis revealed significant heterogeneity across studies ($I^2 = 99.50$, $p < .001$). To evaluate the robustness of the association results, we performed a leave-one-out sensitivity analysis by iteratively removing one study at a time and recalculating the pooled prevalence estimate. The pooled estimate remained stable, indicating that results were not driven by any single study.

No study examined the consequences of non-adherence for aTRH; however, several studies examined differences in BP between adherent and non-adherent groups (Brinker et al., 2014; Ceral et al., 2011; Ewen, Cremers, et al., 2015; Ewen, Meyer, et al., 2015; Irvin et al., 2012; Jung et al., 2013; Pandey et al., 2015; Štrauch et al., 2013; Velasco et al., 2015). Only six studies examined determinants of non-adherence beyond baseline BP (Brinker et al., 2014; Ceral et al., 2011; Irvin et al., 2012; Pandey et al., 2015; Štrauch et al., 2013; Velasco et al., 2015); these suggested that age, sex, race, income and other socioeconomic indicators, and heart rate were all associated with non-adherence to antihypertensive therapy.

Subgroup analyses. All studies provided sufficient information to perform subgroup analysis by (1) type of adherence measure; (2) study setting; and (3) definition of resistant hypertension. There was no significant association between adherence measures and study settings ($\chi^2 = 18.67$, $p = .18$, $V = .62$), adherence measure and definition of resistant hypertension ($\chi^2 = 8.67$, $p = .28$, $V = .60$), or study setting and definition of resistant hypertension ($\chi^2 = 1.07$, $p = .59$, $V = .21$).

Adherence measures. Seven types of adherence measures were employed across studies. The most common measure was a physical test (Brinker et al., 2014; Ceral et al., 2011; Ewen, Cremers, et al., 2015; Ewen, Meyer, et al., 2015; Florczak et al., 2015; Jung et al., 2013; Rosa et al., 2014; Štrauch et al., 2013; Velasco et al., 2015), typically assessed using liquid chromatography–mass spectrometry in either blood or urine. Studies using this type of measure defined non-adherence as at least one drug below detectable levels; all differentiated between partial and complete non-adherence. Three studies used DOT (i.e., witnessed taking of drugs in a clinic setting followed by ambulatory BP monitoring with a drop in BP suggesting non-adherence; Bunker et al., 2011; Elmula et al., 2013; Hameed et al., 2016); three used a combination of self-report and objective measures (Beaussier et al., 2015; de Souza et al., 2009; Pandey et al., 2015); two used MEMS (Burnier et al., 2001; Grigoryan et al., 2013); two used physician interview (J. P. Garg et al., 2005; Yakovlevitch & Black,

1991); two used prescription refill data (Daugherty, Powers, Magid, Masoudi, et al., 2012; Sim et al., 2013); two used self-report scales only (Irvin et al., 2012; Massierer et al., 2012); and one used MPR (i.e., the number of doses of a given medication taken over a specified time period, divided by the number of days in the same time period; Porter et al., 2014) to measure adherence. Studies using MEMS or refill data generally defined non-adherence as >80% of doses collected. Each study's operational definition of non-adherence is described in Table 3.1.

The highest pooled non-adherence estimates were observed for physical tests (47.9%, $k = 9$) and DOT (44.6%, $k = 3$). The lowest estimate was observed for the MPR study (3.3%). The pooled non-adherence estimate for combination measures was 33.4% ($k = 3$). See Figure 3.3 for Forest plot.

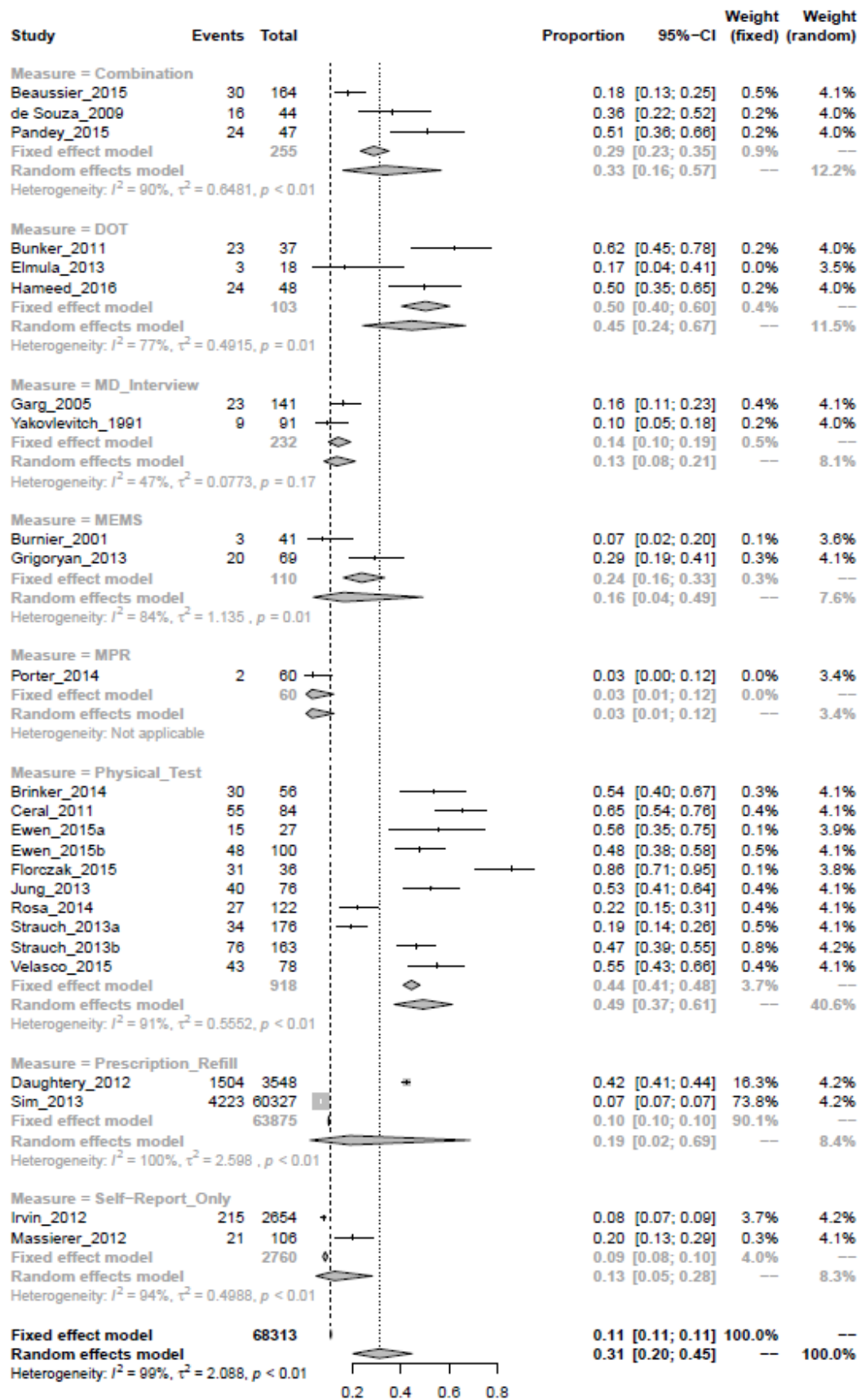


Figure 3.3. Forest plot for subgroup analysis of medication non-adherence estimates by adherence measure.

Given the diversity of measures, and the discrepancies between the non-adherence estimates they produced, we performed a sensitivity analysis excluding studies that used less reliable and/or valid measures of adherence (i.e., self-report and MPR). With these measures excluded, the summary estimate of non-adherence remained stable at 31.1% (95% CI [24.9, 38.1], $k = 21$) and between-study heterogeneity remained significant ($I^2 = 99.56$, $p < .001$). Furthermore, we conducted a separate analysis using direct measures of adherence only (i.e., DOT, physical tests, and combination measures). As expected, the summary estimate for these measures was higher than the overall estimate (45.7% non-adherence, 95% CI [36.1, 55.1], $k = 15$) and heterogeneity remained significant ($I^2 = 90.22$, $p < .001$).

Study setting. Four studies were set in primary care (Daugherty, Powers, Magid, Masoudi, et al., 2012; Grigoryan et al., 2013; Jung et al., 2013; Sim et al., 2013), ten in general hospitals (Beaussier et al., 2015; Burnier et al., 2001; Elmula et al., 2013; Ewen, Cremers, et al., 2015; Ewen, Meyer, et al., 2015; Florczak et al., 2015; Irvin et al., 2012; Porter et al., 2014), and ten in referral clinics (Bunker et al., 2011; Ceral et al., 2011; de Souza et al., 2009; J. P. Garg et al., 2005; Hameed et al., 2016; Massierer et al., 2012; Rosa et al., 2014; Štrauch et al., 2013; Velasco et al., 2015; Yakovlevitch & Black, 1991). The lowest estimates were observed for studies set in primary care (25.8%, $k = 4$); the highest for studies set in referral clinics (34.1%, $k = 11$). The estimate for studies set in general hospitals was 29.2% ($k = 9$). See Figure 3.4 for Forest plot.

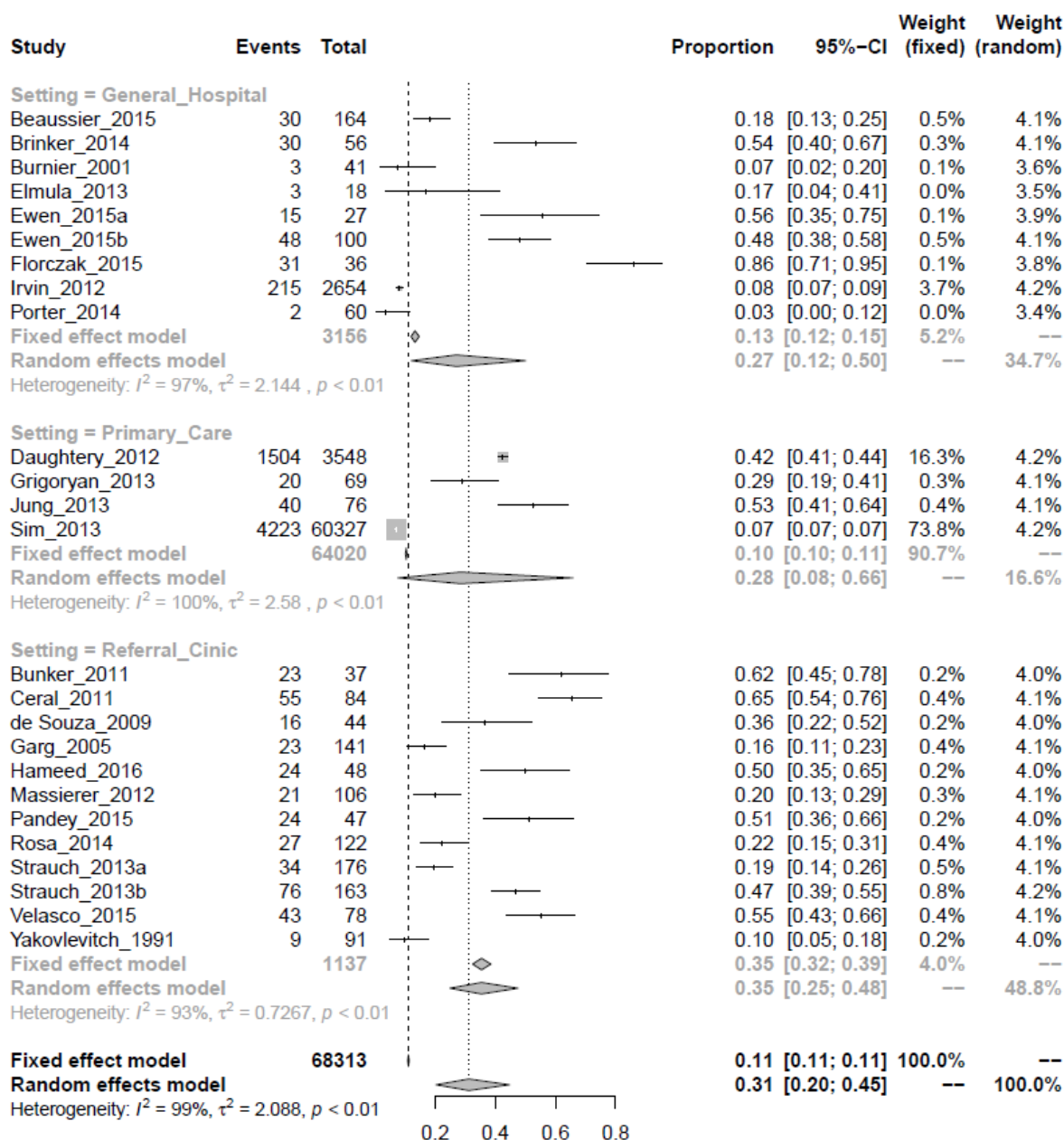


Figure 3.4. Forest plot for subgroup analysis of medication non-adherence estimates by study setting.

Definition of resistant hypertension. Seven studies adhered to the AHA/ESH/ESC definition of resistant hypertension (Brinker et al., 2014; Daugherty, Powers, Magid, Masoudi, et al., 2012; Irvin et al., 2012; Pandey et al., 2015; Sim et al., 2013; Štrauch et al., 2013; Velasco et al., 2015). There was no significant difference between pooled estimates for studies that used the AHA/ESH/ESC definition (30.5%, 95% CI [13.7, 54.9], $I^2 = 99.83$, $k = 7$) and studies that used other definitions (32.1%, 95% CI [22.5, 43.5], $I^2 = 91.96$, $k = 17$).

Discussion

These findings suggest that, depending how adherence is measured, approximately 31% of cases of aTRH may be potentially explained by poor adherence. In the studies using objective indicators such as bioassays we estimated that this non-adherence figure is closer to 50%. While there are numerous caveats to this analysis, these findings from a broad range of studies from throughout the world suggest that a substantial proportion of those currently diagnosed with and treated for resistant hypertension may not have the condition. Therefore, it is likely that treatment intensification in those with hypertension who appear not to be responding to treatment may be frequently unwarranted where non-adherence has not been assessed.

Adherence is recognised as a key factor in the effectiveness of antihypertensive medication; however, unreliability of adherence assessment has limited its use in clinical practice (Hamdidouche et al., 2017a). A diverse range of adherence assessment methods were used across studies, and the type of measure used to assess adherence had a significant impact on non-adherence estimates. Physical tests of urine or blood were by far the most common, with 9 studies using this method as the sole assessment, and 3 additional studies using physical tests in conjunction with self-report measures. Direct measures, i.e., physical tests and DOT, yielded the highest estimates, while MPR and pharmacy data yielded the lowest estimates. Although different measures yield highly variable estimates of non-adherence, each measure provides important information that can contribute to our understanding of non-adherence in different ways. For example, although MEMS have been touted by some as a gold standard, the measure recorded is not a direct confirmation that a pill has been taken but merely the container has been opened; as such, they tell us nothing about those who intentionally modify or skip doses. Although physical tests can confirm that a patient has swallowed their medication, these measurements give only a single snapshot of behaviour and so daily-life adherence between visits may be under- or overestimated. Furthermore, certain pharmacokinetic considerations must be made when interpreting results of these tests for different antihypertensive agents. Additionally, although self-report measures are subject to a host of biases, they have the potential to elucidate reasons for non-adherence (e.g., illness perceptions, treatment-related beliefs, or cognitive deficits) in a way that more objective measures cannot. Therefore, it is unlikely that there will be a single-gold standard measure that will not make some trade-off on reliability or validity. Interestingly, studies that used a combination of physical and self-report measures yielded an estimate closest to the total

summary estimate; perhaps suggesting that a combination of objective and subjective measures is the best way to accurately determine non-adherence.

The definition of resistant hypertension varied substantially between studies. Though this was not a significant moderator of non-adherence estimates, this selective observance of the established definition of resistant hypertension should be considered. The most frequent way in which individual study definitions of resistant hypertension differed from that put forward by the AHA/ESH/ESC was the exclusion of patients who required four or more antihypertensive agents to achieve BP control. Exclusion of this important subgroup of aTRH patients has limited the conclusions we can draw regarding the impact of non-adherence for aTRH; in fact, it may be that the proportion of resistant hypertension accounted for by non-adherence would have been higher had these patients been more consistently accounted for within these studies.

This review identified that certain study-level characteristics moderate non-adherence estimates. However, only six of the included studies examined potential patient-level predictors of non-adherence, and none of these looked beyond basic demographic factors such as age, sex, race or indicators of socioeconomic status. Though some research has examined patient-level factors affecting non-adherence in hypertension (e.g. Kurdi, Chen, & Elliott, in press), to date the aTRH literature has largely neglected intensive study of non-adherent patients. The primary focus of these studies has been to identify patients whose hypertension is truly resistant to pharmacological treatment. Though this is a critical movement within the study of hypertension, it is insufficient to identify non-adherence among aTRH patients without intention to intervene. Patients who are non-adherent to their antihypertensive medications may not be truly resistant; they are, however, still at elevated cardiovascular risk relative to those whose BP is under control. Little attention has been paid to patient-level factors that affect non-adherence for aTRH patients; this is an important limitation of the literature that merits consideration. Investigation of potential predictors of non-adherence for aTRH, using well-established theoretical frameworks and a diversity of measures of adherence, is necessary to inform the development of behaviour-change strategies to promote optimal adherence (Morrissey et al., 2016; Morrissey, Durand, et al., 2017; Nieuwlaat et al., 2014), decrease risk of adverse cardiovascular events, and reduce unnecessary prescribing and economic burden on the healthcare system.

In addition to the measurement challenges, there are several additional limitations to be considered. The study of medication adherence for aTRH is increasing rapidly; as such,

this review is somewhat limited by the exclusion of articles published after January 2016. However, given that the majority of studies included in this meta-analysis were published within the last 5 years, we can tentatively assume that these are methodologically consistent with more recently published articles that might have been included. The majority of studies we included were descriptive in nature; it has been argued that study bias may be even more confounding for observational studies, and so assessing risk of bias for this type of review is critical. However, there are fewer well-established tools available for assessing quality and risk of bias for observational studies, as compared to tools for assessing randomised control trials. For this reason, we used broad criteria identified in a systematic review by Sanderson, Tatt and Higgins (2007); however, given that a variety of study designs were included, applying the same assessment criteria to all studies proved difficult. Furthermore, given the broad inclusion criteria, the vastly different ways of measuring adherence behaviour, and that aTRH as a condition remains poorly defined in the literature, it is unsurprising that the studies included were significantly heterogeneous and that certain subgroups were considerably small (particularly for MPR, MD interview and MEMS). However, to forgo the meta-analysis because of heterogeneity in this instance fails to address the question of how exactly to synthesise this data in a meaningful and useful way (Lau, Ioannidis, & Schmid, 1998).

Limitations notwithstanding, this review had several important strengths. The systematic approach taken ensures that the existing body of literature has been accurately represented, and the statistical techniques employed attempt to explain the considerable variability within this literature. Furthermore, the review was conducted by a multidisciplinary team that included behavioural scientists and clinicians involved in the care of people with aTRH. This wealth of methodological and clinical knowledge allowed for a diversity of views to be represented during the review process and has resulted in a review with important implications not only for health science but also clinical practice.

The present study represents the first attempt to systematically synthesise the disparate range of studies that have estimated the prevalence of non-adherence in aTRH. The findings provide an imprecise estimate of non-adherence for this condition. The current evidence suggests that a substantial proportion of people receiving pharmacological treatment for hypertension may not be adherent, and therefore may be inappropriately classified as having aTRH. Given the considerable economic cost of treating hypertension, greater effort must be made to predict non-adherence and intervene with those who choose or simply forget to take their antihypertensive medication.

4. Study 2: Medication adherence for resistant hypertension: Assessing theoretical predictors of adherence using direct and indirect adherence measures

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Abstract

Objectives. This study examined theoretical predictors of long-term medication adherence (i.e., treatment-related beliefs, coherence of beliefs from experience with medication, habit strength and pill burden) for patients with apparent treatment-resistant hypertension in primary care, using a composite adherence score derived from direct and indirect measures (i.e., prescription refill, self-report, and bioanalytical assays of urine).

Design. Cross-sectional study.

Methods. Individual patient records were screened for prescription refill adherence. Patients provided a urine sample for adherence screening and completed a battery of psychometric scales, including two self-report adherence measures ($N = 204$). Convergence of adherence measures was assessed, a composite adherence score was calculated, and hierarchical multiple regression was used to examine the role of theoretical predictors of adherence.

Results. Non-adherence estimates ranged from 20.3–41.1%, depending on the assessment method used. Associations among adherence measures were weak to moderate

($p=.00-.53$). Medication-taking habit strength was the strongest predictor of adherence, explaining 19% incremental variance in adherence beyond treatment-related beliefs. Beliefs and coherence did not predict adherence, even for patients with weaker habits. Pill burden was not associated with habit strength or adherence for this sample.

Conclusions. Associations among unique adherence measures were weak overall, providing further evidence that multiple measures are necessary to accurately assess adherence. Habit strength is a key predictor of adherence for chronic conditions. Both habit strength and pill burden represent important intervention targets for improving long-term medication adherence. Longitudinal inception studies are needed to properly test CSM propositions and elucidate the role of beliefs, coherence and habits in predicting adherence at various stages of the chronic illness trajectory.

Keywords. medication adherence; resistant hypertension; common-sense model; health beliefs; habit; pill burden

Introduction

Medication non-adherence is a major contributor to negative health outcomes and elevated healthcare costs. Poor adherence is of particular concern among hypertensive patients who appear to be resistant to treatment. Resistant hypertension is characterised by uncontrolled blood pressure despite concurrent treatment using three or more antihypertensive medications of different classes, or concurrent use of four or more antihypertensive medications regardless of control status (Calhoun et al., 2008; Mancia et al., 2013). Non-adherence to antihypertensive medications precludes a diagnosis of true resistant hypertension; as such, until adherence is confirmed, patients are instead classed as having apparent treatment-resistant hypertension (aTRH). Although patients who are non-adherent cannot be classed as truly resistant to treatment and are instead classified as ‘pseudo-resistant’ (Calhoun & Grassi, 2017), these patients remain at elevated risk of adverse cardiovascular events as long as their non-adherence is not effectively managed.

One potentially useful theoretical framework for describing and predicting non-adherence among patients with aTRH is the Common-Sense Model of Self-Regulation (CSM; H. Leventhal, Phillips, & Burns, 2016). The CSM posits that individuals create mental representations of their illness based on the sources of information available to them in order to make sense of and manage the health problem (Hagger, Koch, Chatzisarantis, & Orbell,

2017). The CSM proposes that components of the individual's illness representation (identity, causes, consequences, timeline and controllability) affect how they will behave in response to a health threat, for example by adhering to a prescribed treatment.

Although the CSM has been widely used to predict adherence behaviour, many CSM-inspired studies focus on behaviour initiation factors (e.g. illness and treatment-related beliefs) over other theoretically important processes involved in behaviour maintenance. Recent empirical work (Phillips, Cohen, Burns, Abrams, & Renninger, 2016; Phillips, Leventhal, & Leventhal, 2013) examined the role of two such processes in predicting long-term adherence: 'coherence' of beliefs (i.e., a certainty in one's beliefs regarding the illness and treatment that results directly from personal experience that a treatment does what it is expected to do), and medication-taking habit strength. This work draws on dual-process theories (Hagger, 2016), which purport that individuals' behaviour is controlled by both deliberative/reflective processes (rational and conscious decision-making influences on action), and implicit/impulsive processes (well-learned, spontaneous, and non-conscious influences). Phillips et al. (2013) posit that long-term medication adherence occurs if: (1) adherence behaviour is successfully initiated due to formation of treatment-favourable beliefs; (2) performance of the treatment provides evidence that the treatment is working, thereby confirming the individual's beliefs, resulting in a 'coherent' CSM and increased likelihood of treatment persistence; and (3) the medication-taking routine is repeated enough to develop automatic contextual cues that maintain the behaviour. Evidence for a variety of behaviours, including adherence, would suggest that the effect of patients' beliefs and intentions on adherence is moderated by habit strength, such that when habits are strong, beliefs are weakly (if at all) predictive of behaviour (Bolman, Arwert, & Völlink, 2011; Sheeran, 2002). Furthermore, beliefs, coherence, and habit should have differential influences on intentional versus unintentional non-adherence: habit strength should theoretically be more strongly related to unintentional non-adherence, because habit strength reflects automatic processes that eliminate the need to remember to take medication; whereas treatment-related beliefs and coherence should be more reflective of intentional non-adherence, because both represent deliberative, intentional processes. In testing this proposed model of long-term adherence, Phillips et al. (2013) and Phillips et al. (2016) found that habit strength was the strongest predictor of medication adherence, and that treatment-related beliefs and experiences did not predict adherence even for patients with weaker medication-

taking habits. Patients' experiences with medication were shown to predict intentional non-adherence, whereas habit strength predicted unintentional non-adherence.

Phillips's work emphasises habit strength as a key factor in maintaining adherence behaviour for long-term treatments. Another important factor that has been consistently associated with poor adherence is daily pill burden and regimen complexity (Burnier, 2006; Mathes, Jaschinski, & Pieper, 2014). Pill burden refers to the number of pills that a patient takes on a regular basis. As this number increases, associated efforts (e.g., with regard to storing, organising, consuming, and understanding various medications) also increase, thus making the daily routine of medication-taking more complex (Gerbino & Shoheiber, 2007; Ingersoll & Cohen, 2008). By definition, patients with aTRH are prescribed multiple antihypertensive medications, which may have implications for habit development. Taking multiple medications is accompanied by increased cognitive load associated with monitoring and selecting the correct pills, thereby increasing the behavioural complexity of the task. Development of automaticity for complex behaviours, such as taking multiple daily medications, may take longer or reach a lower level of automaticity than for simple behaviours (Lally, Van Jaarsveld, Potts, & Wardle, 2010; Verplanken, 2006). Therefore, we hypothesise an association between greater antihypertensive pill burden and weaker habit strength.

Study Overview. This article aims to replicate and extend existing work examining theoretical predictors of long-term medication adherence for patients with aTRH in primary care. Specifically, we draw on previous research by (Phillips et al., 2016; Phillips et al., 2013), which used the CSM extended to include coherence and habit as the guiding theoretical framework to understand medication adherence in patients with hypertension. We aim to extend this work by examining the effect of antihypertensive pill burden on habit and adherence in a specific sample of hypertension patients (i.e., those who appear to be resistant to treatment). Furthermore, this work will incorporate expert recommendations (DiMatteo, 2004; Vrijens, Antoniou, Burnier, de la Sierra, & Volpe, 2017) to assess adherence using multiple direct and indirect measurement methods (i.e., self-report, pharmacy refill data, and urine assay). Previous research has suggested that, while measurement type significantly moderates adherence estimates (Durand et al., 2017), combining measures of adherence improves measurement sensitivity and increases diagnostic accuracy (H. Liu et al., 2001; Schäfer-Keller, Steiger, Bock, Denhaerynck, & De Geest, 2008). Therefore, this study will utilise a composite adherence measure that incorporates both direct and indirect measures of

adherence to provide a comprehensive adherence assessment. The hypotheses to be tested are as follows:

Hypothesis 1 (H1): habit strength and CSM coherence will each account for incremental variance in patient adherence to that accounted for by patients' treatment-related beliefs, with habit strength accounting for the greatest amount of unique variance.

Hypothesis 2 (H2): patients' treatment-related beliefs and medication-taking habit strength will interact such that beliefs will predict adherence only for patients with weaker habits.

Hypothesis 3 (H3): habit strength will be more strongly related to unintentional non-adherence than to intentional non-adherence; conversely, CSM coherence and treatment-related beliefs will be more strongly associated with intentional non-adherence than with unintentional non-adherence.

Hypothesis 4 (H4): habit strength will be weaker for those with higher antihypertensive pill burden.

Method

Design. The study design was cross-sectional with retrospective measurement of certain outcomes (i.e., adherence as measured by prescription refill).

Procedure. Ethical approval was granted by the Clinical Research Ethics Committee at Merlin Park University Hospital, Galway (Ref: C.A. 1386). Forty general practices in the University-affiliated research network WestREN (Kavanagh, O'Brien, Glynn, Vellinga, & Murphy, 2010) were invited to participate in a two-phase study of resistant hypertension in primary care. In Phase 1, patient records were screened in Socrates® patient management software, first using a standard Anatomical Therapeutic Chemical drug search to identify patients on any antihypertensive medication as defined by the British National Formulary 69th Edition (Joint Formulary Committee, 2015). Records of patients identified as being on one or more antihypertensive medications were then reviewed by two researchers (PH and MC) to determine if patients were hypertensive or not, and what antihypertensive medications they were currently prescribed. A detailed account of the patient record screening process is available in P. Hayes et al. (2018). Patients meeting the criteria for aTRH were sent a letter introducing the study and inviting them to participate in Phase 2. This involved patients attending a clinical appointment at their GP clinic, during which they

completed a psychometric questionnaire, were fitted with a 24-hour ambulatory blood pressure monitor, and provided a urine sample for biochemical analysis.

Participants. Participants were primary care patients identified as having aTRH in a review of patient records in 16 participating GP clinics in the west of Ireland. In Phase 1, 646 individual patient records were identified as meeting diagnostic criteria for aTRH. All patients had been prescribed ≥ 3 antihypertensive medications for at least three months. Of the patients screened during Phase 1, 95 (14%) were not invited to participate at the advice of their GP due to significant morbidity and/or infirmity (e.g., nursing home residents, patients undergoing active chemotherapy or radiotherapy for cancer, patients with severe psychiatric illness, and patients who were housebound due to, e.g., neurological illness, dementia, cardiac or renal failure, etc.). From a single practice, which was outside of the referral area of a resistant hypertension clinic (P. Hayes et al., 2018), 77 patients were also not invited to participate in Phase 2. A further 21 patients were not invited to take part owing to a variety of reasons (i.e., moving practice, no longer taking antihypertensive medications, or death). Of the remaining 453 patients, 239 (52.75%) agreed to participate in Phase 2 of the study. Responders and non-responders did not differ significantly on any demographic (i.e., age, sex, GMS status) or clinical variables (i.e., blood pressure, number of antihypertensive medications, duration of antihypertensive treatment, classes of antihypertensive agents, kidney function, heart failure, diabetes mellitus). Prescription refill records were available for 517 patients (i.e., 80% of patients identified in Phase 1). Self-report data was provided by 237 patients. A spot urine sample for bioanalytical testing was provided by 235 patients. Adherence data using all assessment methods was available for 204 patients.

Measures.

Adherence measures.

Self-reported medication adherence. Two scales were used to assess patients' self-reports of adherence: the Morisky Medication Adherence Scale (MMAS; Morisky, Ang, Krousel-Wood, & Ward, 2008) and the Medication Adherence Report Scale (MARS; Horne, 2004). The MMAS (Morisky et al., 2008) is an eight-item measure with seven yes/no items and with answer options ranging from 'always' to 'never' on a five-point scale. The MMAS has been extensively validated (Krousel-Wood et al., 2009; Morisky & DiMatteo, 2011). Conventional scoring was used to create a composite variable of the 8 MMAS items, with higher scores indicating better adherence. Internal consistency for the MMAS was .62. The

MMAS was used with permission from its developer. The MARS (Horne, 2004) is a five-item measure with answer options ranging from ‘always’ to ‘never’ on a five-point scale, where higher scores indicated better adherence. Internal consistency for the MARS was .77.

Intentional and unintentional non-adherence. To represent intentional versus unintentional non-adherence, composite scores were calculated from the MMAS and MARS by averaging the Z-scores of intentional (skipping, altering or adding doses) and unintentional (forgetting) items (Phillips et al., 2013). Internal consistency for intentional and unintentional non-adherence composites was .77 and .72, respectively. For both composites, items were ordered so that higher scores indicate greater *non-adherence*.

Prescription refill records. Prescription refill records were available for patients on the General Medical Services (GMS) scheme (a means-tested scheme providing free healthcare services and medication cover for eligible individuals in Ireland, e.g. those aged ≥ 70 years or on a reduced income) via Socrates[®] practice management software. A majority of patients were in receipt of quarterly scripts (i.e., prescriptions for medications to cover a three-month period) as opposed to monthly scripts, thus precluding the use of the typical $< 80\%$ cut-off for non-adherence (Karve et al., 2009). Therefore, using this measure, patients were considered adherent if they had collected $\geq 75\%$ of their printed scripts from the practice over the last 12 months (i.e., three quarterly scripts/nine monthly scripts).

Biochemical assay of urine. Adherence was assessed by bioanalytical screening for 25 of the most commonly prescribed antihypertensive medications or corresponding metabolites (see Table 4.1) in spot urine using high-performance liquid chromatography coupled to mass spectrometry (HPLC-MS/MS), using a methodology similar to Jung et al. (2013) and Tomaszewski et al. (2014). Additional information regarding sample preparation and analysis are provided in Appendix F. Total non-adherence was defined as complete absence of any prescribed antihypertensive medications (or their metabolites, where appropriate) in a spot urine sample on screening. Patients whose urine analysis confirmed the presence of fewer medications than prescribed were classified as partially non-adherent. Five medications (lercanidipine, nebivolol, spironolactone, felodipine, and candesartan) could not be detected using HPLC-MS/MS and were therefore excluded from analysis. In line with Jung et al. (2013), adherence ratios were calculated for each patient – based on the medications that could be detected – by dividing the total number of antihypertensive medications detected in spot urine into the total number of detectable antihypertensive medications prescribed, whereby total non-adherence was equal to 0 and perfect adherence was equal to 1. Sensitivity

analyses (i.e., excluding all participants for whom fewer than three antihypertensives could be detected using HPLC-MS/MS) revealed that this did not significantly bias the results; therefore, all participants were included in the analyses.

Table 4.1.

Antihypertensive Medications and/or their Metabolites Examined in Urine

No.	Antihypertensive medication (metabolite)	Ion mode
1.	Amiloride	Positive
2.	Amlodipine	Positive
3.	Atenolol	Positive
4.	Bendroflumethiazide	Negative
5.	Bisoprolol	Negative
6.	Bumetanide	Positive
7.	Candesartan	Positive
8.	Diltiazem	Positive
9.	Enalapril	Positive
10.	Doxazosin	Positive
11.	Felodipine	Positive
12.	Furosemide	Negative
13.	Hydrochlorothiazide	Negative
14.	Indapamide	Positive
15.	Lercanidipine	Positive
16.	Lisinopril	Positive
17.	Losartan	Positive
18.	Nebivolol	Positive
19.	Olmесartan	Positive
20.	Perindopril	Positive
21.	Ramipril (ramiprilat)	Positive

22. Spironolactone (canrenone)	Positive
23. Telmisartan	Positive
24. Valsartan	Positive
25. Verapamil	Positive

Note: depending on their chemical structure (i.e. positively or negatively charged ions), medications/metabolites were detected by positive or negative ion mode scanning, respectively.

Adherence composite. As each adherence measure has established construct validity but is also subject to varying kinds of measurement biases (Osterberg & Blaschke, 2005), a unit-weighted composite adherence score was calculated by standardising and summing scores from each individual adherence measure (Bobko, Roth, & Buster, 2007). Use of multiple methods to assess medication taking behaviour is recommended in this literature due to the inherent limitations of each individual measure (Bond, 2016).

Pill burden. Antihypertensive pill burden was operationalised as the number of daily antihypertensive medications prescribed, which was obtained from patient records.

Treatment-related beliefs. Health beliefs relevant to the patients' hypertension medication were measured using the Illness Perceptions Questionnaire–Revised (IPQ–R) treatment control items (Moss-Morris et al., 2002) and the Beliefs about Medicines Questionnaire (BMQ; Horne et al., 1999). Both scales have response options ranging from 'strongly disagree' (=1) to 'strongly agree' (=5). Scores on the IPQ-R subscale represent how well patients think their medication can control their hypertension, with higher scores indicating better control. Scores on the BMQ Specific Necessities subscale represent how necessary patients believe their hypertension medication is for their health, with higher scores indicating a greater necessity. Scores on the BMQ Specific Concerns subscale represent how concerned patients are about their hypertension medication, with higher scores indicating greater concern. A composite variable (average) of treatment-specific health beliefs was used, consisting of the IPQ scale items, the BMQ Specific Necessity scale items, and reverse-scored BMQ Specific Concern scale items. This measurement approach replicates the approach taken by Phillips et al. (2013), wherein items were selected for their theoretical

alignment with the core constructs and processes specified in the CSM¹. Internal consistency for the treatment-related beliefs composite was .67.

Illness coherence. Two survey items assessed illness coherence according to the CSM: ‘Have you noticed the positive benefits of the hypertension medicine? Yes/No’, and ‘Have you experienced any solid (convincing) evidence that the hypertension medication does what it is supposed to do? No evidence/Some evidence/Solid evidence’ (Phillips et al., 2013). These items were standardised and averaged to make a composite score for CSM-coherence, with higher scores indicating more coherent CSM beliefs. Internal consistency of the coherence composite was .61.

Habit strength. The strength of patients’ antihypertensive medication-taking habits was assessed using the Self-Report Behavioural Automaticity Index (SR-BAI; Gardner, Abraham, Lally, & de Bruijn, 2012). The SR-BAI consists of four items drawn from the Self-Report Habit Index (Verplanken & Orbell, 2003) that were most confidently and consistently judged to capture behavioural automaticity. The SR-BAI has been demonstrated to be a reliable, valid and parsimonious self-report measure of habit (Gardner et al., 2012). Items are rated on a seven-point response scale ranging from ‘strongly disagree’ (=1) to ‘strongly agree’ (=7), with higher scores indicating stronger medication-taking habits. Internal consistency for the SR-BAI was .87.

Statistical analyses. Analyses were conducted in SPSS 23. Missing self-report data were imputed using expectation maximisation. Analyses were conducted both with and without the imputed data included to ensure that the imputation did not bias the data. Associations among predictor and criterion variables were examined using Spearman’s rho correlations. Hierarchical linear regression was conducted for the composite measure of adherence and each continuous outcome (i.e., adherence measured by self-report and urine assay). Logistic regression was conducted for dichotomous outcome variables (i.e., adherence measured by prescription refill). Analyses for individual adherence measures are presented in Supplementary Tables I–IV. As per Phillips et al. (2013), the treatment-related beliefs variable was entered in the first step of the regression, the CSM coherence variable was

¹ This approach to assessing treatment-related beliefs was first utilised by Phillips et al. (2013) for its theoretical alignment with the CSM as it was intended by its developer, Professor Howard Leventhal. Although this approach has previous predictive validity, we are not aware of any study that has specifically set out to validate this approach to operationalising treatment-related beliefs. Until further psychometric evaluation of this approach is conducted, results regarding the role of treatment-related beliefs should be interpreted with caution.

entered in the second step, and the habit strength variable was entered into the last step. For moderation analysis, the independent variable and moderator of interest were mean-centred and entered together in the first step, and the interaction of the two variables (the product of the mean-centred variables) was entered in the second step of the regression.

Results

Sample characteristics. A total of 204 participants with data available for all adherence measures were included in this analysis. Sample characteristics are described in Table 4.2.

Table 4.2.

Sample Characteristics

Variable	<i>M</i> (<i>SD</i>) / %	Possible range / observed range
Female sex	42.2%	
Age	69.86 (10.69)	18+ / 32–96
Married or in a relationship	60.3%	
Completed secondary education	81.5%	
No. of antihypertensive medications	3.68 (0.70)	3+ / 3–8
Adherence		
MARS	24.25 (1.75)	5–25 / 5–25
MMAS	6.34 (1.06)	0–8 / 0–8
Prescription refill (% adherent)	79.7%	
Urine assay		
Total non-adherence	2.1%	
Partial non-adherence	23.8%	
Adherence ratio	0.84 (0.23)	0–1 / 0–1

Prevalence of non-adherence to medication. Non-adherence estimates ranged from 20.3–41.1%, depending on the method of measurement (see Table 4.2). The lowest and highest non-adherence estimates observed were for prescription refill and self-report (MMAS), respectively. Using a cut-off of 23 on the MARS² (determined using Receiver Operating Characteristic analysis; R. Kumar & Indrayan, 2011) and 6 on the MMAS (Morisky et al., 2008) to denote non-adherence, the respective self-reported non-adherence estimates were 36.7% on the MARS and 41.1% on the MMAS. According to the urine assay

² The cut-off for the MARS (and the MMAS) to denote non-adherence was used for descriptive purposes only. The use of MARS scores to produce a dichotomous adherent/non-adherent variable is not typical, nor is it recommended. Continuous MARS scores should continue to be utilised in future predictive studies of adherence.

measure, 26% of patients had evidence of non-adherence to at least one of their prescribed antihypertensive medications.

Associations among adherence measures. Adherence summary statistics are shown in Table 4.2. Both self-report and urine assay measures of adherence were significantly skewed, thereby violating the assumption of normality. As such, Spearman rank correlation coefficients (ρ) were used. As expected, the MMAS and the MARS were significantly correlated ($\rho = .52, p < .001$). Both self-report measures were significantly associated with prescription records; however, the correlation coefficients suggested only weak to moderate associations. There was no significant association between adherence measured by urine assay and any other measure of adherence. The composite adherence score was significantly correlated with each component measure ($p < .001$). Correlation coefficients are displayed in Table 4.3.

Composite adherence score. All adherence values were standardised and analysis of internal consistency was carried out to establish that individual adherence items were sufficiently related to form a composite score. All items were positively correlated and Cronbach's α remained stable when each item was iteratively removed, suggesting that all adherence measures could be reliably included in a composite measure. The scores for each component measure were converted to Z -scores and the sum of the standardised scores was calculated to produce a unit-weighted composite score (i.e., all component measures were equally weighted). A unit-weighted composite was deemed the most appropriate, given the measures are theoretically related and each has its own valid strengths and limitations. Internal consistency for the composite adherence measure was .76. Correlation coefficients between the composite measure and each individual measure of adherence are displayed in Table 4.3.

Table 4.3.

Correlations among Predictor and Criterion Variables (N = 204)

	1	2	3	4	5	6	7	8	9
1. Prescription refill	-								
2. MARS	.30‡	-							
3. MMAS[®]	.17*	.53‡	-						
4. Urine assay	.00	.01	.04	-					
5. Composite	.44‡	.74‡	.82‡	.25‡	-				
6. Beliefs	.02	.19†	.19†	.05	.22†	-			
7. Coherence	.02	.04	.13*	.04	.11	.32‡	-		
8. Habit strength	.08	.36‡	.35‡	-.02	.36‡	.22†	.06	-	
9. Pill burden	.01	.00	-.08	.07	-.08	.05	.05	.02	-

Note: * $p < .05$, † $p < .01$, ‡ $p < .001$. Use of the MMAS[®] is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, MMAS Research) LLC 14725 NE 20th St. Bellevue WA 98007.

Associations among predictor variables. No strong relationships were observed between independent variables ($r < .4$). Variance inflation factor values (<5) and tolerance values ($>.1$) for all independent variables were adequate, thereby showing that there was no issue with multicollinearity in the data.

Hypothesis testing. The subsequent analyses (H1–H3) utilise a composite measure of adherence. Regression tables for each individual measure of adherence are available in Appendix G. Results for H1 and H2 are displayed in Table 4.4. Results for H3 are displayed in Table 4.5. Results for H4 are displayed in Table 4.3.

H1. The first hypothesis was partially supported. Favourable treatment-related beliefs significantly predicted adherence in the first step. Counter to the hypothesis, CSM coherence did not have any significant predictive value beyond treatment-related beliefs. As hypothesised, the incremental variance explained by the measure of habit strength in the third

step of the regression was significant. Habit strength explained 19% of the variance in patient adherence in addition to that already explained by beliefs and coherence.

H2. Contrary to the hypothesis, the interaction between patients’ treatment-related beliefs and habit strength was not significant for the composite adherence measure.

H3. The third hypothesis was partially supported. As hypothesised, habit strength was more strongly associated with patients’ unintentional non-adherence ($\beta = -.45$, $t_{(203)} = -7.04$, $p < .001$) than intentional non-adherence ($\beta = -.22$, $t_{(203)} = -3.08$, $p < .01$). However, counter to the hypothesis, neither treatment-related beliefs nor CSM coherence was associated with intentional or unintentional non-adherence.

H4. The fourth hypothesis was not supported. As seen in Table 4.3, there was no association between pill burden and habit strength ($\rho = .05$) and no association between pill burden and adherence ($\rho = -.08$) in this sample.

Table 4.4.

Hierarchical Regression Analysis of Theoretical Predictors of Adherence (H1, H2, H4)

	β	Adj. R^2	ΔR^2	F	ΔF
H1					
Treatment-related beliefs	.14	.04	.05	7.59†	7.59†
CSM coherence	-.01	.04	.00	3.88*	0.20
Habit strength	.44‡	.22	.19	15.51‡	36.96‡
H2					
Beliefs x habit strength	-.07	.23	.01	16.48‡	0.95

Note: * $p < .05$, † $p < .01$, ‡ $p < .001$.

Table 4.5.

Comparison of Prediction of Unintentional vs. Intentional Non-Adherence (H3)

	<u>Unintentional non-adherence</u>			<u>Intentional non-adherence</u>		
	β	$t_{(203)}$	p	β	$t_{(203)}$	p
Beliefs	-.05	-0.79	.43	-.07	-1.01	.32
Coherence	-.04	-0.56	.58	-.03	-0.35	.73
Habits	-.45	-7.04	< .001	-.22	-3.08	< .01

Discussion

The current study examined theoretical predictors of medication adherence (i.e., favourable beliefs, experiential feedback and habit strength) for patients with aTRH. As previously demonstrated by Phillips and colleagues (2016; 2013), habit strength was the strongest predictor of a composite measure of adherence consisting of self-report, prescription refill and urine assay data (see supplementary tables for results using individual measures). Also in line with Phillips et al. (2013), treatment-related beliefs and habit strength did not interact, suggesting that medication-taking habits are more predictive of adherence than treatment-related beliefs even when the habit is weak. Contrary to previous findings, treatment-related beliefs and CSM coherence were not more predictive of intentional non-adherence than habit strength; in fact, habit strength was the only significant predictor of either intentional or unintentional non-adherence, although the relationship was stronger for unintentional non-adherence. Finally, there was no association between habit strength and the number of antihypertensive medications prescribed, nor between pill burden and adherence. Cumulatively the current findings provide additional support for the extended CSM proposed by Phillips et al. (2013) for predicting medication adherence in the long-term. However, as discussed in detail in the limitations section below, more research is needed to further validate this model.

The current study also examined concordance between prescription refill records, self-report, and bioanalytical assessment of spot urine using HPLC-MS/MS for the assessment of antihypertensive medication adherence in primary care. It is repeatedly argued that there is no gold standard measure of adherence and that, in order to overcome each

measure's limitations with respect to validity and reliability, a combination of measures should be used (DiMatteo, 2004; Durand et al., 2017; A. K. Gupta, Arshad, & Poulter, 2010; Lam & Fresco, 2015; Vrijens et al., 2017). Results indicated significant associations between indirect measures of adherence for a sample of aTRH patients prescribed multiple daily medications. There was no significant relationship between bioanalytical measures and any other measure of adherence. Despite this, analysis of internal consistency revealed that all adherence measures were sufficiently related to produce a meaningful and useful composite adherence score. Composite measures of adherence have the potential to overcome limitations of each individual adherence measure while also combining their strengths, potentially resulting in the most comprehensive adherence assessment available. Composite adherence measures have been utilised in previous research and shown to be highly sensitive and demonstrate good specificity (H. Liu et al., 2001; Schäfer-Keller et al., 2008). Our analyses show that multiple adherence measures may be statistically compiled to provide a comprehensive estimate of adherence behaviour that can be utilised in similar predictive studies. Future research should consider such an approach to further evaluate the utility of composite adherence measures, ideally utilising longitudinal designs and incorporating additional validated measures such as electronic monitoring.

Urine assays were not associated with any other measure of adherence. Barring direct observation, bioanalytical testing of bodily fluids is the only adherence assessment that can verify ingestion of medication. However, these measures provide only a single snapshot in time and may not be reflective of typical adherence behaviour. It is possible that the act of ingesting medication is too distinct from the adherence behaviours assessed by indirect measures (e.g., collecting a prescription) to produce a statistical association. Interestingly, although urine assays were not associated with either self-report measure of adherence, they were significantly associated with items reflecting *intentional* non-adherence across both the MARS and the MMAS ($p \geq .15, p < .05$). Relatively few patients reported intentional non-adherence, which, although consistent with previous adherence research (Z. Moon, Moss-Morris, Hunter, & Hughes, 2017), may explain why a significant association did not emerge for total self-report adherence scores. Similarly, only 27 patients reported not taking their medication the day before the clinical appointment (i.e., the period for which the urine analysis is most relevant), which may suggest a potential reporting bias. Although further research with greater variability in terms of intentional versus unintentional adherence is needed (see limitations below), this may have important clinical applications for patients who

are deliberately non-adherent but choose not to report this to their GP. Objective physical measures may allow clinicians to identify adherence issues for patients who are reluctant to discuss, for example, their concerns about treatment or related side-effects. This approach may be particularly cost-effective for aTRH patients, for whom the cost of an assay may be less than a monthly supply of antihypertensives (P. Gupta et al., 2017). Future research should evaluate the feasibility of integrating biochemical assessment of antihypertensive adherence into routine primary care.

Habit strength was the strongest predictor of adherence, i.e. overall adherence, intentional non-adherence, and unintentional non-adherence. This is consistent with previous findings, and provides additional support for an extended CSM that includes habit strength as a core component (Phillips et al., 2016; Phillips et al., 2013). Contrary to the fourth hypothesis, however, pill burden was not associated with habit strength or adherence. This conflicts with the existing literature, which suggests that habit formation is theoretically more difficult for those taking complex medication regimens. The absence of association between pill burden and habit strength in this study may be due to the restricted range of pill burden in the current sample. All patients were prescribed at least three antihypertensive agents, in addition to their other medications. Future studies may benefit from samples that include the full range of pill burden, particularly the lower end of this spectrum, to adequately test this hypothesis. An increasing number of patients are being treated with multi-medication regimens, due in part to the increase in multimorbidity internationally (Barnett et al., 2012; Fortin, Bravo, Hudon, Vanasse, & Lapointe, 2005; Glynn et al., 2011); therefore, the role of pill burden with regard to both habit formation and adherence, as well as potential strategies to reduce pill burden warrant further investigation. Polypills (i.e., pills that combine multiple active pharmaceutical ingredients) may present a solution to some of the challenges of increased pill burden. Evidence suggests that polypills improve adherence, are generally well-tolerated, and reduce risk factor levels for cardiovascular disease (A. K. Gupta et al., 2010; Munger, 2010; Sherrill, Halpern, Khan, Zhang, & Panjabi, 2011; Webster et al., 2016); however, more research is needed to evaluate the clinical effectiveness and feasibility of implementing this type of intervention on a large scale (Coca et al., 2017; Huffman, Xavier, & Perel, 2017; Webster, Castellano, & Onuma, 2017). Reminder packaging has also been used to improve adherence where pill burden is an issue (Dupclay, Eaddy, Jackson, Raju, & Shim, 2012), which may be a more feasible solution to the problem of pill burden. Collaboration with clinical and community pharmacists may facilitate implementation of

these strategies to reduce pill burden and thereby improve adherence. Further research is needed among patients with a variety of chronic conditions and treatment regimens to examine the impact of pill burden and the effectiveness of efforts to reduce pill burden for improving adherence and treatment outcomes.

This study is not without limitation. First, despite recruiting a sample almost three times larger than that of Phillips et al. (2013), our sample was also highly adherent with relatively strong habits. Greater variability on these constructs would allow a better test of these theoretical hypotheses, particularly with regard to CSM coherence, which was not significantly predictive of adherence in any of these analyses. This relatively restricted sample is theoretically more likely to be a similar stage in the dynamic process outlined in the CSM (H. Leventhal, Weinman, Leventhal, & Phillips, 2008; Phillips et al., 2013), and therefore may provide limited insight into processes that occur at earlier stages in the model, for example gaining feedback on the efficacy of treatment. Although the current study has important theoretical ramifications, the cross-sectional design limits the certainty with which relationships between CSM constructs and adherence can be determined. Therefore, longitudinal research among incident samples utilising longitudinal measurement of CSM constructs is now needed to properly test CSM propositions. Following newly diagnosed patients from treatment initiation to a behaviour maintenance stage is essential to properly assess the importance of treatment-related beliefs and other reflective processes, in combination with automatic factors, for predicting long-term adherence behaviour. Second, the current study is subject to certain measurement challenges. Certain adherence measures, specifically self-report and urine assay, may have been subject to the toothbrush effect, whereby patients may 'load up on' or adhere to medication regimens a few days before the clinical appointment (Pullar, 1991). Prescription records were taken over a 12-month period; however, given the nature of the prescribing records available (i.e., quarterly prescription refills for most patients, thus prohibiting the use of $\geq 80\%$ as a standard cut-off), prescription refill adherence was operationalised as a dichotomous adherent/non-adherent variable. It is possible that, had more detailed prescription refill information been available, stronger correlations between adherence measures might have been observed. Furthermore, although we screened for 25 of the most commonly prescribed antihypertensive medications using HPLC-MS/MS, there were five medications that could not be reliably detected. As such, there were a number of participants ($n = 61$) for whom not all prescribed antihypertensive medications were assessed. Had all prescribed antihypertensives been assessed, non-

adherence estimates may have been higher for the urine assay measure. Furthermore, although treatment-related beliefs were operationalised consistently with Phillips et al. (2013), this approach to assessing beliefs as conceptualised by the CSM requires further psychometric validation. Finally, it is possible that had adherence and/or habit strength been assessed for individual antihypertensive medications, as opposed to antihypertensive treatment in general (e.g., patients may be habitual in taking their beta blocker but intentionally skip their diuretic on occasion), a different pattern of results might have emerged. This is an important measurement consideration that future research examining the role of pill burden for adherence should address.

Limitations notwithstanding, this study makes several important contributions to the literature. First, it provided an opportunity to compare adherence scores as measured by drug levels in urine, self-report, and prescription refill records within a large sample of aTRH patients in primary care. Second, this study used rigorous and systematic statistical methods informed by psychometric theory (Bobko et al., 2007) to create a composite adherence score for a large sample of patients that can be replicated for future cohorts. Third, our replication of previous empirical findings using an enhanced methodology of adherence assessment by including a physical measure of patient adherence in the form of urine assays provides additional evidence for the key role of habit strength in predicting long-term adherence behaviour. Together these findings highlight important targets for further research and intervention (i.e., habit development and pill burden) for improving adherence to antihypertensive medications. Future research should validate these findings using inception samples with longitudinal measurement of CSM constructs and multiple methods of adherence measurement to properly test CSM propositions, and ultimately use the extended CSM as a framework for the development of behaviour change interventions to enhance adherence.

5. Study 3: A qualitative comparison of high and low adherers with apparent treatment-resistant hypertension

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Abstract

Background. Poor adherence is a leading cause of apparent resistance to antihypertensive treatment. Recent empirical research has investigated predictors of adherence for primary care patients who are apparently resistant to treatment; however, questions remain regarding the variability in adherence behaviour among this group.

Objectives. This study aimed to investigate factors that may elucidate medication adherence among patients with apparent treatment-resistant hypertension (aTRH) using qualitative methods.

Methods. Fourteen semi-structured interviews were conducted with patients undergoing treatment for aTRH in primary care in the West of Ireland. Patients who self-reported both high and low adherence in a previous quantitative study were purposively sampled. Data were analysed using thematic analysis. A public and patient involvement research group were active partners in developing the study protocol and interview topic guide.

Results. Three major themes were identified: beliefs about treatment, habits and routine, and health and health systems. High adherers reported favourable beliefs about antihypertensive treatment that had been validated by experience with taking the treatment over time, described strong medication-taking habits and stable routines, and positive relations with their GP. Low adherers expressed less coherence in their beliefs and used less effective strategies to support their medication-taking in daily life.

Conclusions. The current findings are consistent with qualitative studies of adherence in other chronic conditions. Results reflect the difficulty for healthcare practitioners in identifying adherent versus non-adherent patients via conversation, and highlight the importance of accurate adherence assessment. Inception studies may provide an opportunity to better understand adherence behaviour across the illness trajectory.

Keywords. Treatment Adherence and Compliance; Medication Adherence; Hypertension; Primary Health Care; Qualitative Research; Public and Patient Involvement (PPI)

Introduction

Resistant hypertension refers to blood pressure (BP) that remains above goal despite concurrent use of three or more antihypertensive agents of different classes (Calhoun et al., 2008; Mancia et al., 2013). Recent epidemiological characterisation (P. Hayes et al., 2018; Sinnott et al., 2017) indicates the prevalence of resistant hypertension may be lower than previously estimated (3–6.5% versus 15–30%; Pimenta & Calhoun, 2012), and a majority of apparent treatment-resistant hypertension (aTRH) cases may be attributable to causes of pseudo-resistance (inadequate dosing, white-coat hypertension, and poor adherence; Calhoun & Grassi, 2017).

Non-adherence to antihypertensive medication is considered the most common cause of aTRH (Jung et al., 2013; Vrijens et al., 2017). Specific illness- and treatment-related factors (e.g., the asymptomatic nature of the condition, the increased number of daily medications required, etc.) combined with more general barriers to adherence for chronic conditions increase the likelihood of patients with aTRH sub-optimally adhering to their medications.

Despite a growing quantitative evidence base for predictors of adherence for aTRH (Durand et al., 2018; Durand et al., 2017), there is a dearth of qualitative research among this

group. Qualitative comparisons between high and low adherers (e.g. Chambers et al., 2011) may illuminate subtle nuances in the drivers of adherence behaviour that may represent important targets for behavioural intervention. The aim of this study was to investigate factors associated with good and poor adherence in aTRH patients in primary care.

Method

This study is reported in accordance with the COREQ checklist (Tong, Sainsbury, & Craig, 2007; Appendix K).

Recruitment. Patients with aTRH were purposively sampled for a two-phase study of resistant hypertension in primary care (Durand et al., 2018; P. Hayes et al., 2018). From this group, sub-samples of highly and poorly adherent patients were invited to participate in the current study. Patients were classed as poorly adherent if they had MARS (Horne, 2004) scores of ≤ 23 , as per Durand et al. (2018). Fourteen interviews were conducted (39% response rate). An iterative approach was used, wherein findings from the data were incorporated into subsequent interviews as they emerged (Ziebland & McPherson, 2006). Recruitment of participants continued until data saturation was reached and no new themes developed (Glaser & Strauss, 1968).

Interviews. The interview topic guide was developed by (1) reviewing existing research on adherence for hypertension, and (2) consulting members of the public in developing the study protocol and topic guide. Public and Patient Involvement (PPI) is reported according to the GRIPP2-SF guidelines (Staniszewska et al., 2017; Appendix L). Interviews were semi-structured and carried out by one researcher (HD) via telephone ($n = 12$) or in a private room in the University ($n = 2$), depending on participants' preference. All participants gave informed consent for the interviews to be conducted, recorded and for anonymous quotations to be used. Transcription was partially outsourced, and the remainder (20%) was conducted by one researcher (HD) to help begin the interpretive process of analysis (Bailey, 2008).

Analysis. The five stages of thematic analysis (familiarisation, generation of codes, searching for themes, reviewing themes, and defining themes; Braun & Clarke, 2006) were followed. To enhance reflexivity, five members of the research team (three GPs, a nurse, and a health psychologist) joined the lead researcher (PhD candidate in health psychology) to examine the coding process, review the data and contribute to the analysis (Richards, 2014;

Morrissey, Casey, Glynn, Walsh, & Molloy, 2018; Morrissey, Glynn, Casey, Walsh, & Molloy, 2017). NVivo v.11 was used to organise and code transcripts to facilitate analysis.

Results

Table 5.1 shows characteristics of high and low adherers.

Table 5.1.

Characteristics of High and Low Adherers

	High adherers (<i>n</i> = 8)	Low adherers (<i>n</i> = 6)	Overall (<i>N</i> = 14)
Demographic characteristics			
Mean age, years (range)	66 (48 – 86)	72 (64 – 83)	68 (48 – 86)
Female, <i>n</i> (%)	5 (62)	3 (50)	8 (57)
Urban, <i>n</i> (%)	4 (50)	2 (33)	6 (43)
Married/living with partner, <i>n</i> (%)	4 (50)	3 (50)	7 (50)
Secondary education or higher, <i>n</i> (%)	6 (75)	5 (83)	11 (79)
General Medical Services (GMS)* cardholder, <i>n</i> (%)	5 (62)	6 (100)	11 (79)
Clinical characteristics			
Mean number of antihypertensive medications (range)	3 (3 – 4)	4 (3 – 5)	3 (3 – 5)
Chronic kidney disease, <i>n</i> (%)	3 (37)	2 (33)	5 (36)
Congestive cardiac failure, <i>n</i> (%)	0 (0)	2 (33)	2 (14)
Diabetes mellitus, <i>n</i> (%)	1 (12)	4 (67)	5 (36)

*Note: the GMS scheme is a means-tested scheme that provides free health care services and medication cover for eligible individuals in Ireland (e.g., those aged ≥ 70 years or on a reduced income)

Results are illustrated with supporting participant quotations. These are identified as belonging to a specific patient from the high (H1, H2, etc.) or low adherer (L1, L2, etc.) group, including gender (M=male, F=female) and years of age (e.g., H1,M,82). Three main themes were identified in the data: Beliefs about Treatment, Habits and Routine, and Health and Health Systems.

Theme 1: Beliefs about Treatment. The first core recurrent theme identified was patients' beliefs about medications and treatment for hypertension. This theme is represented by two subthemes: Necessity versus Concern and Coherence of Beliefs.

Subtheme 1: Necessity versus Concern. Both high and low adherers believed that their antihypertensive medications were necessary to control their BP.

"I think they're all obviously necessary or I wouldn't be on them." H7,M,86

"Oh well if you're on medicine, the only reason you're on them is that we need them you know." H3,F,70

Both groups stated that they would never intentionally stop taking their medicines. Most patients regarded their antihypertensive medications as particularly important.

"I'd never stop taking them. Oh jeeny no! I would never stop taking my medication. No way would I do that. I want to live." H4,F,67

"The most important one is the blood pressure." L4,M,54

Both groups expressed ambivalent beliefs; despite believing their medications were necessary, patients had a strong dislike towards taking medication.

"I hate it. But I have to take it. I know that myself. I have to take it for my BP."
L6,F,69

"I wouldn't be over the moon about it, but certainly if I know it's what's required and if that's what the doctor has told me to do, I will go along with it. Now I wouldn't be taking it like I would be taking an ice-cream [laughter]. I'd take it you know. I take it as I have to take it." L1,M,78

High adherers, however, despite their dislike of medicines, described knowing that taking their medicines was important.

"I don't like taking all these meds. But then I think well isn't it great that they're there, because otherwise what would happen?" H6,F,75

"Possibly a long time ago when I started on them maybe I would have felt when was this going to stop. But eventually you find that these are your friends." H8,M,83

Low adherers expressed multiple concerns about taking medications. Some were concerned that their medications could be harmful. Others were concerned about taking medications long-term.

“Well I suppose I don’t like taking it, for the simple reason I’d be afraid they’d be doing something that... You know if you’re taking tablets for one thing you could be damaging something else.” L5,M,70

“Of course I think about [the long-term effects of taking medication] sometimes. I say you know I’m on a lot of medication for quite a number of years.” L1,M,78

Low adherers expressed either a desire to take fewer medications than currently prescribed, or to stop taking medication altogether.

“I would like to be on less, just from a general health point of view in terms of what my liver has to break down. And I would hope. I would hope that maybe I will be on less.” L3,F,48

“Well I’d love it if there was just one tablet, rather than the ones I’m taking like, that would do it all, but like that’s not going to work [laughter], I’ve discovered.” L2,F,64

Subtheme 2: Coherence of Beliefs. The second sub-theme of Beliefs about Medications represents the extent to which patients felt there was evidence to support their beliefs about their treatment.

Highly adherent patients described ‘coherent’ beliefs; these patients felt that they had experienced convincing evidence that their antihypertensive medications do what they are intended to do.

“Before I started into a routine, I used to forget to take my medicine, and then I would feel a little bit dizzy or not well anyway. So my medicines, I need them. Because when I was missing taking them or forgot to take them on time, I would feel ill. I’d know myself that I hadn’t taken my tablets.” H3,F,70

“They benefit me. So I actually need everything I’m taking. The tablets, they make me feel better.” H2,F,79

Low adherers expressed more uncertainty as to whether their medications were having an effect. They were also less sure about the potential consequences of not adhering to their medication.

“I have no idea. I never know whether my BP is up or down, or good or bad.”

L3,F,48

“I wouldn’t notice a difference at all if I didn’t discover I had forgotten them you know.” L1,M,78

High adherers, in contrast, were cognisant of potential health consequences of not taking their medications.

“Things like that [hospitalisation] have convinced me that I can’t afford not to be careful [with my medication].” H8,M,83

“Well I’ll be afraid now, tell you the truth. I mean if I did [stop taking my medication] I’d be afraid I might start to lose my breath again.” H5,M,69

Low adherers were more likely to question the efficacy of their treatment due to the lack of feedback.

“There’s no reinforcer there. No. I do it because of kind of blind faith... And I always thought well who’s to say that that BP tablet is still doing everything it should be doing?” L3,F,48

“Well I wouldn’t find myself any different. I don’t know are they doing anything inside or what.” L4,M,54

Patients from both groups described a desire for more frequent BP monitoring and subsequent medication reviews. Patients felt this would motivate them to adhere to antihypertensive medicine, as they would be able to see its effects.

“In terms of taking your medication, there’s no better incentive than knowing that it’s working. So for something like BP where you aren’t getting feedback from the condition itself, you do need something to show you it’s doing the job.” L3,F,48

“It’s very hard to know with [BP]. But how do you know unless you’re taking blood pressure every day regularly, and then going off it and sort of seeing the effect that has.” H6,F,75

Theme 2: Habits and Routine. The second theme related to patients' habits and routine regarding their medications. This described the extent to which medication-taking had become routine in their daily lives, as well as strategies patients used to support their medication-taking.

All patients described ways in which they integrated taking medicine into their daily routine. High adherers linked medication-taking to activities they completed every day.

"I have it up on the table there right beside where I take my breakfast. I have everything organised." H7,M,86

"Well I take one medication, half a tablet three times a day. Normally I would take it breakfast, lunch, dinner in the evening." H6,F,75

Low adherers made similar statements about their medication-taking routine, but were vague in describing their cues to action.

"I take them every day. I take them in the morning." L3,F,48

High adherers described taking medicines as something they did automatically.

"I'm [taking medication] for a good number of years now, and automatically I just do it. So it's become a habit for me really." H1,F,60

Both groups referred to occasionally forgetting their medications. This was typically associated with a disruption in their daily routine.

"Maybe an odd time now I might forget. I might be going somewhere. I might forget to bring them with me. And I'd say to myself Jesus I didn't bring my tablets." L4,M,54

"Say I'm going out for the evening with friends normally when I would take the dose, I might have forgotten to take it with me or something." H6,F,75

The highly adherent group, however, described supports they had in place to help them remember in the context of such events. These included both instrumental support (e.g., pill boxes) and social support.

"I miss the odd day like. It's very seldom now it happens. They're here beside me when I have my breakfast you see. I can't miss them. The wife here has them in a special box. One for Monday, one for Tuesday, one for Wednesday... I take them every morning when I get up, so I can't get mixed up." H5,M,69

“Let’s say on Monday morning in about 20 minutes I have the whole week, and each day I’d bring the one day downstairs and take them at the time it’s prescribed for that day. And I found that really very good.” H8,M,83

Some low adherers, despite using similar adherence supports, still reported missing doses.

“I have them on a little container there, and I put them into the container Monday, Tuesday, Wednesday, Thursday, Friday, Saturday, Sunday. I normally make them up every Sunday like that. And I’d say to myself Jesus I’ve still a day left. How come?” L4,M,54

Theme 3: Health and Health Systems. The third theme related to patients’ health status and the primary care system. This described the role of patients’ health and healthcare in influencing their medication-taking decisions. Within this theme there was one subtheme of Managing Multiple Medications.

All patients described the role of GPs in managing their health. All spoke favourably of their own GP and described their relationship in positive terms.

“I’m happy with my doctor as well. I find him very good and very understanding. Apart from the medical climate, he’s a very nice guy as well.” L1,M,78

“They don’t call me Mrs. Smith [pseudonym]. They call me Jane, and I like that, because it relaxes the pressure more when they talk to you like that you know. Than me talking Mrs. Smith and all. It’s great.” H3,F,70

Overall patients had confidence in their GP and trusted them with their care.

“Oh I trust my life with my doctors. I do indeed.” H3,F,70

“I have the upmost confidence in my doctor.” H7,M,86

Patients highlighted the importance of good doctor-patient communication. Overall patients felt they could discuss things with the GP and they would be heard. Patients felt it was important the GP took time to explain treatments in a way they could easily understand. Having a clear understanding of why they were taking medications was important.

“When I’m talking to [the GP] about it, he specifies the reason why I’m on the tablets. And once I know the reason why, and I know I have to take them, that’s it. I’ll take them.” L6,F,69

"I had a very good experience. Yeah. Because I felt [the GP] listened to me."

H2,F,79

Highly adherent patients showed a willingness to follow their GP's instructions despite personal concerns about treatment.

"I may have ideas and attitudes about it you know, but the reality is that somebody who knows something about these things is suggesting what would help." H8,M,83

"I mean if it was something that was going to ease the situation, I'd certainly have no problem with it at all. Even though basically I could say my goodness I'm keeping a chemist shop open [laughter]. No, no. I would always. I may have ideas and that and attitudes about it you know, but the reality is that somebody who knows something about these kind of things is suggesting what would help." H8,M,83

Others accepted advice from their GP and were willing to follow their instruction without question.

"I'm told I have to take them, and I've to take them for the rest of my life. And that's that." H4,F,67

"You need to take them when you're told to take them and that's it." H5,M,69

Some low adherers expressed reluctance to discuss their concerns about medicines with their GP.

"You hate quizzing doctors about [de-prescribing] [laughter]." L5,M,70

Whereas others were open with the GP about their dislike of medicines.

"I don't like taking them. And if you talked to [the GP], he'd be the very one to tell you because he says to me don't look at me now, but I'll have to put you on something. And I say is it an absolute necessity. I hate taking medication."

L6,F,69

Despite the generally positive view of individual GPs, many patients felt that pressures inherent to the primary care system adversely affected their care.

"Well I suppose I think it's important that doctors don't become kind of complacent because they're so busy." H6,F,75

“I know that they’re pushed for time, but you know there’s nothing to stop them saying okay, right, once every six months everybody who’s on BP tablets come in and we’ll just double check your blood pressure. [...] And you know if it needs to be followed up then you have to make an appointment.” L3,F,48

Some patients also suggested that GPs were out-of-touch with the needs of patients and the burden associated with managing a chronic condition.

“I just said to [the GP] is that an awful lot of medication, and he said it’s not really he said.” L6,F,69

“I said should I get a BP monitor. I mean how does he know about my BP? He said well look, you can get a BP monitor, but then you’ll drive yourself cracked. You don’t need to take it every day you know. He said get it taken in here whenever you want. But he’s not thinking of the cost, you know.” L3,F,48

Subtheme 1: Managing Multiple Medicines. Although this study was concerned with aTRH, most patients described living with more than one chronic condition. Many described the increased treatment burden of living with multimorbidity. Both high and low adherers described this as a challenge to adherence.

“There’s so much. If I was to work it out individually myself with about twelve bottles or whatever, I’d never figure it out.” H7,M,86

“And then I have arthritis, and I’m on eight paracetamol a day. But I’m trying not to take the eight a day. I try and work it around two in the morning the same time as my blood pressure. And two in the evening then with my cholesterol tablet. [...] Now I’m on a diabetes tablet as well.” L6,F,69

Patients were frustrated at having to take multiple antihypertensive medications in particular.

“But being on so many [antihypertensives] and then if [my BP] goes a bit high you know. I’ll say God I’m on all that now and it still goes high.” H4,F,67

The high prevalence of multimorbidity among the sample meant that often their healthcare was managed by more than one HCP. Conflict between the GP’s advice and other healthcare practitioners’ was an issue that frustrated patients and reduced their confidence in their care.

“In the hospital they put me off my medication you know for a while. I didn’t realise I should have gone back to the doctor sooner and got back on it. So when I went back to the doctor he said to me you shouldn’t have been off it. But

I didn't know any better like. I thought this was great when they put me off it in the hospital.” H1,F,60

Some patients expressed concern that they may be on inappropriate medications or doses. These patients sometimes sought advice from other HCPs involved in their care.

“If I go to, say, a cardiologist once a year. I do say to him from time to time, am I on the right medication do you think? Because I've always been put on this medication. I've been hospitalised a few times for my heart. You're put on medication then leaving. And I kind of wonder afterwards, well should this be checked up on or... You know I go once a year, which isn't all that often, and you're on all this medication. So it does occur to me, and I do say to him am I on the right meds do you think?” H6,F,75

Discussion

Summary. In this qualitative study of adherence among patients with aTRH, three major themes were identified: beliefs about treatment, habits and routine, and health and health systems. High adherers reported favourable beliefs about antihypertensive treatment that had been validated by experience with treatment over time, described strong medication-taking habits and stable routines, and positive relations with their GP. Low adherers expressed less coherence of beliefs and used less successful strategies to support medication-taking in daily life. Both groups reported ambivalence about taking their medications (Phillips et al., 2014). High and low adherers reported similar experiences of the primary care system, as well as managing multiple medications.

Strengths and limitations. While there has been recent useful epidemiological characterisation of resistant hypertension (P. Hayes et al., 2018; Sinnott et al., 2017), there has been no qualitative investigation of patient experiences of its treatment in the community. This study provides useful new findings in this regard. The use of PPI to guide the research is a key strength. Reflexivity was enhanced by the multidisciplinary research team coming together to review the data and coding. One limitation is the likelihood of sampling bias. The current sample may be more highly adherent than is truly representative, as highly non-adherent patients may be unlikely to self-select into an adherence interview. Furthermore, the majority of interviews were conducted via telephone, which has been criticised as an interview medium (Novick, 2008). However, allowing participants to choose their interview

mode may have increased study participation and engagement (Cachia & Millward, 2011; Sturges & Hanrahan, 2004).

Comparison with existing literature. To our knowledge, this is the first qualitative study of patients with aTRH in primary care. Results are consistent with existing theory and research in several ways; the themes identified map onto the Common-Sense Model of Self-Regulation (CSM; H. Leventhal et al., 2016), a social-cognition model that suggests individuals form lay representations of their illness that guide coping strategies to manage illness threat (Hagger et al., 2017). Coherent treatment-favourable beliefs and medication-taking habits, key components of the CSM (Phillips et al., 2016) were identified as core themes. Health status and systems, which play a key role in the development of illness representations, were also identified as pertinent themes.

There was no mention by any patient of digital supports for adherence, such as smartphone apps (Morrissey et al., 2018; Morrissey, Glynn, et al., 2017). Though not the focus of this study, the absence of digital intervention despite its increased use in healthcare is striking. It may be that the current cohort of older adults would not consider using digital technologies to support adherence without being specifically advised to do so by their GP. This may not be the case in future when generations who have grown up with this technology enter into later stages of the lifespan.

Comparison with qualitative literature on adherence in hypertension. Results of this study are largely consistent with general qualitative findings in the area of adherence in non-resistant hypertension. According to a systematic review of lay perspectives on hypertension and antihypertensive adherence (Marshall et al., 2012), patients with hypertension believe in the necessity of their medications but may be unintentionally non-adherent due to prospective memory failure (or ‘forgetfulness’). Additional qualitative research highlights patients’ concerns that medications may be harmful, particularly in the long term (Gascón et al., 2004; Pages-Puigdemont et al., 2016; Saleem et al., 2012; Tsiantou, Pantzou, Pavi, Koulierakis, & Kyriopoulos, 2010). Incongruent and ambivalent beliefs about hypertension and its treatment have also been identified in previous qualitative work (Schlomann, & Schmitke, 2007). Some qualitative work suggests that coherence of treatment-favourable beliefs from noticing benefits of taking medications is an important factor in adherence in hypertension (Herrera, Moncada, & Defey, 2017). Having a good interpersonal relationship with the GP is also seen as an important factor in promoting adherence in hypertension (Tsiantou et al., 2010). The exclusively positive view of the GP in this study conflicts with previous findings, which

suggest patients' experiences of interactions with healthcare practitioners vary considerably (Gascón et al., 2004; Pages-Puigdemont et al., 2016; Saleem et al., 2012; Schlomann, & Schmitke, 2007).

The current findings make additional novel contributions to the literature. Interestingly, the role of habits appears underemphasised in the qualitative literature on adherence in hypertension, with only a small handful of studies highlighting weak habit strength as a barrier to adherence (Khatib et al., 2014). Similarly, there is limited discussion of polypharmacy and treatment burden in the existing qualitative adherence literature. Though some studies have described treatment burden as an important factor in antihypertensive adherence (e.g., Jamison, Graffy, Mullis, Mant, & Sutton, 2016), this is more typically associated with studies of patients with multimorbidity than hypertension alone (Rosbach, & Andersen, 2017; Van Merode, Van De Ven, & Van Den Akker, 2018).

Implications for research and practice. This study aimed to qualitatively compare high and low adherers to antihypertensive medications. One key finding from this study is that high and low adherers are not as easily distinguished from one another as may be expected. Both high and “low” adherers stated that they always took their medications and rarely forgot, and used similar strategies to support adherence in daily life. This highlights how difficult it can be to identify poor adherence in both research and clinical contexts. Greater consideration of how we can identify adherence issues in practice is needed.

This sample represents a relatively narrow cohort of patients, which may have had an impact on the results of this study. For example, cost of antihypertensive treatment was not identified as significant, perhaps because most participants were GMS-eligible (see Table 1). Furthermore, this restricted sample is theoretically likely to be at a similar stage of adherence behaviour development/maintenance, versus those initiating treatment (H. Leventhal et al., 2008; Phillips et al., 2013). Further research with representative incident cohorts may provide richer information regarding variation in adherence behaviour at different stages of the illness and self-management trajectory.

Conclusion. These findings are consistent with the study of adherence for other chronic conditions in that treatment beliefs, habits and quality of patient-healthcare provider relationships appear central to our understanding medication adherence. The treatment burden associated with aTRH and frequent presence of other chronic conditions mean that the complexities of self-management in the context of polypharmacy are particularly pertinent.

The findings also reflect the difficulty in identifying adherent versus non-adherent patients and highlight the importance of adequate adherence assessment in primary care.

6. General Discussion

Chapter Overview

This chapter will present a summary of the overall findings of this research and evaluate the contribution made by this research to understanding medication adherence behaviour for resistant hypertension in general practice. Findings from this research will be discussed in relation to existing literature and approaches to designing interventions targeting medication non-adherence will be presented. Implications of these findings for future research and clinical practice will be described. The limitations of each study will be described and approaches to addressing these limitations will be suggested. Finally, this chapter will end with concluding remarks.

Summary of the Overall Findings of this Research

- According to this research, poor medication adherence for patients with aTRH is an issue in all healthcare contexts (i.e., primary, secondary, and specialist care settings).
- Approximately one-third of cases of aTRH in the published literature may be attributable to medication non-adherence. As a direct result, a significant proportion of patients may be inappropriately classed as resistant to antihypertensive treatment. This can result in unnecessary treatment escalation as well as referral for unwarranted invasive diagnostic testing and specialist treatment.
- Methodological factors, particularly the type of adherence assessment measures used, have contributed to a lack of clarity around the estimated prevalence of medication non-adherence behaviour among this high-risk patient group. The type of adherence assessment used in a study can account for variations seen in the adherence estimates observed within samples.
- Psychological/behavioural factors predict antihypertensive non-adherence for aTRH. Specifically, medication-taking habit strength significantly predicts adherence such that stronger habits are associated with better adherence.
- Treatment-related beliefs, habits and quality of patient-healthcare provider relationships all appear central to our understanding of medication adherence.
- The high treatment burden associated with aTRH, as well as the frequent presence of other co-morbid chronic conditions, mean that the complexities of self-management in the context of polypharmacy are particularly pertinent for this group.

- Accurately/adequately identifying adherent versus non-adherent patients is a key challenge to the effective management of poor adherence in primary care.

Contribution of this Research

The significance of aTRH for cardiovascular morbidity and mortality has been demonstrated in the literature (Calhoun et al., 2008; Daugherty et al., 2012; Pierdomenico et al., 2005; Tobe & Lewanczuk, 2009). However, due to a lack of empirical investigation focusing on patients with aTRH who display poor antihypertensive adherence, factors associated with non-adherence and potential targets for clinical intervention to enhance adherence for this group were not established. Furthermore, much previous empirical work examining adherence for aTRH utilised single adherence assessment methods, many of which have been demonstrated to be unreliable and potentially biased when used in isolation. The findings of this research indicate that approximately one-third of aTRH cases may be explained by poor adherence to antihypertensive medication, suggesting that a significant proportion of patients are inappropriately classed as resistant to treatments that they may not be taking. Furthermore, psychological and behavioural factors, as well as treatment-related factors, are central to predicting adherence to antihypertensive medication in aTRH and represent key targets for clinical intervention.

Conceptual and Theoretical Ramifications

This research makes a significant contribution to health psychology theory in several ways. In particular, the current findings strengthen emerging arguments that understanding of and intervention in illness self-regulation may be improved by placing a greater emphasis on automatic processes that influence health and illness (Orbell & Phillips, 2018). Study 2 represents a replication and extension of previous work that extended the CSM to a model of long-term adherence (Phillips et al., 2016; Phillips et al., 2013). With this successful replication, the evidence regarding the primary importance of habit strength as opposed to treatment-related beliefs for adherence has garnered strong empirical support that warrants changes from the traditional CSM approach to observational research and intervention design. Specifically, these findings suggest that greater emphasis needs to be placed on the development of behavioural automaticity in relation to intervening on the long-term maintenance of medication-taking behaviour. That is not to say that illness- and treatment-related beliefs are unimportant with regard to adherence behaviour and health outcomes. Indeed, Study 3 highlights that, from a patient perspective, reflective and contextual factors

are important in determining whether a patient will adhere to treatment, despite the limited predictive power of beliefs in Study 2. Although there have been concerns regarding the predictive importance of reflective CSM factors (Brandes & Mullan, 2014; Doyle & Mullan, 2017), there is insufficient evidence to conclude that beliefs are not important in predicting adherence (Phillips et al., 2017). The current findings instead emphasise that longitudinal research is now needed to further advance the CSM as a predictive model of long-term adherence. Attempts to properly assess the importance of beliefs and other reflective factors and processes, in combination with automatic factors such as habits, via large-scale studies utilising inception samples at diagnosis/treatment initiation with long-term follow-up to a behaviour maintenance stage should be the next step towards CSM refinement.

This research also has significant implications for the conceptualisation of adherence behaviour. In Studies 1 and 2, the findings revealed a striking lack of convergent validity for the various adherence measurements. While all measures reveal something in relation to medication-taking behaviour, the lack of concordance between them presents both a conceptual and practical measurement challenge for research in this area. Greater precision in the conceptualisation of medication-taking behaviour may provide the clarity that is needed to inform how adherence should be operationalised. For example, the behavioural distinctions between initiation and persistence and the temporal window being captured by a given adherence measure may need clearer specification. The measures reviewed and used in Studies 1 and 2 vary in the extent to which they align with particular conceptualisations of adherence. Therefore, this research reveals that there is more work to be done in relation to the conceptualisation of medication-taking behaviour in this literature.

A core challenge to adequate antihypertensive adherence is the lack of experiential feedback from the condition itself, given its asymptomatic nature. This means that many patients experience a lack of direct evidence that the treatment is doing what it is intended to do (i.e., improving their health by reducing BP). This can prevent a coherent system of treatment-favourable beliefs from forming, and therefore may result in patients prematurely discontinuing a required treatment. Although coherence of treatment-favourable beliefs was not significantly predictive of adherence in Study 2, it was identified a key factor in adherence behaviour within Study 3. Further evaluation of the effect of coherence of beliefs is particularly warranted given recent evidence that providing feedback on behaviour can dramatically improve adherence to antihypertensive medication. P. Gupta et al. (2017) demonstrated marked improvements in adherence following repeated screening for non-

adherence to antihypertensive treatment using biochemical analysis of urine and/or serum. In their study, results of the initial biochemical analysis were discussed with each patient at a clinical appointment. Urinary adherence ratios (i.e., the ratio of detected to prescribed antihypertensive medications, as in Study 2) increased from 0.33 to 1 (i.e., 100% adherence) between the first and the last clinical appointments. This observed increase in urinary adherence ratios in patients who were poorly adherent at study outset was associated with significantly improved BP control relative to baseline (mean difference \approx 19.5 mmHg SBP and 7.5 mmHg DBP, $p < .01$). These findings suggest that repeated biochemical analyses with appropriately delivered patient feedback could be considered as a therapeutic approach to tackling poor adherence to antihypertensive medication in clinical practice. Although promising, this approach will require extensive validation before being integrated into routine care.

This research identifies habit strength as primarily important in promoting adherence among community-dwelling older adults living with aTRH. Notably, the current sample had all been prescribed antihypertensives for a period of at least three months and was therefore likely to have already formed coherent treatment-favourable beliefs and moved into a maintenance stage of adherence behaviour. This is consistent particularly with the relatively low reporting of intentional non-adherence (as opposed to unintentional non-adherence) observed for this sample in Study 2. This highlights the importance of tailoring behavioural interventions to the needs of the target population; while the current sample and similar samples from the population of those with established resistant hypertension may benefit from habit-focused interventions, patients at earlier stages in the illness trajectory (i.e., diagnosis and/or treatment initiation) may be more amenable to interventions targeting illness- and treatment-related beliefs and/or providing reinforcing feedback on medication-taking behaviour. Specific approaches to intervening with patients to improve adherence are discussed in detail later in the chapter.

It is worth noting the potential pitfalls associated with the conceptualisation of habit strength as a predictor of adherence. Though this terminology is widely employed in adherence research (e.g., Bolman et al., 2011; Hoo, Boote, Wildman, Campbell, & Gardner, 2017; J. Murphy, Eustace, Sarma, & Molloy, 2018; Phillips et al., 2016; Phillips et al., 2013; etc.), some argue that conceptualising habit strength in this way, particularly in cross-sectional studies (Mansouri Hanis & Mansori, 2017), is potentially problematic. For example, there is an argument that good adherence and strong medication-taking habits are two sides of

the same coin (i.e., good adherence essentially equates to having strong medication-taking habits); however, it is entirely possible that a person may be highly adherent without the behaviour ever becoming habitual (i.e., they adhere to their medication as prescribed in a conscious and deliberative way, without shifting towards habitual action). Describing habit strength as a correlate of adherence, as opposed to a predictor, may address some of these potential conceptual concerns. Future research should give greater consideration to the terminology used in describing the relations between these variables and the conceptual ramifications this may have.

Findings from Study 3 highlight emerging arguments in the adherence literature that ambivalence may play an important role in predicting adherence. Ambivalent attitudes are characterised by both strong positive and strong negative evaluations. In the context of medication adherence, these may be best conceptualised as strong necessity and strong concern beliefs, in accordance with the Necessity-Concerns Framework (Horne, Chapman, et al., 2013; Horne & Weinman, 1999). This is reflected in Study 3, wherein patients' necessity beliefs were strong across both high and low adherers, but low adherers also expressed strong concerns about their medications. These findings contribute to emerging evidence that a re-evaluation of how the Necessity Concerns Framework is applied may be warranted. For example, Phillips et al. (2014) used polynomial regression, a multidimensional analysis technique, to assess the combined effects of necessity beliefs and concerns for predicting adherence to stroke-prevention medication in a stroke-survivor population. Their results indicated that those with ambivalent beliefs had poorer adherence than those who were indifferent towards their medications (i.e., those with weak necessity beliefs and weak concerns). While these findings provide compelling evidence that polynomial regression is an effective technique for evaluating the complex and multidimensional interplay of necessity and concern beliefs, they may also have implications for interventions to enhance adherence by means of modifying patients' beliefs. For example, motivational interviewing, a directive counselling style for eliciting behaviour change by exploring and resolving ambivalence (W. R. Miller & Rollnick, 2012), may be an appropriate technique to improve adherence for those with ambivalent treatment-related beliefs.

Adherence Assessment

Findings from this research bolster existing arguments that multiple diverse adherence measures are required to form adequate assessment of adherence behaviour in both research and clinical practice. Study 1 demonstrates that the measure used to assess adherence has a

significant impact on the adherence estimates observed. Despite this, only three studies included in our review utilised a combination of adherence measures. Study 2 aimed to address this limitation of the existing aTRH literature by using a combination of direct and indirect adherence measures to assess adherence for a large sample of aTRH patients in primary care. Results indicated a weak association between self-report and prescription refill (indirect) measures and no association between these indirect measures and a direct measure of antihypertensive drugs in spot urine among this sample. Finally, Study 3 highlights that adherence issues may be particularly difficult to identify through discussion with patients alone, as differences in attitudes, beliefs and habits between high and low adherers are subtly nuanced. Together these studies indicate that a patient's score on one adherence assessment does not dictate their score on another, and that multiple empirically validated tools are required to provide a complete picture of a patient's adherence behaviour.

Study 2 is novel in its use of bioanalytical assays of spot urine to assess adherence in conjunction with two other more traditional adherence assessments. Physical tests of bodily fluids to assess adherence are increasingly used in research, as demonstrated by the relatively large number of studies included in Study 1 that used physical tests ($k = 9$) or a combination of physical tests and another adherence assessment ($k = 3$). Assessing adherence by urine screening is a useful tool in detecting poor adherence, especially in the context of multi-medication regimens. It has distinct advantages over other adherence assessment methods, the upmost of which being its ability to demonstrate with (some) certainty that medications have/have not been ingested; however, it is limited by resource demands in terms of time, technical expertise (both in terms of carrying out the analysis, and interpretation of results in light of key pharmacokinetic considerations) and equipment, its inability to provide feedback at the point of care, and the cross-sectional nature of the assessment. Despite its usefulness in a research context, and promising preliminary results regarding its usefulness as a therapeutic tool (P. Gupta et al., 2017), the clinical utility and feasibility of integrating bioanalytical assays of urine, blood or plasma to assess adherence into routine primary care has yet to be adequately assessed. Further research is also needed to evaluate the reliability and validity of biochemical assays of urine for informing clinical decision-making prior to integration into routine healthcare practice.

In the absence of a formalised system to support bioanalysis of bodily fluids, clinicians must rely on traditional measures of adherence, primarily evaluation of prescription refill records, patient self-report, and physician assessment. Prescription refill records are

often relied upon in primary care to indicate patient adherence. These records allow assessment of adherence behaviour over extended periods of time and for large groups of patients, which is useful both clinically and in a research context. However, prescription refill records lack specificity as they cannot identify those patients who collect their medications but do not ingest them. Self-report remains the most common method for assessing adherence in research and clinical care (Stirratt et al., 2015). Although useful with regard to their low cost, ease of administration, and ability to provide feedback at the point of care, self-reports tend to overestimate adherence behaviour compared with other methods, and generally have high specificity but low sensitivity. Additionally, self-report tools vary considerably in their item phrasing, recall periods, and response scales, to such a degree that associations among different self-report scales are likely to be weak, as demonstrated in Study 2. Physician assessment of adherence is decreasingly relied upon in research given the wide availability of other better-validated measures; however, in busy clinical settings, it is possible that this proxy for adherence behaviour is still used to inform clinical decision-making. This type of judgement on a patient's adherence behaviour outside of the office setting has been shown to be unreliable, with previous research indicating that physicians' adherence assessments correlate poorly with prescription refill history (Meddings et al., 2012). Despite the limitations of each measure, the quality of adherence assessments may be maximised through efforts to use a combination of psychometrically validated self-report scales that facilitate improved estimation and recall and reduce social desirability bias; properly populated prescription record databases for both publicly and privately insured patients; and empirically supported interview techniques to elicit conversation about adherence issues in clinical settings. In situations where this is not practicable, the choice of measurement should be based on its usefulness in light of the assessment goals, as specific methods may be more applicable to certain situations, depending on the type of adherence being assessed, the precision that is required, and the intended application of the results (Farmer, 1999; Nguyen, La Caze, & Cottrell, 2013). These considerations are particularly important in the context of interventions to enhance adherence, as inadequate adherence assessment may mask the true effectiveness of interventions.

Applying the Current Findings to the Development of Behavioural Interventions to Enhance Adherence

Together the findings from the current research provide valuable insight into future directions for behavioural intervention development guided by the CSM to improve

adherence for asymptomatic chronic conditions such as aTRH. Despite significant advances in behavioural science in recent decades, many current methods of enhancing adherence for chronic health conditions are complex, labour-intensive, and not particularly effective (Haynes, Ackloo, Sahota, McDonald, & Yao, 2008; McDonald, Garg, & Haynes, 2002; Nieuwlaat et al., 2014). The absence of established behavioural science theory from the development and implementation of many existing adherence interventions (see Morrissey, Durand, et al., 2017, for a systematic review and meta-analysis of interventions to enhance adherence and BP control in hypertension) is a fundamental issue that has limited progress in this area of research. This section will describe potential ways in which the current findings and, more broadly, the extended CSM may be used to guide future intervention development. The following section is broken down into content, context, and modes of delivery.

Content.

Interventions to promote habit formation. Study 2 contributes to the increasingly compelling evidence for the primary importance of habit strength in promoting adherence to long-term medication regimens. Interventions that aim to automatise behavioural responses (e.g., adhering to a prescribed treatment) and create habits in this regard have considerable promise (Orbell & Phillips, 2018). Interventions to promote medication-taking habits may be of particular relevance to patients for whom adherence problems are unintentional, for example due to prospective memory failure or an inconsistent medication-taking routine. However, findings from Study 2 revealed that habit strength was the strongest predictor of both unintentional and intentional non-adherence, which may suggest that many patients with diverse adherence issues may benefit from habit-forming interventions.

Action planning. Strategic automatization of adherence behaviour may be achieved through *action planning*, a key element of the CSM that has been shown to promote the adoption of new goal-directed behaviours, maintenance of goal-directed behaviours over time, and changes in existing health-risky behaviours. Action planning, sometimes also referred to as implementation intention, refers to a process of consciously considering and deciding upon actions to take in pursuit of a goal (Hagger & Luszczynska, 2014). This typically involves explicitly pairing expected environmental cues with intended actions, for example in the form of an “if [cue] – then [action]” statement (Gollwitzer, 1999). Cues may be somatic (e.g., “*If I experience breathlessness, then I will take my reliever inhaler*”) or environmental/situational in nature (e.g., “*If I have eaten my breakfast, then I will take my medication*”), meaning that action planning may be usefully applied to a variety of health

conditions, including asymptomatic conditions such as hypertension. An additional process termed *coping planning* (R. Schwarzer, 2008), which involves specifying plans to overcome anticipated barriers to carrying out the intended action, may also be employed to enhance the effectiveness of planning for translating intention into action. Planning may be particularly helpful for older patients (Zogg, Woods, Saucedo, Wiebe, & Simoni, 2012) and those with poor prospective memory (Wolff, Warner, Ziegelmann, Wurm, & Kliegel, 2016).

Although the act of action planning is itself conscious and reflective, evidence suggests that it promotes desired behavioural outcomes via automatic mechanisms (Orbell & Phillips, 2018). First, identifying a contextual cue and rehearsing the action plan associated with that cue makes it more accessible in memory and ensures the cue is detected when encountered. Second, by forming a strong cue–action link in memory, the cue is enabled to automatically elicit the desired action through implicit goal activation (Sheeran, Gollwitzer, & Bargh, 2013) or activation of associated cognitive schemas (Papies & Hamstra, 2010; Papies, Stroebe, & Aarts, 2008). This type of intervention has been shown to be effective for promoting adherence behaviour (Brom et al., 2014; Brown, Sheeran, & Reuber, 2009; Jackson et al., 2006; L. L. Liu & Park, 2004).

Habit formation and piggybacking. Theoretically, patients may form habits spontaneously by means of behavioural repetition; however, for patients whose medication-taking behaviour has not been repeatedly performed in a stable context, this may not necessarily be the case. Interventions that encourage and support patients to form strong medication-taking habits may be useful in this regard. Effective habit development requires selection of an appropriate contextual cue and consistent repeated performance of the behaviour following recognition of that cue. The cue must be salient and occur at the same frequency as the desired action. If part of an existing behavioural routine (e.g., eating breakfast), the cue should ideally be identified at the *end* of that routine (e.g., clearing plates from the table) to decrease the likelihood of the behaviour running on to another element of an ongoing task, hence resulting in the opportunity to act being missed (Judah, Gardner, & Aunger, 2013). Ensuring people have the capability (e.g., necessary knowledge and skills) to perform the behaviour is also essential to promote habit formation. Finally, ensuring that any necessary equipment (e.g., medications, pill boxes, alarms, etc.) is available, visible, and easily accessible is required (Wood & Runger, 2016; Lally & Gardner, 2013).

Even when the necessary behavioural scaffolding is in place, habits do not form quickly (Lally, van Jaarsveld, Potts, & Wardle, 2010). It may be desirable, therefore, to

integrate planning via implementation intentions to speed up habit development (Orbell & Phillips, 2018). Judah et al. (2013), for example, demonstrated that action planning can lead to increased automatic engagement in behaviour in their intervention study that paired flossing with an existing tooth-brushing habit (i.e., flossing after the cue of brushing). Orbell and Verplanken (2010) also found that implementation intentions to floss following a specific situational cue resulted in significantly stronger flossing habits relative to controls. This approach of pairing a new health behaviour to an existing habit, termed “piggybacking” (Rothman et al., 2015), may also be useful for the development of medication-taking habits.

Interventions to promote coherence of treatment-favourable beliefs. Study 3 highlights that, despite its limited predictive value in Study 2, coherence of treatment-favourable beliefs may also represent an important target for behavioural intervention to enhance adherence. Despite the fact that hypertension has no associated symptoms, thereby making the attainment of evidence that the treatment is working effectively more difficult, there are a number of potential intervention strategies to promote coherence of treatment-favourable beliefs among this population. P. Gupta et al. (2017), described in detail above, demonstrate that providing physical feedback from assays of bodily fluids had a profound effect on adherence behaviour. Home and/or ambulatory BP monitoring can provide a similarly useful proxy for physical feedback regarding the effectiveness of antihypertensive medication. A systematic review of interventions utilising home BP monitoring to improve adherence found mixed effectiveness depending on the study setting and additional intervention components; however, the authors acknowledge that further research evaluating the independent effects of home BP monitoring in primary care settings is warranted (Ogedegbe & Schoenthaler, 2006). Study 3 indicates that there is an appetite among patients for more frequent office BP monitoring and/or a willingness to engage with home BP monitoring. This may be particularly useful for patients at earlier stages of the illness trajectory as they are initially gaining feedback as to whether their treatment is effective.

An integrated approach to intervention development. There is emerging evidence that interventions for medication adherence should target both reflective and automatic systems, which is consistent with assertions that complex interventions are more effective and have longer-term effects than interventions based on single strategies (McDonald, Garg, & Haynes, 2002; Boulware, Daumit, Frick, 2001). For example, Ogedegbe and Schoenthaler (2006) indicate that the most effective interventions to enhance antihypertensive adherence that included home BP monitoring (targeting the reflective system) as a component were

complex interventions that included additional strategies such as timed medication reminders (targeting the automatic system). In another example, O'Carroll, Chambers, Dennis, Sudlow, and Johnston (2014) report an intervention that aimed to increase antihypertensive adherence among stroke survivors. The intervention addressed both reflective (patients' treatment-related beliefs) and automatic processes (habit formation via implementation intentions), which together should theoretically account for both intentional and unintentional non-adherence. Relative to a control group, participants who received the intervention had increased adherence by approximately 10% (measured electronically over three months). The effects of the intervention could be explained by changes in beliefs (specifically, a reduction in concerns about treatment) and reduced forgetting to take medications. However, effects were dependent on patients not having a previously established medication-taking routine. This emphasises important methodological considerations for future intervention research, particularly the need for adequate baseline assessment of behaviours of interest and utilisation of inception samples for whom adherence behaviour is novel. Implications for future research are discussed in greater detail below.

Contexts. Many of the approaches to intervening with patients to improve adherence described above may be easily implemented into routine primary care. Action planning interventions, for example, are easy to deliver (Oettingen, 2012) and can be integrated into key documents such as appointment letters, prescriptions, information leaflets, and waiting room literature, creating a key opportunity to encourage patients to develop if-then plans for taking their medication (Rothman et al., 2015). Additionally, providing examples of how patients can pair their medication-taking with activities they do at the same time and place every day, for example eating their breakfast in the kitchen at 8 a.m. every morning, may promote the development of habitual medication-taking behaviour by facilitating repetition of the behaviour in a stable context (Danner, Aarts, & de Vries, 2007) or “piggybacking” the behaviour onto an existing habit (Judah, Gardner, & Aunger, 2013). Integrating these techniques into GP training programmes may have considerable and far-reaching benefits for patient adherence. These techniques are low-cost, low-intensity, and can feasibly be delivered in the context of a brief GP consultation.

Modes of delivery. Behavioural interventions to enhance adherence may be delivered via any of several modes. These modes may be categorised as (1) human, either face to face or via technologic communication in real time (e.g., audio call, instant message, etc.); (2) printed material, such as letters, posters, leaflets, and so on; and (3) digital. Examples of how

human and printed material modes might be utilised within primary care settings have been presented in the preceding section on intervention contexts. The potential role of digital intervention in promoting adherence is discussed in more detail below.

Digital intervention. There is an increasing emphasis on the role of technology in promoting health. Although patients in the current research did not allude to using technology to support their medication-taking or other health-related behaviours, Morrissey et al. (2018) suggest that many older adults living with hypertension would be willing to engage with this type of technology, particularly with the involvement of their GP. Digital interventions based on mobile devices, particularly smartphones, represent a potentially powerful modality for hypertension control (e.g., S. Liu et al., 2013; McLean et al., 2016). Digital interventions offer tremendous potential to manage, monitor and improve patient health in ecological settings in a format that is highly personalised, interactive, engaging and rewarding (West & Michie, 2016). They can facilitate sharing of health (e.g., blood pressure) or behavioural (e.g., adherence) data with healthcare professionals or family members given the connectedness of a smartphone (Patrick, Griswold, Raab, & Intille, 2008). Furthermore, digital intervention content can be delivered with a high degree of fidelity (i.e., the degree to which an intervention is delivered as intended; Carroll et al., 2007), which has been a significant challenge for behavioural intervention research (Hardeman et al., 2008; Lorencatto, West, Christopherson, & Michie, 2013).

Several of the intervention strategies described above may be delivered via technologic means, either online or via mobile phone-based applications (apps). Indeed, a recent content analysis of smartphone apps for hypertension management found that the most frequently downloaded apps comprised a BP tracking function through a wireless BP monitor alongside a pill reminder system (N. Kumar, Khunger, Gupta, & Garg, 2015). Digital interventions provide the capability to integrate multiple behaviour change techniques to target reflective and automatic systems for improving adherence behaviour. A particular advantage of digital interventions is the ability to tailor the intervention to the needs of the individual user. For example, a patient receiving an intervention targeting treatment-related beliefs and comprising an action planning component whose poor adherence is due to prospective memory failure may engage only with the habit-promoting aspect of the intervention, thereby reducing patient burden.

Implications for Research

In light of the current findings, there are a number of avenues which warrant further investigation. This research provides a basis for future intervention research targeting medication adherence, as discussed above. Based on the findings of this research, future interventions should be designed to target medication-taking habit formation. Adherence may also be improved for patients at early stages of the illness trajectory by targeting patient beliefs regarding the necessity of and/or concerns about treatment and providing biofeedback on the effects of antihypertensive medication adherence on BP control. An integrated approach to intervening with patients to improve adherence that targets both reflective and automatic systems may yield the best results.

Inadequate and selective assessment of potential causes of pseudo-resistance in the existing literature has resulted in inflated estimates of the prevalence of resistant hypertension and the proliferation of costly invasive treatments that have limited if any demonstrable effectiveness among those who may be pseudo-resistant due to poor adherence (Bakris et al., 2014; Bhatt et al., 2014; Krum et al., 2014; Rosa et al., 2015; Symplicity HTN-2 Investigators, 2010). According to P. Hayes et al. (2018), following best practice guidelines for the assessment of resistant hypertension, including retrospective assessment of adherence using prescription refill records over 12 months, reduced the prevalence figure for true resistant hypertension to 3.3%. This, together with findings from the current research regarding the poor convergence among adherence measures utilised in published studies, highlights the importance of complying with guidelines for the assessment of resistant hypertension (Calhoun et al., 2008; Mancia et al., 2013), including adequate adherence measurement using multiple validated measures. Future research must evaluate all potential causes of pseudo-resistance in order to contribute meaningfully to this rapidly expanding literature.

Although this research was concerned with aTRH, it is apparent from Study 3 that the majority of participants in this research were living with multiple chronic conditions that require extensive pharmacological treatment. It is possible that we need to shift our focus from studying specific conditions in isolation towards examination of self-management behaviours, including adherence, for people living with multimorbidity (Barnett et al., 2012; Cassell et al., 2018). Although studying adherence for specific conditions has provided useful insight into this complex and multifaceted behaviour, the increasing prevalence of multimorbidity internationally presents practical challenges to adherence assessment and

intervention that perhaps warrant a new approach to adherence research. For example, a patient's motivation to adhere to their antihypertensive medications may differ from their arthritis medication; their concerns about steroid treatment may not reflect their concerns about other pharmacological treatments; or their habit for taking their diuretic may not be as strong as for their beta-blocker. In turn, interventions to enhance adherence to medications for specific conditions may be limited by their inflexibility with regard to specific medications. Additionally, the impact of pill burden on patient adherence is best explored in the context of multimorbidity, for which it is likely to be a more significant barrier to optimal adherence relative to a single condition that requires multiple tablets. Further research into adherence for multimorbidity with consideration for how best to measure adherence for individual medications/treatments is warranted.

The need for longitudinal inception studies to adequately assess the role of various CSM factors over the course of illness trajectories has been highlighted throughout this thesis. Study 1 indicates that a mix of retrospective and prospective designs have been utilised in the existing resistant hypertension literature. Prospective designs typically yield superior quality data, given that data points are uniformly defined and collected, rather than obtained from available records that utilise non-standardised outcome definitions. Ideally, prospective cohort studies should follow patients from the time of diagnosis (i.e., disease inception) and treatment initiation; however, feasibility issues have prevented the proliferation of this approach in behavioural epidemiology. Essentially, it is the only approach that can reasonably explain evolving behavioural patterns over time. Although the development of an inception cohort study requires significant resources and forethought, this approach has considerable advantages over other epidemiological approaches. For example, follow-up periods, outcome assessments, terminology and definitions for use in data collection and coding, *et cetera*, can be standardised from study outset to minimise variability and assure data quality. Obtaining input from clinical and scientific experts from a broad multidisciplinary group of collaborators when developing eligibility criteria, disease definitions, variables of interest and their definitions, data collection methods, statistical analysis plans, and logistical plans for study implementation can enhance the quality of the evidence (Bernard, Armstrong-Wells, & Goldenberg, 2013). Specifically, inception studies of adherence for hypertension should include insight from behavioural scientists, GPs, nurses, pharmacists, pharmacologists, cardiologists, nephrologists, epidemiologists, biostatisticians, and clinical research methodologists to ensure that essential considerations (particularly

consideration of power and sample size, and statistical analysis plans to address each hypothesis) are made before data collection ensues in order to prevent design pitfalls that otherwise may become apparent only years later. Furthermore, having a dedicated multidisciplinary team involved in study execution is essential to fulfil the study objectives (Bernard et al., 2013). Although there are considerable challenges with regard to the resources necessary to implement a prospective inception cohort study, as well as the ongoing management and quality assurance procedures necessary to optimise such a study, this approach can provide critical observational evidence that can advance theoretical refinement of the CSM and progress the behavioural science of medication-taking behaviour.

Implications for Practice

This research has several important implications for primary care. Studies 1 and 2 clearly demonstrate that antihypertensive non-adherence is a significant problem within healthcare services. Given that the majority of cases of hypertension are managed in primary care, this has important implications for patient management in this setting. Calhoun et al. (2008) suggest that non-adherence may be less common among patients who are seen by specialists. However, subgroup analysis in our systematic review of the evidence suggests that non-adherence for resistant hypertension is less common in primary care settings (25.8%) than in general hospitals (29.2%) or in specialist hypertension clinics (34.1%), and that this was independent of the effect of the measure used to assess adherence in each setting. One potential explanation for this is that patients with unidentified adherence issues may be referred prematurely for specialist treatment. Effective assessment and management of non-adherence in primary care settings could prevent unnecessary escalation of treatment and referral to specialist hypertension clinics. More frequent and comprehensive assessment of adherence using multiple methods in primary care is necessary to achieve this goal. This type of assessment would facilitate identification of patients who may benefit from adherence-enhancing interventions and provide opportunities for GPs to intervene at the point of care. Indeed, for aTRH, behavioural intervention for those patients with adherence issues could result in patients being de-classified as resistant to treatment and even deprescribing of unnecessary additional antihypertensive medications (Reeve, Shakib, Hendrix, Roberts, & Wiese, 2014; Scott et al., 2015; Woodward, 2003).

Study 3 highlights that interactions with the GP as well as primary care system-related factors are important in determining patient adherence. Patients felt that a good relationship with their GP was important, but that issues inherent to the primary care system reduced their

confidence in their care. Facilitating the development of strong doctor-patient relationships and instilling confidence in patients regarding their care may contribute to improved adherence in primary care settings. This may be achieved by ensuring patients meet the same GP as often as possible and are allowed greater freedom in choosing their doctor within large practices (Stavropoulou, 2011). Treating patients as equal partners in managing their health, involving patients in medication-related decision-making, and resolving potential issues around prescribing as early as possible may also contribute to this end.

Strengths and Limitations

This research has a number of strengths and limitations that merit consideration. In this section, issues related to the methods chosen for each study will be discussed in terms of the strengths and limitations of the overall research. Factors that were omitted from this research but should be considered in future research will also be described.

Study 1 consisted of a systematic review and meta-analysis of medication adherence among patients with aTRH. This review had several important strengths. First, this review and meta-analysis used state-of-the-art methodology to provide the first systematic and statistically rigorous estimate of non-adherence behaviour for patients with aTRH. Second, the multidisciplinary approach taken in conducting the review, which included input from behavioural scientists, physicians experienced in the community management of hypertension, and a biostatistician, has ensured that the review is both methodologically rigorous and clinically useful. Third, the objective of this review was well-focused on (1) the extent of medication non-adherence among patients with aTRH and (2) study-level moderators of non-adherence estimates. Focusing on these two clinically and methodologically important factors further enhanced the utility of this study. Fourth, the large number of studies included in the meta-analysis ($k = 24$) improves the reliability of summary estimates and allows for the real-world diversity of adherence measures and clinical settings to be examined.

The review findings must also be considered in light of certain limitations. First, the findings of systematic reviews are only as reliable as the studies they include (A. X. Garg et al., 2008). Methodological issues existed across studies included in this review. However, each study met the inclusion criteria and contributed to answering the review question. Furthermore, given the epidemiological nature of the review questions, it was elected that the methodological limitations identified within studies were not sufficiently problematic to

warrant exclusion. Second, the studies included in the meta-analysis were significantly heterogeneous ($I^2 > 90\%$). Despite this, meta-analysis was deemed tenable in this instance given the similarity in clinical aspects of the included studies and the outcome of interest for the review (Higgins, Thompson, Deeks, & Altman, 2003). A random-effects model was utilised to account for some of the heterogeneity; however, the significant between-study variability should be considered when interpreting the meta-analysis findings. Furthermore, the measures of adherence observed in the included studies varied considerably in terms of reliability and validity. This may have compromised the reliability of the subgroup analysis by adherence measure. Although there is an influential precedent for this approach in the literature (DiMatteo, 2004b), a summary estimate resulting from this type of analysis may be challenging to interpret. However, in the absence of a sufficiently large prospective study of aTRH that includes adequate adherence measurement, such a figure provides a clinically useful estimation of the extent of the problem of non-adherence for patients with aTRH. Sensitivity analyses excluding (1) less reliable and/or valid measures of adherence (i.e., self-report and MPR) and (2) indirect measures of adherence were conducted to elucidate results of the subgroup analysis, which provide further support for the reliability of these findings. Finally, considering the rapid increase in research outputs on the current topic in recent years, the cut-off of December 2015 for study inclusion limits this review. Several additional studies of adherence in resistant hypertension have been published since January 2016 (e.g., Azizi et al., 2016; Corrêa et al., 2016; de Jager, van Maarseveen, Bots, & Blankestijn, 2018; Hamdidouche et al., 2017b; Heimark et al., 2016; Holmqvist et al., 2016; Ott et al., 2016; Patel et al., 2016; Petit et al., 2018; Smith et al., 2016); however, these studies are largely consistent with those included in Study 1 in terms of the types of designs, samples, clinical settings, adherence measures, and correlates of adherence studied. Overall these studies present similarly heterogeneous results in terms of adherence estimates with little to no investigation of patient-level factors associated with adherence behaviour. One recently published study (Petit et al., 2018), in addition to Study 2, examined patient-level factors associated with adherence beyond clinical and demographic variables; however, this study does not draw on any specified theoretical framework in its selection of variables, which remains a significant limitation of this literature. With this in mind, Study 1 presents a comprehensive overview of this research literature that is largely consistent with findings that have emerged in the last two years.

Study 2 consisted of a cross-sectional evaluation of the role of theoretical factors drawn from the CSM (specifically, patients' treatment-related beliefs, coherence of beliefs derived from experience with treatment, and habit strength) in patient adherence to medication for aTRH. This study contributes to the literature by providing an important replication of recent findings regarding the role of medication-taking habit strength for long-term adherence to treatment (Phillips et al., 2016; Phillips et al., 2013), with a larger sample than in existing research and with different and multiple measures of adherence. This study also allowed for associations between unique measures of adherence to be examined for a large sample of patients with a chronic illness and utilised a composite adherence score derived from three measures to account for limitations in reliability and validity of individual adherence measures. Furthermore, the study extends existing research by evaluating the role of pill burden on the theoretical relationships of interest that may have direct clinical implications for adherence interventions.

Study 2 was limited by certain measurement challenges. First, with regard to the prescription refill measure of adherence, a cut-off of 75% was used given that the majority of patients were in receipt of quarterly scripts (i.e., prescriptions for medications to cover a three-month period) as opposed to monthly scripts. This prohibited the use of 80% as a cut-off for this measure, as is typically seen in this literature (Karve et al., 2009); however, a 75% cut-off is also utilised by the national Primary Care Reimbursement Service pharmaceutical reimbursement policy for GMS-eligible patients on three-monthly prescriptions, which serves to enhance the validity of this approach. Although this is a limitation of the prescription refill measure of adherence, this is reflective of the limited specificity of the prescription refill information available in general practice for patients on long-term antihypertensive medications and highlights the need for additional adherence assessments in primary care. Second, with regard to pill burden, only antihypertensive medications were recorded; therefore, we cannot be sure if patients were prescribed additional medications for other conditions and, if so, how many. This is a limitation that should be addressed in future research, particularly given the increasing prevalence of multimorbidity in primary care (Glynn et al., 2011). Third, as per Phillips et al. (2013), coherence of beliefs was assessed using two survey items that have not undergone rigorous psychometric assessment. This is problematic in a number of ways. Single-item scales are presumed to have unacceptably low reliability (Wanous, Reichers, & Hudy, 1997), particularly when assessing a potentially complex psychological construct such as coherence of beliefs. These are also more

vulnerable to random measurement errors as well as unknown biases in meaning and interpretation (Hoeppner, Kelly, Urbanoski, & Slaymaker, 2011). Additionally, it is difficult for any method of content validity assessment to determine whether such a small item pool actually reflects the desired construct (Arias, Lloreda, & Lloreda, 2014), particularly in the absence of a comparator measure. However, in the absence of a well-established measure of coherence of beliefs, and given that the survey-item measure has previously demonstrated predictive validity (Phillips et al., 2016; Phillips et al., 2013), this was deemed the most pragmatic measurement approach. Future work should aim to develop and psychometrically evaluate a measure of the coherence construct as originally specified by the CSM. Fourth, also as per Phillips et al. (2013), treatment-related beliefs were assessed using a composite of the BMQ (Horne et al., 1999) and the IPQ-R treatment control items (Moss-Morris et al., 2002), an approach that has not been formally validated. This may have had an impact on the results regarding treatment-related beliefs. That said, both sets of items were derived from and selected based on theoretical alignment with critical aspects of the CSM as intended by its developer (H. Leventhal et al., 2003; H. Leventhal et al., 1980), and regard specifically conscious, treatment-related beliefs. This variable is therefore both theoretically and empirically supported (Phillips et al., 2013). Furthermore, other aspects of the methodology besides the measurement approach may have made a stronger contribution to the limited predictive power of beliefs on adherence in this study; that is, the current sample was highly adherent and had strong habits overall, had been prescribed antihypertensive medications for at least three months, and therefore was likely to be at a behaviour-maintenance stage in their adherence, where beliefs are theoretically less important than habits for predicting behaviour. Finally, with regard to the composite measure of adherence, there is an argument that combining different types of measures in this way may actually reduce their diagnostic accuracy. Although using multiple measures of adherence is a key strength of this research, a statistically compiled composite measure of adherence may obscure some of the variation in adherence behaviour as assessed by valid single measures. Additionally, giving equal weight to each measure in compiling this composite score may also be seen as a limitation; however, in the absence of a compelling theoretical or empirical argument for weighting any one measure over another, equally weighting these measures was deemed the most pragmatic decision in this context. Future research could benefit from employing more advanced statistical analysis techniques to assess the validity of such a measure before replicating this approach.

Study 3 consisted of a qualitative comparison of high and low adherers. This study represents the first qualitative investigation into adherence for aTRH and, as such, provides novel insight into adherence behaviour for this group. The study boasts several additional strengths. First, this study is strengthened by the use of PPI in developing the study protocol. Members of the HRB PC CTNI PPP-R group were consulted in the development of the interview topic guide, and decisions regarding practical elements of how the study should be carried out. This ensured that the study protocol allowed participants to feel comfortable to participate and share their experiences of taking antihypertensive medication, and that factors important to the patients were represented in the interview topic guide. Second, well-established gold-standard approaches to collecting (Yardley, 2000) and analysing (Bailey, 2008; Braun & Clarke, 2006; Howitt, 2010; Malterud, 2001; Patton, 1990; Richards, 2014) qualitative data were employed to ensure the quality and rigour of the data and analysis. In addition, the COREQ formal reporting checklist for in-depth interviews and focus groups was used to ensure complete and transparent reporting, and enhance the rigour, comprehensiveness and credibility of the study (Tong et al., 2007); the GRIPP2-SF tool for reporting PPI in research was also utilised to ensure the quality and transparency of PPI reporting in this study, as well as to contribute to a stronger and more consistent international PPI evidence base (Staniszewska, Brett, Mockford, & Barber, 2011; Staniszewska et al., 2017). Another strength of this study is the multidisciplinary approach to the thematic analysis. Having the research team come together to review the data, coding procedures, and thematic analysis served to heighten reflexivity within the study, as well as to ensure that the diverse perspectives of those involved in the care of people with aTRH in the community were represented in the study findings.

Study 3 is not without limitation. First, the majority of interviews were conducted via telephone, which has been criticised as an interview medium (Novick, 2008). Cachia and Millward (2011), however, argue that the telephone medium and interview modality are complementary; telephone conversations naturally follow an agenda-driven format initiated by the caller, similar to traditional semi-structured interviews. Furthermore, empirical research by Sturges and Hanrahan (2004) comparing telephone with face-to-face semi-structured interviewing demonstrated that interview medium had no effect on either length of transcripts or type and depth of responses. The telephone mode may also overcome disadvantages inherent to face-to-face interviews by providing a methodologically valid, convenient and cost-effective alternative that enhances participants' privacy (Cachia &

Millward, 2011; Sturges & Hanrahan, 2004). Offering both face-to-face and telephone interviews in future health research may increase study participation and allow a greater diversity of views to be represented. Second, although consulting with members of the public in designing the study protocol is a strength, PPI in this study was limited to consultation only. In the context of PPI, consultation involves asking members of the public for their views and using these views to inform decision-making about any aspect of the research process. Although consultation is an important starting point for PPI in research, it is considered a relatively modest approach to involving patients in research activities. Future research may benefit from more meaningful engagement with members of the public and patients through other in-depth approaches to PPI, such as collaboration or user-controlled research (Faulkner, 2010; Turner & Beresford, 2005). Finally, the PPI group consultation was used to inform the development of the interview topic guide, which helped to ensure the topic guide did not reflect biases that the researcher may have had as a PhD candidate immersed in related research; it is possible, however, that the questions used to guide the interviews were reflective of the CSM in such a way that they could have influenced the themes that were generated from the data. In order to limit this possibility, a combination of inductive and deductive approaches were used in the data analysis, whereby the main categories and themes were identified from the data (inductive) and refined in light of existing theory (deductive). However, there remains a possibility that the framing of the interview questions may have influenced the participants' responses and therefore had an effect on the themes that could be produced.

Multidisciplinary health research. An over-arching strength of this research is its emphasis on multidisciplinary collaboration. Multidisciplinary approaches are increasingly acknowledged as necessary to address complex contemporary health challenges (Coen, Bottorff, Johnson, & Ratner, 2010). The current research was led (HD) and supervised (GJM) by behavioural scientists, with consistent meaningful input from GPs (AWM and PH) and a nurse (MC) with extensive knowledge of the primary care system and experience of carrying out large-scale research studies within it. This collaboration for the length of the project ensured the research questions are clinically useful and the study methodologies are rigorously and feasibly designed. Collaborators from other disciplines with an interest in health research also contributed to each of the three studies described within this thesis. This ensured that the relevant expertise was utilised at all stages of the research process and that gold-standard techniques beyond the realm of expertise of the core team could be utilised.

In Study 1, collaboration with a biostatistician (JN) ensured that the analyses conducted (i.e., random-effects meta-analyses) were appropriate to the research question and the data available. The methodological, clinical and statistical knowledge of the research team involved in Study 1 combined to produce a rigorous, clinically useful contribution to the literature. In Study 2, collaborators from biochemistry (BH) and pharmacology (AC and DPF) advised on, conducted, and aided in the interpretation of bioanalytical testing of spot urine for commonly prescribed antihypertensive medications. This collaboration with colleagues in the basic sciences allowed access to new methods and analytic techniques that monodisciplinary social science research typically cannot utilise. In Study 3, a GP with extensive expertise in qualitative research methods (LGG) came together with the core research team to review and analyse the qualitative data. This not only heightened reflexivity, but also ensured that the diverse perspectives of those involved in the care of patients with aTRH were represented in the study results.

Multidisciplinary collaboration is a key strength of this research. However, future research examining adherence for aTRH could benefit further from partnership with researchers from other health-related disciplines. For example, having had the input of a clinical or community pharmacist may have improved the quality of data collected from participants regarding their pill burden in the current research, as many participants were indeed living with multiple chronic conditions that may have required extensive pharmaceutical treatment beyond just antihypertensive treatment. Furthermore, additional research questions may be answered through similar collaboration with other health-related disciplines such as health economics, for example investigation as to whether bioanalytical testing for antihypertensive drugs may be integrated into routine primary care for patients with aTRH, and whether this might be a cost-effective approach in Ireland as it appears in other countries (P. Gupta et al., 2017). This type of meaningful, integrated multidisciplinary health research is not only desirable but essential to address the increasingly complex needs of an ageing population living with multiple chronic conditions and receiving polypharmacy going forward.

Conclusions

Despite its pertinence for the diagnosis, evaluation, and treatment of resistant hypertension, medication adherence among patients with aTRH was hitherto under-investigated and poorly understood. Poor adherence to antihypertensive treatment is a pervasive problem among patients with aTRH at all healthcare levels, with approximately

one-third of cases potentially attributable to patients not taking their antihypertensive medications as prescribed. There is considerable heterogeneity among published research in this area, particularly in terms of adherence assessment methodology and study setting, both of which are key study-level factors that have a clear impact on research findings. Utilising multiple diverse measures of adherence in a single clinical setting where the majority of cases of hypertension are managed provided a more complete picture of adherence behaviour for aTRH in primary care. There was little to no association among adherence measures in this research, providing further evidence for assertions that multiple measures are not only desirable but required to adequately assess adherence in research and clinical practice. Theoretical predictors of adherence drawn from the CSM were assessed as predictors of a composite measure of adherence, revealing that medication-taking habit strength was the strongest predictor of adherence behaviour for patients with aTRH. There was no association between antihypertensive pill burden and adherence or habit strength for this sample, likely because of the restricted range of pill burden assessed in the current research (i.e., 3–8 antihypertensive medications). Qualitative interviews with a subsample of high and low adherers surveyed for the quantitative study supported the key role of habit strength in determining adherence, but also highlighted the importance of treatment-favourable beliefs, coherence of beliefs stemming from experience with treatment, and positive experiences with the GP and the primary care system in promoting good adherence. Concerns about the effect of taking medication in the long term, lack of feedback from the condition itself, managing multiple conditions and multiple daily medications, and inadequate resources in the primary care system were all cited as important barriers to optimum adherence.

The findings from this research provide important insight into antihypertensive non-adherence for patients with aTRH receiving treatment in primary care in Ireland. Together these studies reflect the complexities of this prevalent behavioural issue and underscore the need for improved adherence assessment in primary care settings. This research also illuminates key targets for behavioural intervention to enhance adherence for aTRH, with the caveat that patients at different stages of the illness trajectory (e.g., treatment initiation versus adherence behaviour maintenance) may benefit from differential intervention. Accurate adherence assessment in combination with effective theoretically-informed behavioural intervention to promote adequate adherence will ensure that patients with aTRH are appropriately classified and their health is effectively managed.

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Appendices

Appendix A: Risk of Bias Assessment (Study 1)

Author & year	Source population	Inclusion / exclusion criteria	Measurement methods	Methods to deal with design-specific sources of bias	Design and / or analytical methods	Use of statistics	Declarations of conflict of interest and / or funding sources
Beaussier et al., 2015	Low	Low	Unclear	Unclear	Low	Low	Low
Brinker et al., 2014	Low	Low	Low	Low	Low	Low	Low
Bunker et al., 2011	Low	Low	Unclear	Unclear	Low	Low	High
Burnier et al., 2001	Low	High	Low	Unclear	Low	Low	High
Ceral et al., 2011	Low	High	Low	Low	Low	Low	Low
Daughtery et al., 2012	Low	Unclear	Low	Low	Low	Low	Low
de Souza et al., 2009	Low	High	Low	Unclear	Low	Low	Low
Elmula et al., 2013	Low	Unclear	Low	Unclear	Low	Low	Low
Ewen et al., 2015a	Low	Low	Low	Low	Low	Low	Low
Ewen et al., 2015b	Low	Low	Unclear	Unclear	Low	Low	Low
Florczak et al., 2015	Low	Low	Low	Unclear	Low	Low	Low
J. P. Garg et al., 2005	Low	Low	High	Unclear	Low	Low	Low
Grigoryan et al., 2013	Low	Low	Low	Low	Low	Low	High

Author & year	Source population	Inclusion / exclusion criteria	Measurement methods	Methods to deal with design-specific sources of bias	Design and / or analytical methods	Use of statistics	Declarations of conflict of interest and / or funding sources
Hameed et al., 2016	Low	Unclear	Unclear	Unclear	Low	Low	Low
Irvin et al., 2012	Low	Low	Low	Low	Low	Low	Low
Jung et al., 2013	Low	Low	Low	Unclear	Low	Low	Low
Massierer et al., 2012	Low	High	Unclear	Unclear	Low	Low	Low
Pandey et al., 2015	Low	Unclear	Low	Low	Low	Low	High
Porter et al., 2014	Low	High	Low	Unclear	Low	Low	Low
Rosa et al., 2014	Low	Unclear	Low	Low	Low	Low	Low
Sim et al., 2013	Low	Low	Low	Low	Low	Low	Low
Strauch et al., 2013	Low	Low	Low	Unclear	Low	Low	Low
Velasco et al., 2015	Low	Low	Low	Low	Low	Low	Low
Yakovlevitch & Black, 1991	Low	Unclear	High	Unclear	Low	Low	Low

Appendix B: General Practice Invitation Letter



Resistant Hypertension in General Practice: Prevalence, Prognosis, Description and Development of a Platform Cohort for Future Research

A study funded by the Health Research Board

What we are seeking?

We would like to invite your practice to participate in this HRB study in order to pragmatically determine the prevalence of Treatment Resistant Hypertension (hypertension despite greater than 3 BP medications) in Irish general practice. Practice selection was based on membership in WestREN and full ethical approval has been granted.

Patients with presumed Treatment Resistant Hypertension, after further assessment of ABPM and adherence in the practice (see below), will be invited to attend a specialist Resistant Hypertension Clinic in Merlin Park Hospital led by Dr Sharif (Consultant Cardiologist).

What do I, and the practice, get out of it?

We will provide you with:

- €1000 for practice time,
- An audit that will fulfil your yearly Medical Council requirement
- Coding of patients deemed to have apparent Treatment Resistant Hypertension.

At the end of the 3-year research period, there will also be a raffle for the eight study ABPM machines (odds of winning one: 50%).

What's required of me and my practice?

1.) Access to a practice computer for 3 days over any 2–3-week period to perform the practice audit. 2.) 50–70 patients discovered through this audit to receive a practice letter of invitation to participate in the study. Those who consent (we estimate 20–40) to participate will:

- Undergo ABPM using a device supplied by us
- Complete a short questionnaire focused on adherence
- Provide a urine/single hair sample

MORE DETAIL

- With your permission, we will come to your practice and perform an audit using a specifically designed tool on 'Socrates[®]' to identify patients with apparent 'Treatment Resistant Hypertension'. We will then code these patients as having apparent 'Treatment Resistant Hypertension' whilst performing an audit for your practice on Resistant Hypertension and the numbers of completed Ambulatory Blood Pressure Monitoring for these patients which will fulfil your medical council requirements for next year.
- You will also have all your 'high risk hypertensive patients' now coded (ICPC Z49) and available for further audits. We will also code any patients where possible compliance issues (ICPC Z11) with medications arise during the audit.
- We would like to invite any patients of yours who are deemed after the audit of having apparent 'Treatment Resistant Hypertension' to meet with your practice team and/or representative from our team to have Ambulatory Blood Pressure Monitoring and urine testing performed in the practice and to complete a questionnaire.
- We will then review the ABPM, Urine / Hair testing and Questionnaire data and let the practice know regarding compliance and ABPM interpretation. Anyone who still seems to have presumed Treatment Resistant Hypertension will then be contacted again (through the practice) and offered the opportunity to attend the specialist clinic for further evaluation. We estimate this number to be about half of those who participate or ten patients in total.

What about patient data and confidentiality?

We have ethical approval from the Irish College of General Practitioners to perform the audit whilst performing a prevalence study to determine the amount of Resistant Hypertension' in Irish general Practice. We will leave your practice with anonymous unidentified data/ numbers **only** and these numbers are not tied to any patient or file. We will sign a practice confidentiality agreement. We have ethical approval also for ABPM/Urine and Hair testing and questionnaire from the University Hospital Galway Ethics Committee in Merlin Park Hospital.

Why is this important?

Arterial hypertension accounts for, or contributes to, 62% of all strokes and 49% of all cases of heart disease. Within the hypertensive population lies a cohort at the upper end of the cardiovascular risk spectrum – those with hypertension resistant to treatment. Pimenta and Calhoun (2012) suggested the prevalence of resistant hypertension to be between 15% and 30% of treated hypertensive patients. They together with the American Heart Foundation (2008) and the UK National Institute for Health and Care Excellence (2011) suggest the need for further research into the prevalence, prognosis and management of patients with resistant hypertension. Everyone agrees that there is a need for further research about how common resistant hypertension is, what happens to patients who have it, and how to treat them.

Will it take long?

We need access for 3 days to a computer in your practice with the Socrates® programme and then over a 2–3-week period we will, with the assistance of your practice nurse, and at a time convenient to the practice, meet with the patients with apparent Treatment Resistant Hypertension. We will at that stage perform the ABPM, Urine / Hair and Questionnaire testing which will rule out those who are non-compliant with medications or who have true 'White Coat Hypertension'.

How can I let you know it's something we might be ok with or want to know more?

Tel: [REDACTED]; monica.casey@nuigalway.ie / peter.hayes@nuigalway.ie



Prof. Andrew W. Murphy

Head of Discipline of General Practice



Dr Peter Hayes

Lecturer in Primary Care



Monica Casey

Research Nurse

Discipline of General Practice, School of Medicine, National University of Ireland Galway

Appendix C: Patient Information Sheet (Study 2)



Patient Information Leaflet 1: Resistant Hypertension Study

Principle Investigators:

Dr Peter Hayes (NUI Galway Research Department of General Practice)/Your GP and his Team

We are inviting you to take part in a research project. Before you agree to take part in the study you must understand why we are doing the study and what will be expected of you if you agree to take part. We are providing you with this information sheet to explain the study to you but if you have any questions about the study after reading this sheet please feel free to ask us.

What is the point of this ‘Resistant Hypertension’ project?

Uncontrolled high blood pressure can cause heart attacks and strokes. Of those who have high blood pressure there are a certain number of people who have difficulty to control blood pressure, we call this ‘resistant hypertension’ and maybe 10-30% of all people with high blood pressure have this difficult to control variety. Everyone agrees that there is a need for further research about how common resistant hypertension (poorly controlled blood pressure) is, and what happens to patients who have it, and how to treat them.

Why am I being asked to take part?

You have been diagnosed with high blood pressure (as I’m sure you are aware) and this seems difficult to control with medication. We are looking to recruit patients who have difficulty to control blood pressure and assess them further. First off we would like to test whether your blood pressure is really high or not. A blood pressure can sometimes be high only in the surgery but not at home. A little box worn on the belt for 24 hours can help with this. We can provide this ‘for free’ to you in your own GP’s practice.

We would also like to test the success of your tablets in controlling your blood pressure by testing in your urine for them (you would give us a sample).

What do I have to do?

Call your practice nurse and let her know you would like to be included in the study.

You will then be asked to attend the practice on a morning that suits you. You will be asked to fill in a questionnaire on your tablets, how you feel about them and how good you are to take them. This takes approximately 20 minutes. You will also be fitted with an ambulatory blood pressure monitor. This is similar to a normal blood pressure cuff (like any other time you have had your blood pressure taken before) and this cuff is attached to a box at your belt. You will wear this, including in bed, for 24 hours and it will take your blood pressure every 30 minutes or so. This will give us 30-50 readings of your blood pressure asleep, at home, here and at work / play. You will return to the practice the next day so the practice nurse/GP can get the results.

You will also give a urine sample which will be tested as to how successfully your tablets are working.

You will be given a consent form to fill in before taking part in the study. You can write your initials in the boxes to indicate that you are happy to take part in the study.

Please be aware that you do not have to take part in the study if you do not want to and your medical care or legal rights will not be affected by your choice. There is no financial incentive offered. This is however an important research area and we really want to improve the lives of people who have high blood pressure.

If the blood pressure monitor worn for 24 hours shows that you still have high blood pressure, you will be offered an appointment with a cardiologist at the University Hospital Galway who has a specialist interest in difficult to control blood pressure and this clinic will do a full assessment on you and come up with a new treatment plan. **You do not of course have to accept the invitation to this clinic at any stage.**

What happens to the information about me you collect?

We will make your data/information anonymous (removing your name) and you will be allocated a unique number for the length of the study. Your data/information will be held on a secure computer that only the research team can access and we will not give your information to anyone else. Your data will be stored securely and in accordance with data protection regulations. It will only be accessed by the trial authorised staff.

During the trial authorised personnel may review your medical chart on your GP's computer to assist with the trial.

Who should I contact with any questions / comments / suggestions?

For any questions about the study you may contact Monica Casey by email or telephone (details below). Monica Casey is a research nurse based at NUI Galway. If you have any questions or would like further information about the study, please get in touch and Monica will be happy to help.

Contact for further information:

Monica Casey

RH Research Nurse, NUI Galway

monica.casey@nuigalway.ie

Contact your own General Practice to make an appointment to participate in the study.

Many thanks.

Appendix E: Questionnaire Tool (Study 2)



Health Research Board Study of High Blood Pressure in General Practice

*Medication Questionnaire*³

Researcher: Hannah Durand, MSc

PhD Candidate,

School of Psychology,

National University of Ireland, Galway

Tel: (091) 492803

E-Mail: h.durand1@nuigalway.ie

³ The MMAS[®] items have been redacted from this thesis due to copyright regulations. Use of the MMAS[®] is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, MMAS Research, LLC 14725 NE 20th St. Bellevue WA 98007.

Please provide the following background information:

Date:	
Participant ID number:	
Sex:	
Age (years and months):	
Height:	
Weight:	
Relationship status:	<input type="checkbox"/> Single <input type="checkbox"/> Married / Living with partner <input type="checkbox"/> Widowed <input type="checkbox"/> Divorced / Separated
Education level:	<input type="checkbox"/> None <input type="checkbox"/> Primary school <input type="checkbox"/> Secondary school <input type="checkbox"/> Third level (certificate, diploma, bachelor's degree, etc.) <input type="checkbox"/> Postgraduate
Smoking:	<input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Former smoker

Here are some ways in which people have said that they use their medicines. For each of the statements, please tick the box which best applies to you

	Always	Often	Sometimes	Rarely	Never
1. I forget to take my medicines					
2. I alter the dose of my medicines					
3. I stop taking my medicines for a while					
4. I decide to miss out a dose					
5. I take less than instructed					

In order for blood pressure medication to work, people have to take it according to their doctor’s instructions. For one reason or another, people can’t or don’t always take all of their pills as prescribed. We want to know how often you have missed your blood pressure medication over the past 7 days. Please rate your agreement with the following statements.

Over the past 7 days...	Strongly disagree 0	1	2	3	Strongly agree 4
1. I took all doses of my blood pressure medication.					
2. I missed or skipped at least one dose of my blood pressure medication.					
3. I was not able to take all of my blood pressure medication.					

Taking my blood pressure medication is something...	Strongly disagree 0	1	2	3	4	5	Strongly agree 6
1. I do automatically							
2. I do without having to consciously remember							
3. I do without thinking							
4. I start doing before I realise I'm doing it							

For the following questions, please circle the number that best corresponds to your views:

1. How much does your high blood pressure affect your life?

0 1 2 3 4 5 6 7 8 9 10

No effect at all

Severely affects my life

2. How long do you think your high blood pressure will continue?

0 1 2 3 4 5 6 7 8 9 10

A very short time

Forever

3. How much control do you feel you have over your high blood pressure?

0 1 2 3 4 5 6 7 8 9 10

Absolutely no control

Extreme amount of control

4. How much do you think your treatment can help your high blood pressure?

0 1 2 3 4 5 6 7 8 9 10

Not at all

Extremely helpful

5. How much do you experience symptoms from your high blood pressure?

0 1 2 3 4 5 6 7 8 9 10

*No symptoms
at all*

*Many severe
symptoms*

6. How concerned are you about your high blood pressure?

0 1 2 3 4 5 6 7 8 9 10

*Not at all
concerned*

*Extremely
concerned*

7. How well do you feel you understand your high blood pressure?

0 1 2 3 4 5 6 7 8 9 10

*Don't understand
at all*

*Understand very
clearly*

8. How much does your high blood pressure affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?)

0 1 2 3 4 5 6 7 8 9 10

*Not at all
affected
emotionally*

*Extremely
affected
emotionally*

1. Have you noticed the positive benefits of the blood pressure medicine?

YES *NO*

2. Have you experienced any solid (convincing) evidence that the blood pressure medication does what it is supposed to do?

No evidence

Some evidence

Solid evidence

	Strongly disagree 0	1	2	3	Strongly agree 4
1. My medication can control my hypertension					
2. There is nothing which can help my hypertension					
3. The negative effects of my hypertension can be prevented by my medication					
4. My medication will be effective in curing my hypertension					
5. There is very little that can be done to improve my hypertension					

We would like to ask you about your personal views about medicines prescribed for your blood pressure. These are statements other people have made about their medicines. Please indicate the extent to which you agree or disagree with them by ticking the appropriate box. There are no right or wrong answers. We are interested in your personal views.

	Strongly disagree 0	1	2	3	Strongly agree 4
1. My health, at present, depends on my blood pressure medicines					
2. Having to take blood pressure medicines worries me					
3. My life would be impossible without my blood pressure medicines					
4. Without my blood pressure medicines I would be very ill					
5. I sometimes worry about long-term effects of my blood pressure medicines					
6. My blood pressure medicines are a mystery to me					
7. My health in the future will depend on my blood pressure medicines					
8. My blood pressure medicines disrupt my life					
9. I sometimes worry about becoming too dependent on my blood pressure medicines					
10. My blood pressure medicines protect me from becoming worse					

We would like to ask you about your personal views about medicines in general. These are statements other people have made about medicines in general. Please indicate the extent to which you agree or disagree with them by ticking the appropriate box. There are no right or wrong answers. We are interested in your personal views.

	Strongly disagree 0	1	2	3	Strongly agree 4
1. Doctors use too many medicines					
2. People who take medicines should stop their treatment for a while every now and again					
3. Most medicines are addictive					
4. Natural remedies are safer than medicines					
5. Medicines do more harm than good					
6. All medicines are poisons					
7. Doctors place too much trust on medicines					
8. If doctors had more time with patients, they would prescribe fewer medicines.					

Appendix F: Supporting Information Regarding Urine Sample Preparation and Analysis (Study 2)

Sample preparation. Urine samples were collected from patients and stored at -80°C until further analysis. 100µl of urine was diluted 1:10 in acetonitrile, adjusting with formic acid to pH 4. Samples were centrifuged at 2000g for 10 minutes at room temperature. An 8-point 1:4 serial dilution standard curve was prepared in urine using a mixed stock containing 25 antihypertensive drugs and was diluted 1:10 in acetonitrile. Samples and standards had 100µl of 10µg/ml internal standard (Sulfameter; Sigma-Aldrich, Ireland) added.

HPLC-MS/MS. HPLC-MS/MS was carried out using an Agilent Technologies 1200 series High Pressure Liquid Chromatograph with an Agilent Technologies 6460 Triple Quadrupole Mass Spectrometer and electrospray was used as the source. A nebuliser gas temperature of 300°C was selected and the gas flow rate was set at 12L/min with a pressure of 35psi. An Agilent Technologies Zorbax SB-C18 2.1x50 mm column was used for HPLC, with a flow rate of 300µl/min. The HPLC was set in gradient mode using 0.1% formic acid in water for mobile phase A and 0.1% formic acid in acetonitrile for mobile phase B. For the first 4 minutes, conditions were set at 2% B/98% A. This gradient was increased to 60% B/40% A at 5 minutes, to 98% B/2% A at 9 minutes and for the remainder of the run. The total run time was 11 minutes per sample with a 4-minute post time to allow the gradient to re-equilibrate. Dynamic multiple reaction monitoring mode was used and each sample was run both in positive ion mode and negative ion mode, scanning for different drugs in each mode as shown in Table 4.1. A qualifier ion for each drug was selected and scanned for alongside the quantifier ion. A metabolite of ramipril (ramiprilat) and spironolactone (canrenone) were also scanned for.

Analysis of urine data. Data were analysed using Agilent MassHunter Software. Qualifier ions were used to confirm the presence of the quantifier ion. Lercanidipine, nebivolol, spironolactone, felodipine and candesartan could not be detected using HPLC-MS/MS and were therefore excluded from analysis. Adherence ratios were calculated based on the medications that could be detected. Lercanidipine has previously been reported as undetectable by HPLC-MS/MS (Jung et al., 2013). Nebivolol requires an extra hydrolysis step so that it can be detected by HPLC-MS/MS (Tomaszewski et al., 2014). Although spironolactone (including its metabolite canrenone), felodipine and candesartan were undetectable, only a small number of patients were prescribed these medications (8–13 patients).

Appendix G: Supplemental Tables I – IV (Study 2)

Supplemental Table I.

Hierarchical Regression Analysis of Theoretical Predictors of Adherence Measured by Self-Report using the MARS (H1, H2)

	β	Adj. R^2	ΔR^2	F	ΔF
<i>H1</i>					
Treatment-related beliefs	.06	.00	.01	1.43	1.43
CSM coherence	-.07	.00	.00	0.97	0.51
Habit strength	.22†	.04	.05	3.88†	9.61†
<i>H2</i>					
Beliefs x habit strength	-.10	.05	.01	4.31†	1.81

Note: * $p < .05$, † $p < .01$, ‡ $p < .001$.

Supplemental Table II.

Hierarchical Regression Analysis of Theoretical Predictors of Adherence Measured by Self-Report using the MMAS (H1, H2)

	β	Adj. R^2	ΔR^2	F	ΔF
H1					
Treatment-related beliefs	.08	.03	.03	6.73 [†]	6.73 [†]
CSM coherence	.05	.03	.01	3.93*	1.12
Habit strength	.45 [‡]	.22	.19	19.65 [‡]	49.21 [‡]
H2					
Beliefs x habit strength	-.04	.22	.00	19.96 [‡]	0.45

Note: * $p < .05$, [†] $p < .01$, [‡] $p < .001$.

Supplemental Table III.

Logistic Regression Analysis of Theoretical Predictors of Adherence Measured by Prescription Refill Records (H1, H2)

	B	SE	Wald	OR [95% CI]
<i>H1</i>				
Treatment-related beliefs	0.17	0.47	0.14	0.84 [0.34, 2.09]
CSM coherence	0.07	0.24	0.09	1.07 [0.68, 1.70]
Habit strength	0.13	0.12	1.08	1.13 [0.89, 1.44]
<i>H2</i>				
Beliefs x habit strength	0.02	0.28	0.01	1.02 [0.60, 1.75]

Note: * $p < .05$, † $p < .01$, ‡ $p < .001$. SE = standard error, OR = odds ratio, CI = confidence interval.

Supplemental Table IV.

Hierarchical Regression Analysis of Theoretical Predictors of Adherence Measured by Urine Assay (H1, H2)

	β	Adj. R^2	ΔR^2	F	ΔF
<i>H1</i>					
Treatment-related beliefs	.08	.00	.01	1.37	1.37
CSM coherence	.04	.00	.00	0.82	0.28
Habit strength	.06	.00	.00	0.78	0.69
<i>H2</i>					
Beliefs x habit strength	.05	.00	.00	0.70	0.49

Note: * $p < .05$, † $p < .01$, ‡ $p < .001$.

**Appendix H: Correlations among Demographic Variables and Adherence Measures
(Study 2)**

Correlations among Demographic Variables and Adherence Measures (N = 204)

	1	2	3	4	5	6	7
1. Prescription refill	-						
2. MARS	.30‡	-					
3. MMAS[®]	.17*	.53‡	-				
4. Urine assay	.00	.01	.04	-			
5. Composite	.44‡	.74‡	.82‡	.25‡	-		
6. Age	-.05	.01	.06	.00	-.02	-	
7. Sex	.05	.10	-.06	.06	.00	-.01	-

Note: * $p < .05$, † $p < .01$, ‡ $p < .001$. Use of the MMAS[®] is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, MMAS Research) LLC 14725 NE 20th St. Bellevue WA 98007.

Appendix I: Invitation to Participate in Study 3



Invitation to participate in an interview for the HRB Study on High Blood Pressure in General Practice

Dear (*Patient*),

We would like to thank you sincerely for coming to the practice and participating in our study looking at the control of blood pressure in your practice.

If you recall you wore a blood pressure measuring device for 24 hours, gave a urine sample to check how well your medications were working and filled out a questionnaire. Thank you for this.

Why have I been contacted?

We are interested to know more about how people who participated in the study use their medication to manage their blood pressure.

What is the point of this interview?

We would like to understand how people experience taking antihypertensive medication over time. By asking questions about how people manage the day-to-day task of taking medication, we hope that we can support people to take medications to manage their health in the future.

What am I being asked to do?

We are wondering whether you would agree to talk to a member of our research team about your experience of taking antihypertensive medication. This interview could be done over the phone, or in a private room in on campus at the National University of Ireland, Galway – whichever you prefer. We would of course arrange for this to take place at a time and date that suits you. The interview should not take more than 30 minutes.

What will happen if I decide to take part in the interview?

You will contact Hannah, a health researcher based in NUI Galway, to arrange a date and time that suits you. The interview will take place over the phone or in the University. The interview will be audio recorded so that we can compare experiences of different people. Once the interview has been transcribed in text, the audio recording will be destroyed. We will make your data anonymous (remove your name). Your data will be held on a secure computer that only the research team can access, in accordance with data protection regulations. We will not give your information to anyone else.

Will I benefit?

Taking part in this study may give you a chance to express your opinions as a person who takes multiple medications to manage your health. By expressing your opinions, you will be contributing to current knowledge about how people use medication to manage their blood pressure that can help us improve medication management for people in the future.

Are there any harms I could suffer?

Apart from giving up your time, no harms are anticipated.

You are not under any pressure at all to participate and should you decline to participate, your care will not be affected in any way with your GP.

If you are interested in participating or would like further information you can contact Hannah Durand (our health research psychologist) by phone at [REDACTED] or email at **h.durand1@nuigalway.ie**

Our very best wishes and thanks for your time,

Ms Hannah Durand, Research Psychologist
Ms Monica Casey, Research Nurse
Dr Peter Hayes, Research GP
Dr X Practice Principal
Mx Y Practice Nurse

Appendix J: Patient Consent Form (Study 3)



High Blood Pressure in General Practice

A study funded by the Health Research Board

PATIENT CONSENT FORM

Please read this form carefully – its purpose is to make sure that you fully understand your part in the research before agreeing to participate.

1. I confirm that I understand what my participation in this study will involve. I have had the opportunity to consider the information provided, ask questions and have had these answered to my satisfaction.
2. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason, and without my medical care or legal rights being affected. I understand that there will be no financial benefit if I choose to participate.
3. I am willing to participate in a one-to-one interview over the phone or in NUI Galway. I agree for the study interview to be audio recorded.
4. I understand that all information I give will be stored securely and will not be used or released in such a way that I could be identified.
5. I agree that the information gathered in this interview can be used for future research.
6. I agree to take part in the above study.

Consent will be agreed with the researcher at the start of the interview.

If you have any questions, please feel free to contact Hannah at [REDACTED]

Appendix K: COREQ Checklist (Study 3)

Manuscript: A qualitative comparison of high and low adherers with apparent treatment-resistant hypertension.

Authors: Hannah Durand, Monica Casey, Liam G. Glynn, Peter Hayes, Andrew W. Murphy & Gerard J. Molloy

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

Developed from:

Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Supplementary Table S1

Consolidated Criteria for Reporting Qualitative Studies (COREQ): 32-Item Checklist

No. Item	Guide questions	Description
Domain 1: Research team and reflexivity		
<i>Personal Characteristics</i>		
1. Inter viewer/facilitator	Which author/s conducted the interview or focus group?	One author (HD) conducted the interviews
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	BA, HDipPsych, MSc
3. Occupation	What was their occupation at the time of the study?	PhD candidate
4. Gender	Was the researcher male or female?	Female

5. Experience and training	What experience or training did the researcher have?	Trained in qualitative methods and design, experience in conducting interviews
<i>Relationship with participants</i>		
6. Relationship established	Was a relationship established prior to study commencement?	Potential participants contacted HD via telephone or e-mail to discuss arrangements for the interviews. Participants had no other relationship with the researcher.
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Participants were informed that the researcher was conducting a PhD in the area of medication adherence for treatment-resistant hypertension, and her goal was to understand patients' perspectives on this.
8. Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	The researcher was closely engaged in the research process and therefore unable to avoid personal bias.
Domain 2: study design		
<i>Theoretical framework</i>		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Thematic analysis was used in this study. A combination of inductive and deductive approaches was adopted.
<i>Participant selection</i>		

10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Patients with apparent treatment-resistant hypertension in the West of Ireland were sampled purposively.
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	Participants were invited via postal letter.
12. Sample size	How many participants were in the study?	There were 14 participants in the study.
13. Non-participation	How many people refused to participate or dropped out? Reasons?	All the participants who agreed on a date and a time took part in the study.
<i>Setting</i>		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	Data were collected via telephone or face-to-face in a private room in the University.
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	No nonparticipants were present.
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	The characteristics of the sample are provided in Table 4.1.
<i>Data collection</i>		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	The interview topic guide was developed (1) by reviewing other research in the area and (2) by brainstorming consultation with a group of patients separate to the study. It was then reviewed by the research team and piloted on a patient with hypertension.

18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	No repeat interviews were carried out.
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	All interviews were audio recorded.
20. Field notes	Were field notes made during and/or after the interview or focus group?	Field notes were made during and after the interviews.
21. Duration	What was the duration of the inter views or focus group?	Interviews lasted between 23 – 54 minutes.
22. Data saturation	Was data saturation discussed?	The researchers decided that data saturation had been achieved after the 14th interview. The transcripts were reviewed as soon as possible after each interview. Saturation was achieved as no further additional new information began to emerge. It was agreed that the addition of new codes was unlikely after the 14th interview.
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	Transcripts were not returned to participants for comment and/or correction.
Domain 3: analysis and findings		
<i>Data analysis</i>		

24. Number of data coders	How many data coders coded the data?	One member of the research team (HD) coded the data. The codes were then reviewed by the other members of the team.
25. Description of the coding tree	Did authors provide a description of the coding tree?	Open coding was first performed. This consisted of transcripts being read thoroughly and descriptive codes being assigned to sections of text. The content of the transcripts was constantly compared with codes that were already established. After forming the codes, they were grouped into categories, which were then grouped into themes.
26. Derivation of themes	Were themes identified in advance or derived from the data?	All six members of the research team came together to review all the data and contribute to the thematic analysis.
27. Software	What software, if applicable, was used to manage the data?	NVivo Version 11 was used to manage the data.
28. Participant checking	Did participants provide feedback on the findings?	Participants did not provide feedback on the findings.
<i>Reporting</i>		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	Participant quotations are presented to illustrate the themes/findings. Each quotation is identified using the participants' unique identification code, which represents their group (high or low adherence), gender, and age.

30. Data and findings consistent	Was there consistency between the data presented and the findings?	There is consistency between the data presented and the findings. The unit of analyses was the theme rather than the prevalence or frequency of statements. Some statements of quantification are included (e.g., statements such as “often” and “sometimes”), but do not always aim at providing estimates of prevalence.
31. Clarity of major themes	Were major themes clearly presented in the findings?	Codes identified in the open coding stage were discussed by study authors until consensus was reached. All major themes are clearly presented in the findings.
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Subthemes within the major themes are clearly presented in the findings.

Appendix L: GRIPP2-SF checklist (Study 3)

Supplementary Table S2

GRIPP2-SF Checklist for Reporting Patient and Public Involvement in Research

Section and topic	Item	Description
1: Aim	Report the aim of PPI in the study	The aim of PPI in this study was to enhance the research quality and relevance by actively involving members of the public in developing the study protocol and interview topic guide.
2: Methods	Provide a clear description of the methods used for PPI in the study	A pre-established Health Research Board Primary Care Clinical Trials Network Ireland (HRB PC CTNI)-affiliated Public and Patient Partnership in Research (PPP-R) group was consulted regarding the protocol of the study and the interview topic guide in a group brainstorming session with two experienced PPI facilitators.
3: Study results	Outcomes—Report the results of PPI in the study, including both positive and negative outcomes	The study protocol was finalised based on the consultation with the PPP-R group. One-to-one interviews were conducted with patients either over the phone or face-to-face in a private room in the University. Factors important to consider when addressing medication adherence for people with long term asymptomatic conditions receiving treatment in primary care settings were addressed in the interview topic guide. Results of the brainstorming session with the PPP-R group were compared to the existing literature on adherence for aTRH, and additional factors identified by the group as being potentially important for the current study were added to the topic guide.
4: Discussion and conclusions	Outcomes—Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	The PPP-R group’s comments and discussion influenced practical aspects of the study, including the recruitment strategy and materials, the interview format (i.e., one-to-one interviews were conducted via telephone or face-to-face in a private location other than the person’s home) and the content of the

		interview topic guide. The PPP-R group's contribution to these aspects of the study ensured that the language in the recruitment materials was accessible and suitable, that participants had the option of where and how the interview would take place, and that the topic guide reflected both factors that are important for patients taking daily medicines as well as important theoretical factors.
5: Reflections / critical perspective	Comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience	The practical comments (e.g., regarding modality of the interviews) made by the PPP-R group ensured that the study protocol allowed participants to feel comfortable to participate and share their experiences with the researcher. The comments by the PPP-R group validated the theoretical constructs of interest in the broader resistant hypertension study as well as the current qualitative investigation.

Appendix M: Interview Topic Guide (Study 3)

I would like to ask you a few questions about how you take your medicines. There are no right or wrong answers; I am just interested in your own beliefs and experiences.

1. Many people find a way of using their medicines that suits them best. This may differ from the instructions on the label or from what the doctor has said. Is this the case for you?
2. Most people sometimes forget to take their medicines. How often does that happen to you?
3. Some people don't like taking medicines – how do you feel about this?
4. Some people don't like taking too many medicines. How do you feel about that?
5. Some people feel that doctors prescribe too many medicines – do you think that is the case?
6. Some people think doctors are too ready to write a prescription for patients. How do you feel about this?
7. Some people are concerned about the side-effects of medicines. Do you have these concerns?
8. Some people have concerns that their medicines may be harmful. Do you ever have concerns like that?
9. Some people who have high blood pressure do not feel that this has an effect on their health. How do you feel?
10. People vary in how effective they believe their medicines are. How effective do you think your tablets are in reducing your high blood pressure?
11. Some people we have spoken to say that they sometimes deliberately don't take their tablets. Do you ever do that for any reason?
12. Some people have what they call a “drug holiday”, that is they take a break from their tablets for a few days – is that ever the case for you?
13. Is there anything else you would like to tell me about how you feel about taking your medication?

Thank you very much for taking the time to help us with this research. Although we have asked you quite a bit about **not** taking tablets, we strongly encourage you to take your tablets the way your doctor recommends.