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REVIEW

Medication adherence and treatment-resistant hypertension: a review

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Abstract

Nonadherence is a common reason for treatment failure and treatment resistance. No matter how it is defined, it is a major issue in the management of chronic illnesses. There are numerous methods to assess adherence, each with its own strengths and weaknesses; however, no single method is considered the best. Nonadherence is common in patients with hypertension, and it is present in a large proportion of patients with uncontrolled blood pressure taking three or more antihypertensive agents. Availability of procedure-based treatment options for these patients has shed further light on this important issue with development of new methods to assess adherence. There is, however, no consensus on the management of nonadherence, which reflects the complex interplay of factors responsible for it.

Keywords: adherence, compliance, treatment-resistant hypertension.

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Introduction

The treatment of most chronic illnesses is often characterised by long-term pharmacological interventions, which have been shown to be effective through a series of rigorous clinical trials. These pharmacological interventions are only effective if patients follow medical advice on the prescribed treatment regimen. Suboptimal or nonadherence is common; on average, around 50% of all prescribed medications for chronic conditions are not taken as prescribed.[1,2] Nonadherence has serious health and socioeconomic implications.

Adherence to medications is associated with improved health benefits and patient outcomes. A meta-analysis has shown that adherence to prescribed beneficial medication, including a placebo, is associated with significantly lower mortality compared with suboptimal adherence.[3]

Nonadherence puts an enormous cost burden on the health service through medication wastage. A report of a study commissioned by the Department of Health, UK, in 2010 estimated the cost of National Health Service primary and community care prescription medicines wastage in England to be £300 million per year and that for antihypertensive medication to be at least £100 million a year.[4]

There is no consistency on how medication adherence is reported in the literature.[5] Adherence can be reported qualitatively as patient being adherent or nonadherent, which will depend on the method used to assess adherence. Medication adherence percentage is a common quantitative measure used. It is defined as the percentage of number of pills taken during a certain period in respect of the number of pills prescribed by a clinician during the same period.[6]

There is no consensus on the threshold to define adherence and nonadherence. Traditionally, a cut-off value of 80% has been used to dichotomise adherence; healthcare usage and costs in many chronic conditions including hypertension, diabetes, hyperlipidaemia, and schizophrenia are noted to be reduced in patients where medication adherence exceeds 80%.[7–11] In hypertension consumption, >80% of the prescribed medications have been shown to maintain blood pressure control.[12]

In this article, we have reviewed medication nonadherence in chronic health conditions with particular reference to treatment-resistant hypertension (TRH).

Medication adherence in clinical trials

Achievement of optimal adherence in a randomised controlled trial is important. Level of adherence influences the magnitude of observed treatment effect; greater adherence increases the

effect size, and poor adherence may fail to distinguish the two treatments. Furthermore, nonadherence to a treatment with worse adverse effects profile may falsely prove to be of similar safety when compared to treatment with a favourable adverse effects profile. Adherence is also an important indicator of how readily a treatment is accepted by patients. Despite its importance, adherence is underreported in clinical trials, with only 33–46% of published randomised controlled trials (RCTs) reporting adherence rates.[5,13] On the other hand, reported rates of adherence are often remarkably high in these RCTs, resulting in potential overestimation of adherence due to underreporting.[5,13–16] This may be related to the extra attention received by study patients, patient selection, and the observer effect altering patient behaviour.

Assessment of medication adherence

Numerous methods exist to assess the medication-taking behaviour of patients, and they are broadly classified into direct and indirect methods (Table 1). Direct methods include direct observation of medication being ingested by the patient, detection of a drug or its metabolite in the blood or urine, detection of a biological marker that is included in the drug formulation, and more recently automatic electronic monitoring of drug ingestion by incorporating a specially designed microchip within each dose of a drug.[17] The direct methods provide proof that medication has been taken by the patient and are the most accurate measure of adherence.

Indirect measures of adherence have been the most widely used methods in research. These include patient interview, pill count, patient diary, patient questionnaire, measurement of physiological markers, and medication event monitoring system (MEMS).

The various measures of adherence have their strengths and weaknesses and may be appropriate in different situations (Table 1). No single measure of adherence can be classed as the gold standard, and a combination of measures may be used to maximise the accuracy.[18,19] As described in the section on apparent TRH, a varied range of adherence measures have been used for the assessment of adherence in TRH with the direct testing of the drug or its metabolite in serum or urine being the commonest in the recent years. This choice is likely a manifestation of the healthcare setting where these studies have been carried out; specialist hypertension centres with access to sophisticated medical laboratories are able to perform these tests. These centres will have a larger proportion of patients with TRH; therefore, developing an assay to detect antihypertensive drugs and their metabolites is cost effective in the long run.

Prevalence of treatment-resistant hypertension

TRH has been defined as uncontrolled blood pressure where at least a diuretic and two other different classes of antihypertensive medications, taken at maximum tolerated doses, are unsuccessful in controlling clinic blood pressure to a target less than 140 mmHg systolic and or 90 mmHg diastolic.[20] The publication of SPRINT trial has challenged the well-established target blood pressures for diagnosis and treatment of hypertension.[21] In light of its findings, the American College of Cardiology/American Heart Association has updated its hypertension guidelines with a radical change in the blood pressure targets used for diagnosis and treatment of hypertension; lowering the level of blood pressure to 130/80 mmHg also affects the definition of treatment-resistant hypertension.[22] The American definition has retained the second element of the definition, which includes patients with controlled blood pressure taking four or more antihypertensive medications.

The former definition is widely used to estimate the prevalence of TRH with reported estimates ranging from 5 to 30%.[23–28] A systematic review by Achelrod et al. report the pooled estimate of prevalence of TRH of 13.7% (95% confidence interval [CI]: 11.19–16.24).[29] Hayek et al. have illustrated that the prevalence of TRH can easily be manipulated depending on the stringency of the definition used.[30] They showed that in the same population the prevalence dropped from 30.9% (SBP >140 mmHg and ≥3 medications or controlled on four medications) to 3.4% (ensuring at least three medications are maximally dosed and one is diuretic).

The wide range of prevalence figures reflects the challenges in separating the true resistance from apparent resistance. Ambulatory blood pressure monitoring (ABPM) has been the gold standard for diagnosis of hypertension, as it helps to exclude white-coat hypertension. In treated hypertensive patients, the term white-coat effect (WCE) is used instead. WCE is one of the main reasons for the widely variable reported prevalence rates of TRH. Clinic or office blood pressure readings have been used in studies to estimate the prevalence of TRH until recently. With the increasing use of ABPM in clinical practice, it is now clear that white-coat effect is common in treated hypertensive individuals.[31] Furthermore, a positive correlation exists between clinic blood pressure and the magnitude of WCE suggesting that individuals with the highest clinic blood pressure have the largest WCE.[31,32] It is therefore not surprising that a large proportion of patients with TRH have been found to have significant WCE.[27,33] De la Sierra et al. found that in a large Spanish registry of 68,045 treated hypertensive individuals, 8295 (12.2%) had TRH, of which 3113 (37.5%) had WCE such that their ABPM results classified them as having controlled blood pressure instead.[27]

The importance of accurately identifying patients with true TRH cannot be overestimated; there is growing evidence to suggest that these patients are at a much higher risk of cardiovascular events, chronic kidney disease, and death.[34,35] Daugherty et al. have shown that, after adjustment, the hazard ratio for developing a cardiovascular event in this population is 1.47 (95% CI: 1.33–1.62).[34] Salles et al. found that over a 5-year follow-up period, patients with true TRH had a 2.4-fold

Table 1. Different measures of adherence and their respective advantages and disadvantages.

Measure	Advantages	Disadvantages
Direct		
Directly observed therapy	Most accurate Able to assess side effects as they appear	Resource intensive Patients may still hide the medications in their mouth before discarding them Provides Yes/No information on adherence
Measurement of medication or its metabolite in urine or serum	Objective	Expensive assays required May only be qualitative; i.e. Yes/No Susceptible to abuse; i.e. mixing medications in urine sample Adherence only tested at a single point in time White-coat adherence occurs when patients know the schedule of tests Variations in medication metabolism
Measurement of biological marker	Objective	Expensive Intrusive – requires collection of bodily specimens
Electronic microchip within a drug	Objective Accurate Can be used as a reference for other measures Information on individual patient medication-taking behaviour	Expensive Requires technical support
Indirect		
Electronic medication monitors	Provides detailed information on pattern and level of adherence Accurate Can identify partial adherence Often used as a standard to compare other measures against	Expensive Requires technical support Overestimation can occur where patients accidently or intentionally open the container It requires medications to be removed from their original packaging
Prescription refill rates	Can identify patients at risk for treatment failure Provide medication-refilling pattern Can provide accurate information in some healthcare systems that require verification for insurance purposes.	Records may be incomplete or difficult to access Assumptions are made about medication-taking behaviours Unable to identify partial adherence
Pill count	Objective and accurate Provides information on long-term adherence	Patients can hoard or keep back medications to appear to be adherent or they simple forget to bring some or all the medications Can be time consuming if taking numerous medications Arbitrary cut-off value used to define nonadherence Cannot identify medication-taking pattern
Measurement of clinical response or physiological markers	Can be simple, quick, and generally easily to perform such as measuring heart rate in patients taking beta-blockers	Other factors may affect the clinical response or the physiological marker
Patient questionnaires	Simple, inexpensive Provide real-time feedback Identify belief and barriers to adherence Validated for use	Affected by patient recall Patients can easily distort the results Relatively poor sensitivity and specificity Affected by language barriers and the questions in the questionnaire
Patient diaries	Simple Can overcome poor recall Can be used for children or patients with learning difficulties by their parents or carers, etc.	Open to manipulation by patients or their carers

(95% CI, 1.0–5.8-fold) increased risk of having a fatal or nonfatal cardiovascular event compared with white-coat TRH patients.[33]

Medication nonadherence and apparent treatment-resistant hypertension

In medicine, the term 'resistant' implies a condition that fails to respond to usual medical therapy. In hypertension, there are eight different classes of antihypertensive medications available – namely, thiazide/thiazide-like diuretics, renin angiotensin system inhibitors, calcium channel antagonists, alpha-adrenergic receptor blockers, beta-adrenergic receptor blockers, central vasodilators, aldosterone receptor antagonists, and miscellaneous. The recommended three first-line antihypertensive agents include calcium channel antagonists, renin angiotensin system inhibitors, and thiazide diuretics. There is emerging evidence that the preferred fourth-line antihypertensive agents are aldosterone receptor antagonists when compared with beta-adrenergic receptor blockers and alpha-adrenergic receptor blockers.[36]

Patients need to sufficiently adhere to the prescribed therapy for it to be considered to have failed. Therefore, assessment of adherence is a crucial aspect of management of patients with chronic conditions such as hypertension. Furthermore, increasing the number of antihypertensive medications may lead to increased risk of adverse effects and possible drug interactions. Medication adverse effects negatively impact patients' adherence and uncertainty on the part of the physician as to whether or not to intensify treatment. This 'clinical inertia' is detrimental to patients with true TRH given the high risks of morbidity and mortality associated with uncontrolled blood pressure. Assessment of adherence may help to overcome this inertia. Studies reporting rates of nonadherence in patients with TRH and the methods used to assess adherence are summarised in Table 2.

Observational cohort or cross-sectional reports from specialist hypertension centres or general hospitals form the mainstay of studies describing the prevalence of nonadherence amongst TRH patients.[37] Ceral et al. used liquid chromatography with mass spectrometry (LC–MS) to detect antihypertensive drugs in sera of 84 patients with apparent TRH.[38] All of the evaluated antihypertensive drugs were present in 29 (34.5%) patients, no drugs were detected in the same number, and the remaining 26 (31%) had some of their antihypertensive drugs in their sera. Jung et al. concluded that low adherence was the commonest cause of poor blood pressure control amongst 375 patients referred with uncontrolled blood pressure.[39] After excluding white-coat effect, secondary causes of hypertension, and optimisation of antihypertensive therapy, 76 patients remained in whom LC–MS was carried out on urine samples. They found that 36 (47%) were adherent and 40 (53%) were nonadherent, of which 12 (30%) had complete nonadherence.

Direct observation has often been used as a surrogate marker for adherence.[40,41] A sustained reduction in blood pressure following observed ingestion of tablets indicates prior nonadherence although any blood pressure reduction observed could be attributable to blood pressure variability, white-coat effect, or regression of blood pressure to the mean. Grassi et al. showed that 32% of patients presenting to emergency department with a systolic blood pressure >180 mmHg and/or diastolic blood pressure >110 mmHg had a drop of least a 20 mmHg in basal systolic blood pressure and/or a 10 mmHg reduction in basal diastolic blood pressure after a 30-minute-period of rest where patients were seated in a comfortable and quiet room without talking or active listening.[42] Some of these limitations can be minimised by using standardised and guideline-recommended blood pressure measurements and ABPM prior to commencing the directly observed therapy to exclude white-coat effect and reduce visit-to-visit blood pressure variability and regression to the mean.[41]

We showed that in patients with TRH, after optimisation of antihypertensive therapy, exclusion of secondary causes of hypertension, and WCE, only half of the patients were truly treatment resistant.[41] In nonadherent patients, the mean 24-hour ambulatory blood pressure drop observed was 19.5/9.4 mmHg when compared to ABPM carried out preceding the directly observed therapy. Although, this method makes intuitive sense in patients with TRH, it is resource and time intensive. Patients require close monitoring, as dramatic drops in blood pressure can often lead to symptomatic hypotension in patients.

Population studies have been able to study adherence rates in much larger populations.[34,43] Sim et al., using hypertension databases of Kaiser Permanente healthcare system in the United States, found that amongst the 60,327 individuals with resistant hypertension 7% were nonadherent. They used proportion of days covered by antihypertensives based on pharmacy refill data and a cut-off of 80% to dichotomise adherence.[43] Daugherty et al. looked at 205,750 incident patients diagnosed with hypertension; 3960 patients went on to develop TRH, on the basis of office blood pressure readings, during a median 1.5 years from initial treatment. Amongst the 3472 patients with TRH who had adherence assessed by prescription refill rate, 430 patients (12.4%) were nonadherent.[34] Interestingly, the same authors reported in a separate analysis that in a cohort of 3550 TRH patients, treatment intensification but not medication adherence was significantly associated with 1-year blood pressure control.[44] A number of possible explanations have been suggested by the authors including clinical inertia, comorbid conditions, and lack of evidence to support the use of ≥3 antihypertensives at the time. It is possible that clinicians may be reluctant to intensify treatment if they are uncertain about a patient's adherence; Rose et al. showed that adherent patients were more likely to receive treatment intensification which improved blood pressure control.[45]

Table 2. Summary of studies reporting rates of nonadherence and the methods used to measure adherence.

Study	Definition of TRH	Adherence method	Sample size	Number nonadherent (%)
Daugherty et al.[34]	AHA/ESH/ESC	Prescription refill rate – nonadherent if proportion of days covered was <80%	3472	430 (12.4)
Sim et al.[43]	AHA/ESH/ESC	Prescription refill rate – nonadherent if proportion of days covered was <80%	60,327	4223 (7.0)
Burnier et al.[47]	SBP ≥140 or DBP ≥90 on ≥3 AHTs on two consecutive visits ≥1 month apart	MEMS – nonadherent if <80% of days covered	41	21 (51.2)
Grigoryan et al.[46]	ABPM ≥135/85 or (≥125/75 if diabetic) on ≥3 AHTs	MEMS – nonadherent if taking <80% of all prescribed doses	69	20 (29.0)
Garg et al.[68]	SBP ≥140 or DBP ≥90 on ≥3 AHTs	Patient interview – physician determines if patient is nonadherent	141	23 (16.0)
Yakovlevich et al.[69]	SBP ≥140 or DBP ≥90 on ≥3 AHTs	Patient interview – physician determines if patient is nonadherent	91	9 (9.9)
Massierer et al.[70]	BP ≥140/90 on ≥3 AHTs incl. a diuretic	Self-reported questionnaire – nonadherent if score ≥3 on 4-item Morisky Medication Adherence Scale (MMAS-4)	86	21 (24.4)
Hameed et al.[41]	SBP ≥140 or DBP ≥90 on ≥3 AHTs	Directly observed therapy (DOT) – ≥5 mmHg reduction in mean 24-hour ambulatory SBP between Pre-DOT and DOT measurements was used to indicate nonadherence	50	25 (50)
Brinker et al.[71]	AHA/ESH/ESC	Therapeutic drug monitoring – nonadherence defined if levels of ≥1 AHTs below minimal detection limit	56	30 (53.6)
Ceral et al.[38]	SBP ≥150 or DBP ≥95 on ≥3 AHTs	Serum drug level – nonadherence defined if levels of ≥1 AHTs below minimal detection limit	84	55 (65.5)
Ewen et al.[72]	SBP ≥140 on ≥3 AHTs incl. a diuretic at highest or maximally tolerated dose	Direct testing of plasma and/or urine – nonadherence defined if levels of ≥1 AHTs below minimal detection limit	100	48 (48.0)
Jung et al.[39]	Clinic BP ≥140/90 or ABPM ≥130/80 on ≥4 AHTs	Direct testing of urine – nonadherence defined if levels of ≥1 AHTs below minimal detection limit	76	40 (52.6)
Rosa et al.[73]	Clinic BP ≥140/90 and ABPM ≥130/80 on ≥3 AHTs	Direct testing of blood – nonadherence defined if levels of ≥1 AHTs below minimal detection limit	72	27 (37.5)
Strauch et al.[74]	Clinic BP ≥140/90 and ABPM ≥130/80 on ≥3 AHTs	Direct testing of blood – nonadherence defined if levels of ≥1 AHTs below minimal detection limit	339	110 (32.4)
Beaussier et al.[75]	SBP ≥140 or DBP ≥90 on ≥3 AHTs incl. a diuretic	Combination of plasma test, urine test, pill count, and patient interview – each element was given a score and a score of <2 defined nonadherence	164	30 (18.3)

ABPM, ambulatory blood pressure monitoring; AHA, American Heart Association; AHTs, antihypertensives; BP, blood pressure; DBP, diastolic blood pressure; ESC, European Society of Cardiology; ESH, European Society of hypertension; MEMS, medication event monitoring system; SBP, systolic blood pressure; TRH, treatment-resistant hypertension.

MEMS, a type of electronic adherence measure where a microchip integrated in the cap of the medication packaging records the date and time whenever it is opened, has been used to assess adherence in TRH patients.[46,47] Grigoryan et al., using MEMS bottle caps, showed that pseudoresistance (nonadherence and WCE) was present in half of the patients with apparent TRH; nonadherence was present in 20 of the 69 (29%) patients.[46] Burnier et al. highlight the superiority of electronic devices in adherence monitoring in that the continuous monitoring itself can improve adherence and blood pressure control as well as provide the clinicians with detailed and objective information on patients' medication-taking behaviours.[47]

A recent systematic review by Durand et al. summarises 24 published studies reporting adherence in TRH patients.[37] There was an average of 86 patients from 21 studies, the largest of which included 339 patients. They report a pooled mean nonadherence rate of 31.2%, with highest rates reported in studies that used direct methods testing patients' sera or urine, followed by studies that used directly observed therapy (47.9 and 44.6%, respectively). The lowest rate of nonadherence was found in a single study reporting on medication possession ratio at 3.3%. Interestingly, a more recently published study by Durand et al. of a primary care hypertensive cohort showed nonadherence estimates ranged from 20.3 to 41.1% depending on the assessment method used. They found a weak-to-moderate association between indirect and direct measures of adherence.[48]

Therefore, white-coat effect and suboptimal adherence are common causes of apparent TRH. Published research in this field often fails to exclude either one or both of these factors when reporting on the prevalence of TRH. Estimated prevalence of apparent TRH of 13.7% will drop taking into account the nonadherence rates and WCE, each estimated to be 31.2 and 37.5%, respectively. Only one very recent study systematically tested and excluded pseudoresistance and showed a true TRH prevalence of 3.3% (95% CI: 3.0–4.0).[49] Even a conservative estimate of 50% pseudoresistance will bring the prevalence of true TRH to around 6–7% of total hypertensive population. The recent change in the American guideline may, however, increase this estimate.

Despite evidence of suggesting high rates of nonadherence in TRH patients, there is very little in the literature reporting on causes of nonadherence.[37] Baseline blood pressure, age, gender, ethnicity, income, and other socioeconomic indicators have been linked to nonadherence in TRH. We and others have shown that pill burden is associated with nonadherence.[50,51] Reasons for nonadherence are rarely attributable to one single factor and are instead complex and multifactorial. The World Health Organization proposed model suggests the factors responsible for medication nonadherence can be categorised into five domains – social- and economic-related factors, health system/healthcare team-related factors, therapy-related factors, condition-related factors, and patient-related factors – which apply to the hypertensive population as well.[52,53]

Management of nonadherence to antihypertensive medication

There is no proven intervention that has been shown to significantly improve adherence.[1] It is important to have a careful consultation with the patient to identify and address the potential causes of suboptimal adherence. The risks and consequences of nonadherence and the resultant uncontrolled blood pressure should be explained using simple language and visual aids. Patients should be asked how they are managing their drugs in regards to dosing frequency, pill burden, and side effects. It may be necessary to change the medication regimen to fewer daily doses and even monotherapy, but frequent changes in medication regimen should be avoided. It may also be necessary to negotiate a reduction in the number of drugs aiming for a higher and more realistic blood pressure target. The importance and effectiveness of lifestyle modifications in lowering blood pressure should be emphasised.[53]

Up to 75% of patients with hypertension require more than one antihypertensive agent to achieve blood pressure control.[54] Single-pill fixed-dose combinations have been recommended, for patients requiring more than one antihypertensive agent, to help improve adherence and consequently blood pressure control.[20,22] A meta-analysis has shown that fixed-drug combinations improve adherence and persistence in hypertensive patients with nonsignificant beneficial trends in blood pressure and adverse effects compared with free drug combinations.[55] A cohort study of 13,350 patients comparing fixed-drug with free-drug combinations also showed that the fixed-drug combination group had superior adherence rates of 70% compared to 42%, and a significantly lower risk of composite clinical outcomes including death or hospitalisation for acute myocardial infarction, heart failure, or stroke.[56] More recently, the use of low-dose fixed triple drug combination antihypertensive pills has been shown to improve blood pressure control compared to usual care in patients with mild to moderate hypertension.[57] This low-dose fixed-drug combination (FDC) treatment is being suggested as the initial therapy compared to the currently accepted practice of monotherapy. Apart from reducing pill burden, it may be associated with reduced adverse effects and consequently increased acceptability by the patients due to the lower doses of individual agents used. Furthermore, targeting of different pathways by different antihypertensive agents may improve efficacy. A pilot study has shown that a single-pill fixed triple drug combination achieved a mean reduction of 22.8/13.6 mmHg in clinic blood pressure and 9.3 mmHg reduction in 24-hour mean arterial pressure after 18 weeks in 13 patients with TRH.[58] Further larger studies are warranted in patients with TRH to assess the effectiveness of FDC and their impact on patients' medication-taking behaviour.

Self-monitoring of blood pressure, where patients monitor their own blood pressure at home, has been used as an intervention to show improvements in blood pressure [59,60] and adherence[61] Patients self-monitoring their blood pressure at home consulted

less often with their primary care physician who helps to bring the costs of self-monitoring on par with usual care.[62] Self-monitoring on its own, however, may not be enough to improve blood pressure control. Complex interventions, including systematic medication titration by doctors, pharmacists, or patients; education; or lifestyle counselling, in conjunction with self-monitoring lead to clinically significant blood pressure reduction, which persists for at least 12 months.[63] A recent randomised controlled trial has shown that self-monitoring, with or without telemonitoring, when used by primary care physicians to titrate antihypertensive treatment in individuals with uncontrolled hypertension, significantly lowers blood pressure compared with titration guided by clinic readings.[64] However, the efficacy of self-monitoring of blood pressure in lowering blood pressure in individuals with TRH has not yet been demonstrated.

Motivational interviewing has a robust evidence base to increase motivation and facilitate change across a range of health-related behaviours. A meta-analysis of hypertension studies,[65] involving seven underpowered randomised controlled trials, shows that motivational interviewing has a significant effect on systolic blood pressure both after intervention and at follow-up. However, most studies had small sample sizes limiting statistical power, and motivational interviewing was often used as one component of multiple interventions. Although there is lack of robust evidence for its efficacy in apparent TRH, it is a low-cost, easy-to-administer intervention that may be tried in this situation.

A recent study suggests that repeated biochemical urine and serum analyses for antihypertensive agents may be used as a therapeutic approach to improve blood pressure control in nonadherent hypertensive patients. In this study, from two hypertension centres in Europe (UK and Czech Republic), discussing results of urine (UK) and serum (Czech Republic), antihypertensive assays with nonadherent patients resulted in improvements in adherence and blood pressure control – an average reduction of 19.5/7.5 mmHg in one centre and 32.6/17.4 in the other.[66] However, this was a retrospective study with unclear follow-up period, and, by the authors' own admission, white-coat adherence effect could not be ruled out.

Finally, a recent randomised controlled trial tested if a smartphone app to increase patient engagement would improve medication adherence and blood pressure control in 411 patients with uncontrolled hypertension. There was a small improvement in self-reported adherence in the intervention group, but there was no difference in the blood pressure control between the intervention and control groups.[67]

Conclusion

A large proportion of patients with apparent treatment-resistant hypertension are nonadherent to prescribed treatment. Availability of urine assays for antihypertensive drugs and metabolites in the recent years has made it easier to identify nonadherence, which has significant detrimental consequences. However, no single management strategy has been shown to be effective in improving adherence in apparent treatment-resistant hypertension. Future research should focus on identifying interventions that will improve adherence in this group of patients.

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