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Measuring adherence to therapy in apparent treatment-resistant hypertension:

a feasibility study in Irish primary care

Abstract

Background
Apparent treatment-resistant hypertension (aTRH) is defined as uncontrolled blood pressure (BP) in patients taking three or more antihypertensive medications. Some patients will have true treatment-resistant hypertension, some undiagnosed secondary hypertension, while others have pseudo-resistance. Pseudo-resistance occurs when non-adherence to medication, white-coat hypertension (WCH), lifestyle, and inadequate drug dosing are responsible for the poorly controlled BP.

Aim
To examine the feasibility of establishing non-adherence to medication, for the first time in primary care, using mass spectrometry urine analysis. Operationalisation would be established by at least 50% of patients participating and 95% of samples being suitable for analysis. Clinical importance would be confirmed by >10% of patients being non-adherent.

Design and setting
Eligible patients with aTRH (n = 453) in 15 university research-affiliated Irish general practices were invited to participate.

Method
Participants underwent mass spectrometry urine analysis to test adherence and ambulatory BP monitoring (ABPM) to examine WCH.

Results
Of the eligible patients invited, 52% (n = 235) participated. All 235 urine samples (100%) were suitable for analysis: 174 (74%) patients were fully adherent, 56 (24%) partially adherent, and five (2%) fully non-adherent to therapy. A total of 206 patients also had ABPM, and in total 92 (45%) were categorised as pseudo-resistant. No significant associations were found between adherence status and patient characteristics or drug class.

Conclusion
In patients with aTRH, the authors have established that it is feasible to examine non-adherence to medications using mass spectrometry urine analysis. One in four patients were found to be partially or fully non-adherent. Further research on how to incorporate this approach into individual patient consultations and its associated cost-effectiveness is now appropriate.

Keywords
hypertension; primary care; pseudo-resistance; treatment adherence; urinalysis.

INTRODUCTION

Both the American Heart Association (AHA) in 2008[1] and the UK National Institute for Health and Care Excellence (NICE) in 2011[2] suggest the need for further research into treatment-resistant hypertension (TRH). Apparent-TRH (aTRH) is defined as uncontrolled blood pressure (BP) in patients taking ≥3 differing groups of antihypertensive medications (one of which must be a diuretic-type medication) or patients who are taking ≥4 medications regardless of type and BP level.[3] The term apparent is used because some of this group will have true treatment-resistant hypertension (tTRH), others undiagnosed secondary hypertension, and more have pseudo-resistant hypertension.[4] Pseudo-resistance exists when factors such as non-adherence to medications, white-coat hypertension (WCH), inadequate drug dosing, and lifestyle issues are responsible for the seemingly poor BP control.[3,4–6]

The *Lancet* commission on hypertension stated that:

'Ideally, diagnosis, initiation, and titration of treatment should be guided by ambulatory, home, or automated unobserved blood pressure …'.[7]

It went on to note:

'Objective assessment of adherence to therapy is possible by testing for the presence of drug metabolites in body fluids, particularly urine. Measurement methods … are sensitive, reproducible, relatively inexpensive, and could help treatment decisions, particularly in patients with difficult-to-control hypertension.'[7]

A number of hospital-based studies have used mass spectrometry urine analysis in patients with aTRH demonstrating non-adherence rates of 25% to 53%.[8,9] To the present authors' knowledge, no similar study has yet been performed in primary care.

This study aimed to examine, for the first time in primary care, the feasibility of establishing non-adherence to medication using mass spectrometry urine analysis. Operationalisation would be established by at least 50% of patients agreeing to participate and at least 95% of samples

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How this fits in

Both the American Heart Association (AHA) in 2008 and the UK National Institute for Health and Care Excellence (NICE) in 2011 suggest the need for further research into treatment-resistant hypertension (TRH). Non-adherence to therapy and white-coat hypertension (WCH) are significant causes of pseudo-resistance (false resistance). Ambulatory blood pressure monitoring is successful in ruling out WCH, but non-adherence to therapy is more difficult to detect, especially when it is non-intentional. The authors have shown that testing a patient's urine, with consent, for evidence of ingestion of their antihypertensive medications is feasible in primary care. Further work measuring the effect this has on the doctor–patient relationship and potential impact on patient prognosis is needed.

being suitable for analysis. A participation rate of 50% was chosen as patients were being asked to participate in a research study rather than a routine clinical service within the practice. Similar studies conducted by the Health Research Board Primary Care Clinical Trial Network Ireland have participation rates of circa 30% (N Burke, unpublished data, 2019). Clinical utility would be confirmed by >10% of patients being non-adherent as this was considered to be sufficiently common to impact on clinical care.

METHOD

Participants

The authors have previously published a cross-sectional study on the prevalence of aTRH in primary care and identified a cohort of patients with this condition (Figure 1).[10,11] Patients who were either on four blood pressure-lowering medications or on at least three with raised blood pressure were eligible.

For this study, 569 patients from 15 university research-affiliated Irish practices were eligible for inclusion. GPs were asked to review the names of these patients to confirm their continuing eligibility and that they were not suffering from significant morbidity, which would preclude their ability to participate, such as those with acute oncological issues, severe psychiatric illness, or individuals who were housebound. All others were invited to attend their general practice on a specific day, between June 2016 and March 2017, to undergo urine assessment and ambulatory BP monitoring (ABPM). Patients were informed by letter that the urine assessment was to examine 'the success of your tablets in controlling your blood pressure'. All participants were required to give explicit signed consent.

A comparison was also planned to examine differences between participants and non-participants (see Table 1.)

Urine sample processing

Urine samples were conveyed to the main laboratory at University Hospital Galway via the routine primary care laboratory transport service. They were then redirected on the same day to the Clinical Research Facility, Galway, and stored at –80°C. Drug assays were then performed in batches at the Biological Mass Spectrometry Core Facility at the National University of Ireland, Galway, utilising a methodology similar to Jung's and Tomaszewski's.[8,9] Technical aspects of the mass spectrometry performed, including sample preparation and sampling, are available from the authors on request. The authors built assays to test 20 of the most commonly prescribed antihypertensive drugs; technical difficulties prevented successful assessment of five common drugs (Box 1).

Drug metabolites were also screened for where indicated. Some angiotensin-converting enzyme (ACE) inhibitors have an unusual pharmacokinetic property, in that they exist primarily as a pro-drug and are broken down by the liver to various active metabolites; this stands true for enalapril, perindopril, and ramipril.[12] The half-life of the various drug metabolites vary and some are quite short, for example, perindopril has a half-life of 3–10 hours.[13] The pharmacokinetics of the breakdown of ACE inhibitors are not linear and many complex binding issues are involved. Metabolites are largely excreted by the kidney but variation exists as some are also partially excreted by the liver itself.[14]

Patients were described as being fully or partially adherent, or fully non-adherent depending on the ratio of the number of drugs present in their urine divided by the number of drugs prescribed. Prescribed drugs that could not be identified were not included in the calculation of adherence ratios.

Ambulatory blood pressure monitoring

White-coat hypertension is defined as having an elevated clinic BP reading ≥140/90 mmHg but a normal 24-hour ABPM daytime mean value (≤135/85 mmHg). The Meditech ABPM-05 (PMS [Instruments] Ltd) device was used.[15] The NICE guideline for the use of ABPM was applied to ensure validity.[2] Clinic-based BP was the last

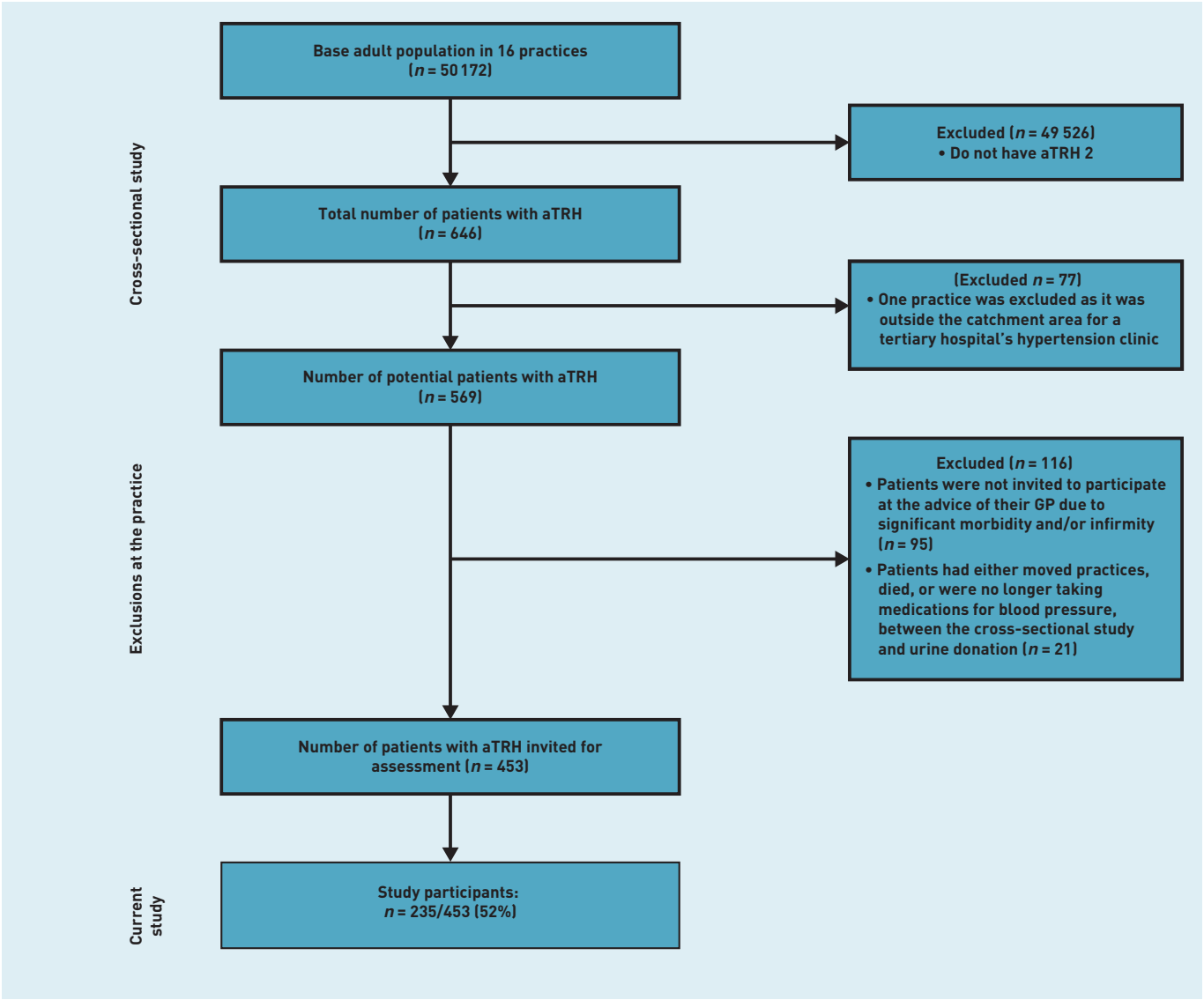

Figure 1. Participant flow through study. ABPM = ambulatory BP monitoring. aTRH = apparent treatment-resistant hypertension. WCH = white-coat hypertension.

recorded BP on the patient's file, within the last year.

Statistical analysis

Graphical, univariate and multivariate, summaries were created for all patient characteristics in order to identify any anomalies or outliers. Summary statistics were generated that were appropriate for the explanatory variable in question.

Two sample *t*-tests, unequal variance, were used to compare the mean of covariates between the groups (adherent and partially or fully non-adherent), and a two-sample comparison of proportions (or χ^2 test) to compare factors.

Multivariable logistic regression was used to model the association between the (log) odds of adherence and explanatory variables of interest, such as patient characteristics, number of and type of medications, morbidity, or BP. These variables were identified through a review of the existing literature. In addition, variable selection was also performed using elastic nets and tree-based methods, but this yielded no further advances in knowledge.[16] All analyses were performed using R (version 3.5).

RESULTS

A total of 453 eligible patients with aTRH were invited and 235 (52%) participated (that is, agreed to having urinalysis). All 235 (100%) samples were successfully transported to the laboratory and analysed. Figure 1 illustrates participant flow through the study and Table 1 shows the characteristics of both participants and non-participants (those who did not have the urinalysis). There were no apparent

Box 1. Antihypertensive drugs tested during mass spectrometry urine analysis

Drug number	Detectable medications	Drug number	Undetectable medications
1	Amiloride	21	Felodipine
2	Amlodipine	22	Lercanidipine
3	Atenolol	23	Nebivolol
4	Bendroflumethiazide	24	Spironolactone
5	Bisoprolol	25	Candesartan
6	Bumetanide		
7	Diltiazem		
8	Doxazosin		
9	Enalapril (enalaprilat)[a]		
10	Furosemide		
11	HCTZ		
12	Indapamide		
13	Losartan		
14	Lisinopril		
15	Olmesartan		
16	Perindopril (perindoprilat)[a]		
17	Ramipril (ramiprilat)[a]		
18	Telmisartan		
19	Valsartan		
20	Verapamil		

[a]*ACE-inhibitor metabolites.* HCTZ = hydrochlorothiazide.

differences between the two groups; the non-participant group had slightly more females and slightly higher proportions of diabetes, kidney disease, or cardiac failure.

Table 2 provides details on the antihypertensive medications they were receiving. A total of 860 antihypertensive drugs were prescribed, an average of 3.7 medications each individual, for these 235 participants. Mass spectrometry urine analysis was performed for 710 of these drugs, 82.6% of the total number of drugs prescribed. The authors demonstrated that 174 patients were fully adherent to treatment (74%), 56 partially adherent (24%), and five fully non-adherent (2%).

Twelve patients declined ABPM and 17 ABPM reports were suboptimal for assessment, as per NICE criteria.[2] A total of 206 (45%) completed valid ABPM and 28% had WCH (*n* = 58). Notably, 45% (92/206) of patients had pseudo-resistance. This is best calculated by using those who did both urine testing and ABPM as the denominator (*n* = 206), and being mindful that 27 patients had both WCH and non-adherence to therapy, and can only be included a single time, thus reducing the impact of the numerator. However, this figure must be interpreted cautiously as lifestyle factors and comedications were not evaluated.

There were no significant associations between the adherence status of participants and patient characteristics, number or type of medications used, morbidity, or BP (Table 3).

Table 1. Characteristics of patients with apparent treatment-resistant hypertension who gave a urine sample for urine toxicology analysis (*n* = 235) versus those who did not (non-participants) (*n* = 218)

Characteristics	Participants (*n* = 235)	Non-participants (*n* = 218)
Mean age, years (SD)	70.8 (10.6)	70.0 (12.8)
Female sex, *n* (%)	98 (41.7)	105 (48.2)
PCRS eligibility,[a] *n* (%)	196 (83.4)	172 (78.9)
Diabetes, *n* (%)	71 (30.2)	79 (36.2)
Chronic kidney disease, *n* (%)	80 (34.0)	91 (41.7)
Cardiac failure, *n* (%)	23 (9.8)	30 (13.8)
Mean systolic clinic BP, mmHg (SD)	142 (18.1)	142.9 (16.4)
Mean diastolic clinic BP, mmHg (SD)	78.2 (10.9)	77.5 (11.4)

[a]*Primary care reimbursement service eligible, which confirms access to free GP visits and/or medications (based on individual means testing). BP = blood pressure. PCRS = primary care reimbursement service. SD = standard deviation.*

Table 2. Pharmacological characteristics of antihypertensive therapy in patients with apparent treatment-resistant hypertension who gave a urine sample for mass spectrometry urine analysis (*N* = 235)

Pharmacological characteristics [a]	*n* (%)
Mean number of BP medications per patient (SD)	3.7 (0.7)
Combination medications	153 (65.1)
Three medications only	103 (43.8)
ACE inhibitors	100 (42.6)
Angiotensin blockers	125 (53.2)
Beta-blockers	146 (62.1)
Calcium channel blockers	176 (74.9)
Diuretics	225 (95.7)
Alpha-blockers	40 (17.0)
Other vasodilators, direct renin inhibitors, %	1 (<1)

[a]Number of participants and percentage, unless specified. ACE = angiotensin-converting enzyme. BP = blood pressure. SD = standard deviation.

Table 3. Comparison of summary statistics of different covariates (patient characteristics, drug class, number of medications, use of combined medications, morbidity, and ABPM readings) among adherent and non-adherent (partially or fully non-adherent) groups (*N* = 235)

Covariate	Non-adherent *n* (%)[a] (*n* = 61)	Adherent *n* (%)[a] (*n* = 174)	*P*-value
Age, mean (SD)	69.9 (11.4)	69.8 (10.4)	0.956
Sex			0.923
Male	35 (57.4)	103 (59.2)	
Female	26 (42.6)	71 (40.8)	
Diabetes			0.982
No	42 (68.9)	122 (70.1)	
Yes	19 (31.1)	52 (29.9)	
Chronic kidney disease			0.429
Not CKD	43 (70.5)	111 (63.8)	
CKD	18 (29.5)	63 (36.2)	
Angiotensin receptor blocker			0.214
No	34 (55.7)	79 (45.4)	
Yes	27 (44.3)	95 (54.6)	
Beta-blocker			0.297
No	27 (44.3)	62 (35.6)	
Yes	34 (55.7)	112 (64.4)	
ACE inhibitor			0.095
No	29 (47.5)	106 (60.9)	
Yes	32 (52.5)	68 (39.1)	
Calcium channel blocker			0.306
No	21 (34.4)	46 (26.4)	
Yes	40 (65.6)	128 (73.6)	
Diuretic			0.460
No	1 (1.6)	9 (5.2)	
Yes	60 (98.4)	165 (94.8)	
3 medications			1.000
>3 medications	34 (55.7)	98 (56.3)	
3 medications only	27 (44.3)	76 (43.7)	
Combination medications			0.385
No	18 (29.5)	64 (36.8)	
Yes	43 (70.5)	110 (63.2)	
Documented CCF			0.791
Not documented	54 (88.5)	158 (90.8)	
Documented	7 (11.5)	16 (9.2)	
Mean systolic day ABPM, mmHg (SD)	137 (15.6)	135 (16.0)	0.435
Mean diastolic day ABPM, mmHg (SD)	73.4 (11.2)	73.1 (9.82)	0.829
Mean systolic night ABPM, mmHg (SD)	131 (19.7)	129 (20.6)	0.513
Mean diastolic night ABPM, mmHg (SD)	67.8 (13.7)	66.7 (11.9)	0.609
ABPM total systolic, mmHg	135 (16.5)	133 (16.8)	0.441
ABPM total diastolic, mmHg	71.2 (11.5)	70.5 (9.80)	0.708
WCH			0.136
No	51 (83.6)	127 (73.0)	
Yes	10 (16.4)	47 (27.0)	

[a]Number of participants and percentage, unless specified. ABPM = ambulatory blood pressure monitoring. CCF = congestive cardiac failure. WCH = white-coat hypertension.

As seen in Table 4, none of the variables were deemed significant predictors of adherence based on the logistic models (regular and penalised) and tree-based models fitted (data are available from the authors on request). The authors believe there may be some interpretive difficulties when using mass spectrometry urinalysis to identify non-adherence in patients taking some types of ACE inhibitors. Therefore,

Table 4. Results from a logistic regression model to investigate the effect of patient characteristics of relevance on the odds of adherence[a]

	Odds ratio	95% CI	*P*-value
Intercept	1.65	0.05 to 82.24	0.78
Age, years	1.02	0.99 to 1.06	0.19
Sex, female/male	1.03	0.54 to 2.0	0.92
PCRS, PCRS/private	0.63	0.2 to 1.66	0.36
Pulse pressure >60 mmHg, yes/no	0.60	0.31 to 1.12	0.11
ACE inhibitor, yes/no	0.50	0.26 to 0.95	0.04
Calcium channel blockers, yes/no	1.83	0.88 to 3.81	0.11
Diuretic, yes/no	0.39	0.02 to 2.6	0.40
Combination medications, yes/no	0.70	0.34 to 1.39	0.31

[a]Variables identified previously in the literature[6,11,12] that were identified as useful predictors of adherence (Table 3) were included in this model. PCRS = primary care reimbursement service. Private = private patient.

the authors have not presented this as a factor determining adherence status here, despite it appearing statistically significant (see Discussion).

DISCUSSION

Summary

In patients with aTRH, the authors have established for the first time in primary care that it is feasible to examine non-adherence to medications using mass spectrometry urine analysis. One in four patients were found to be either partially or fully non-adherent Combining this with ABPM suggested that 45% of patients were pseudo-resistant.

The participation of 52% of patients was just above the suggested threshold of 50%. However, this was a participation rate for a formal research study conducted on limited and discrete days by staff external to the practice. The authors think it reasonable to suggest that, now that feasibility has been demonstrated, patient participation with a fully integrated service conducted by usual practice staff will be higher. The tasks of processing a patient's urine specimen in order to send to the laboratory and performing ABPM occur daily in routine general practice.

In the present study, 100% of samples were suitable for analysis. Transporting urine samples safely from primary care to hospital laboratories and then to adjoining research facilities for freezing is not without challenges. The authors of this study have now shown that this process is feasible, and that from multiple, geographically disparate sites in primary care (some in excess of 60 miles distant) urine samples can be safely and efficiently delivered for testing using routine transport systems.

The clinical importance of conducting the analyses was confirmed in finding that almost one in four patients were non-adherent.

Strengths and limitations

This study was based in one geographical area with a patient participation rate of 52%. However, the practices are representative of an Irish general practice area and participation rates are typical for such research studies.[17]

In the logistic regression model presented in Table 4, it is suggested that ACE inhibitors may be associated with non-adherence ($P = 0.04$). As outlined previously, the metabolism of ACE inhibitors is complex and caution is required in interpretation of this finding. Further pharmacokinetic research clarifying the predictive value of a negative test in these instances is warranted. Similarly, indapamide is also a unique drug as it has a lengthy half-life and can persist in urine for up to 60 hours after consumption.[18] Therefore a patient on indapamide could be incorrectly identified as adherent when the opposite could be true.

Most drugs, ACE inhibitors and thiazides apart, are cytochrome P450 dependent for metabolism. The ability to detect medications depends on a range of uncontrollable patient-specific and pharmacokinetic factors, which must be considered, such as time of last dose, the presence of various comorbidities (diabetes and chronic kidney disease), rapid metaboliser status (cytochrome P450), and whether concurrent medications are being taken.

In the future, specific attention may need to be placed on advising participants and researchers about standard approaches to taking last doses of medications, and the harvest and storage of urine samples, as this will facilitate between-study comparisons. As this study confirmed that drugs were taken qualitatively but not quantitatively, the authors cannot say that drugs were taken at the right time or in the correct doses.

A further limitation of the study is the fact that the authors performed mass spectrometry urine analysis for only 20 drugs compared with 40 by Tomaszewski *et al*.[9] However, these 20 accounted for 82.6% of the cohorts prescribed drugs. The authors also accept that using single clinical BP readings as a marker for hypertension may be suboptimal, as day-to-day variability in readings is possible.

Comparison with existing literature

Jung *et al* were the first to use mass spectrometry urine analysis in patients with aTRH,[8] when they showed that 53% of 78 patients attending a hypertension clinic were non-adherent.[8] Similarly, Tomaszewski *et al* reviewed 208 patients with hypertension attending a hypertension clinic and found that 25% were non-adherent.[9] In a methodologically similar but larger study (n = 1348), Gupta *et al* found proportions of non-adherence in UK and Czech populations attending hypertension clinics of 41.6% and 31.5% respectively.[6] The non-adherence rate found in the present study is similar to that of Tomaszewski *et al* and much lower than that of Gupta *et al* and Jung *et al*.[6,8,9] It is intuitive that adherence may be higher in primary care than in specialist hypertension clinics, where more complex patients have been referred for assessment. The authors' recent systematic review, based on medication adherence rates among patients with aTRH, confirms this.[19]

Certain patients may also improve their adherence just before testing — the 'tooth-brush effect'.[20] Simply, Jung *et al* did not inform patients that adherence was being assessed.[8] In both Gupta's and Tomaszewski's studies,[6,9] patients were explicitly informed that their urine would be assessed for drug adherence, albeit just before the sample was taken. In this study, patients were informed in advance and the authors accept that this may potentiate the 'tooth-brush effect'.

Jung *et al* noted that patients who were adherent had significantly lower clinic systolic and diastolic BPs.[8] Tomaszewski *et al* found significant associations between higher adherence and lower clinic and 24-hour-day BP readings.[9] Gupta *et al* found significant associations between non-adherence and decreasing age, being female, increasing numbers of medications, and being prescribed diuretics.[6] The researchers found no such significant associations in the present study. The sample size in this study of 235 persons is similar to those of Jung and Tomaszewski, but smaller than that of Gupta. However, the baseline BPs in this primary care population were, as expected, much lower than those of the specialist settings, possibly impacting on the identification of any such associations owing to the reduced BP variability.

In work based on the Spanish Ambulatory Blood Pressure Monitoring Registry, de la Sierra, showed that just over one-third of patients with aTRH (37.5%) had WCH.[21] This estimate is consistent with the findings presented here, and highlights its importance.[7]

Implications for research and practice

The authors previously examined non-adherence to therapy in aTRH via meta-analysis, and found a pooled prevalence of non-adherence of 30%.[19] Interestingly, the strongest contributor to variance in non-adherence rates was the method of adherence assessment used. Direct measures such as urine drug analysis gave the highest prevalence. Perhaps patients with adherence issues may be best identified by a combination of direct and indirect methods, such as with mass spectrometry urine analysis and the use of a valid questionnaire, for example, ProMAS Medication Adherence Scale and others.[22] Interestingly, this type of joint assessment gave figures closest to the pooled prevalence estimate identified in the meta-analysis.[19] The authors also recently published a comparator article between three measures of adherence (patient questionnaire, mass spectrometry urine analysis, and prescription refill data), and found that associations among these measures were weak overall.[11]

Further work is also needed to explore how patients and physicians would feel about the acceptability of using mass spectrometry urine analysis in routine consultations. There exists clear potential for undermining the patient–doctor relationship.[7] This is particularly important given the limitations of specific drug assays outlined above. Mass spectrometry urine analysis is currently costly (40–80 GBP per sample)[8] and explicit cost-effectiveness analyses are now required for the primary care setting.

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Ethical approval

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Provenance

Freely submitted; externally peer reviewed.

Competing interests

Andrew Murphy and Liam Glynn have received funding in the past from MSD pharmaceutical company. Eoin O'Brien has previously conducted validation studies of blood pressure monitors for various manufacturers and advised manufacturers on device development. The other authors have declared no competing interests.

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