

# Detecting non-adherence by urine analysis in patients with uncontrolled hypertension: rates, reasons and reactions

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1 **Detecting non-adherence by urine analysis in patients**  
2 **with uncontrolled hypertension: rates, reasons and**  
3 **reactions**

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5

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19

20 Conflicts of interest:

21 There are no conflicts of interest.

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25 **Summary table**

<p>What is known about topic</p>	<ul style="list-style-type: none"> <li>• Poor adherence is a well-recognised cause of apparently resistant hypertension.</li> <li>• Accurately measuring patient adherence has historically been very challenging.</li> <li>• Urine analysis by high-performance liquid chromatography-tandem mass spectrometry has recently become routinely available as a method of screening for non-adherence.</li> </ul>
<p>What this study adds</p>	<ul style="list-style-type: none"> <li>• The most common reasons for non-adherence were adverse effects of medication and forgetfulness.</li> <li>• Adherence rates for thiazide/thiazide-like diuretics and spironolactone were lower than for other classes of antihypertensive drug.</li> <li>• Approximately one third of non-adherent patients disputed their results. Further research on the effect this assay may have on the patient-clinician relationship is warranted.</li> </ul>

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31

32 **Abstract**

33

34 Poor adherence with pharmacotherapy is well recognised as one of the main barriers  
35 to achieving satisfactory blood pressure control, although accurately measuring  
36 patient adherence has historically been very challenging. Urine analysis by high-  
37 performance liquid chromatography-tandem mass spectrometry has recently become  
38 routinely available as a method of screening for non-adherence. In addition to  
39 measuring rates of adherence in hypertensive patients, this study aimed to investigate  
40 the reasons for non-adherence given by patients and how patients react when they are  
41 informed of their results. This was a retrospective observational study looking at  
42 results from the routine use of this assay in a specialist hypertension clinic in  
43 Birmingham, UK, in patients with uncontrolled hypertension and those under  
44 consideration for renal denervation. Out of the 131 patients analysed, only 67 (51%)  
45 were taking all their medications as prescribed. Forty-three patients (33%) were  
46 taking some of their medications, whilst 21 patients (16%) were completely non-  
47 adherent. The most common reasons cited for non-adherence were adverse effects of  
48 medication and forgetfulness. Adherence rates for thiazide/thiazide-like diuretics and  
49 spironolactone were lower than for other classes of antihypertensive drug. Despite the  
50 objective nature and high sensitivity of the test, 36% of non-adherent patients  
51 disputed the results. A minority of patients did not attend follow-up. Further research  
52 investigating the implications of a 'non-adherence' result on the patient-clinician  
53 relationship is required.

54

55

56

57 **Introduction**

58

59 Although effective and well-tolerated once-daily antihypertensive medications are  
60 widely available, poor adherence with recommended treatments continues to be one  
61 of the main barriers to satisfactory blood pressure (BP) control (1, 2). A recent meta-  
62 analysis of data on more than 376,000 patients from 20 studies assessing drug  
63 adherence for seven preventative drug classes (including five antihypertensive drug  
64 classes), found that the mean adherence over all studies was only 57% after a median  
65 of two years (3). A longitudinal study by Vrijens *et al* using a database of over 4700  
66 patients prescribed once a day antihypertensive medication from 21 phase IV clinical  
67 studies, demonstrated that by the end of one year, almost half of the patients had  
68 stopped taking their antihypertensive medication (4).

69

70 Measurement of patient adherence has historically been very challenging, and as a  
71 result, suboptimal adherence to a prescribed drug regimen often goes unrecognised in  
72 everyday clinical practice. One of the main problems with measuring behaviours such  
73 as adherence is that the act of measurement itself can have some bearing on the  
74 behaviour, the so-called Hawthorne effect. If patients are aware their medication-  
75 taking is being monitored, this in itself can stimulate adherence (5). Consequently,  
76 patients underreport non-adherence and also take medication immediately prior to  
77 testing or clinic appointments, so-called 'white coat adherence' (6). Conversely,  
78 clinical judgement alone is believed to overestimate the rate of non-adherence to  
79 antihypertensive medication (7).

80

81 Adherence can be measured directly or indirectly. Direct measurement involves either  
82 observing ingestion of the drug or by detecting its presence in plasma or urine.  
83 Indirect measures assume ingestion based on proxy-evidence such as self-reporting or  
84 number of dosages removed from a container (5). Traditional methods of measuring  
85 adherence (computerised records of prescription pharmacy refills, pill counts,  
86 questionnaires, patients' diaries) are inexpensive but have severe limitations and have  
87 been shown to overestimate it (8). Electronic monitoring methods such as the  
88 medication event monitoring system (MEMS; AARDEX Group, Ltd, Sion,  
89 Switzerland) have been regarded as the gold standard for monitoring adherence in  
90 clinical trials, because of their automaticity and precision of timing when patients take  
91 or omit doses. Although MEMS is based on an indirect measurement, it has been  
92 extensively validated and used in drug trials since 1988, including several studies  
93 conducted in the field of hypertension (8). Biochemical methods of testing can detect  
94 whether a drug has been ingested but until recently have been considered relatively  
95 costly. They are highly sensitive but cannot provide any information on when doses  
96 were taken or omitted and are affected by the white coat adherence phenomenon.  
97 Urine analysis by high-performance liquid chromatography-tandem mass  
98 spectrometry (HP LC-MS/MS) has recently come to the fore as a useful method of  
99 screening for non-adherence in hypertensive patients (9). A group at the University of  
100 Leicester in the United Kingdom were among the first to develop this test that is able  
101 to screen for 52 of the most commonly prescribed antihypertensive drugs or their  
102 metabolites using a random urine sample. The test is inexpensive and we have been  
103 using this test in routine clinical practice in the hypertension clinic at University  
104 Hospitals Birmingham NHS Foundation Trust since November 2013. Studies  
105 published to date making use of such an assay to measure adherence rates have not

106 looked at the reasons for non-adherence or whether adherence rates change on  
107 subsequent testing. How patients react when they are informed of their results and  
108 what explanations they give for not taking their medications are two of the questions  
109 we hoped to answer with this retrospective observational study. Subsequent work will  
110 aim to investigate the potential implications this assay can have on medication taking  
111 behaviour and on the patient-clinician relationship.

112

### 113 **Materials and Methods**

114

115 This was a retrospective observational study looking at results from the routine use of  
116 urine adherence testing in the hypertension clinic at University Hospitals Birmingham  
117 NHS Foundation Trust, which receives referrals from primary and secondary care  
118 physicians in the West Midlands for investigation and management of patients with  
119 uncontrolled hypertension. Following consultation with a hypertension specialist,  
120 patients were asked to provide a urine sample for analysis. Patients included all those  
121 being worked-up for consideration of renal denervation and those with uncontrolled  
122 and apparently 'resistant' hypertension in whom non-adherence needed to be  
123 excluded. By definition, patients with resistant hypertension included those with BP  
124 that was not controlled to target, that is, a clinic systolic BP of greater than 140  
125 mmHg and/or diastolic BP greater than 90 mmHg, despite treatment with at least  
126 three antihypertensive medications (usually including a diuretic). Following  
127 explanation that their urine would be tested for the presence of their prescribed blood  
128 pressure medicines, patients were asked to provide a random urine sample for  
129 analysis. Prior to attending clinic, patients were not given any warning about this test  
130 in order to exclude white coat adherence. Patients provided verbal consent and none

131 refused. Samples were frozen at minus 20°C and sent to University Hospitals of  
132 Leicester NHS Trust pathology department for analysis. Samples were analysed using  
133 HPLC-MS/MS for the presence of antihypertensive drugs or their metabolites. The  
134 technique has been described in detail elsewhere (9). Data on all patients undergoing  
135 the test during a two year period between November 2013 and November 2015 was  
136 collected retrospectively from electronic patient records. This included 131 patients in  
137 total. Data collected included: basic demographics, the names of prescribed  
138 antihypertensive medications, the reason for the test being carried out, and the  
139 medications detected in the urine sample. Data on the response of the patient when  
140 informed of the results and the reasons given by the patient for non-adherence (when  
141 applicable) were obtained from electronic clinic letters. Because this information was  
142 collected retrospectively, some information was lacking in a minority of patients.

143

## 144 **Results**

145

146 One-hundred-and-thirty-one urine samples from 131 patients were analysed. The  
147 median number of antihypertensive drugs prescribed was 4 (IQR 3-5; mean 4.14); the  
148 median number of drugs detected in the urine was 3 (IQR 1-4; mean 2.76) (Figure 1).

149

150 In five cases, when furosemide was the only drug not detected in the urine, it was  
151 deemed not to be clinically significant by the investigators due to its short half-life,  
152 and these five patients were considered to be adherent. Only 67 patients out of the 131  
153 (51%) were taking all their medications as prescribed ('adherent'); 43 patients (33%)  
154 were taking some of their prescribed medications and therefore deemed 'partially  
155 adherent' with their treatment; 21 patients (16%) were not taking any of their



156 medications and were categorised as ‘completely non-adherent’ (Figure 2). Out of 122  
157 patients with uncontrolled hypertension prescribed 3 or more drugs (including a  
158 diuretic in 106 cases), only 55 (45%) were completely adherent with prescribed  
159 medications and could be deemed truly ‘resistant’.

160

161 When patients were separated into ‘new referrals’ and ‘follow-up’ categories, a  
162 significant difference in adherence was observed: adherent 38% versus 59%; partially  
163 adherent 38% versus 30%; non-adherent 25% versus 11%; Kendall’s tau-b 0.219, p=  
164 0.009.

165

166 From the 64 patients categorised as partially or completely non-adherent, six patients  
167 did not attend follow-up after providing the urine sample. When the remaining 58  
168 patients were presented with their results, 25 admitted to non-adherence (43%), whilst  
169 21 denied non-adherence (36%) and disputed the result according to documentation in  
170 electronic clinic letters (Table 1). Twelve patients (21%) neither denied nor admitted  
171 it and it was unclear as to the reasons for non-adherence. The reaction was not known  
172 in the non-attenders.

173

174 Out of the 25 patients who admitted non-adherence, the most common reason cited in  
175 the clinic letter was adverse effects of medication (9 patients; 36%), closely followed  
176 by forgetfulness (8 patients; 32%); in 6 cases there was no documented reason given.

177 Other explanations included running out of medication, misunderstanding  
178 instructions, prescription cost and apathy (Table 2).

179

180 In the 12 cases where non-adherence was neither admitted nor denied, a language  
181 barrier was felt to be the main factor behind non-adherence in six cases (lack of  
182 English was noted in the clinic letters). In five cases there was no documentation of  
183 patient reaction in the notes, and in one case a carer had been administering the  
184 medication.

185

186 Data from the detection rates with the most commonly prescribed classes of  
187 antihypertensive drugs were analysed, which can be seen in Table 3. Adherence rates  
188 for thiazide/thiazide-like diuretics, including indapamide, bendroflumethiazide and  
189 hydrochlorothiazide (53.95%) and the aldosterone antagonist spironolactone (47.83%)  
190 were lower than for other classes of antihypertensive drug.

191

192 We also analysed adherence rates according to the number of antihypertensive drugs  
193 prescribed (Figure 3). There was a trend towards decreasing adherence rates with the  
194 higher number of drugs prescribed, although this did not reach statistical significance  
195 ( $p=0.115$ ) because the vast majority of patients were prescribed between three and  
196 five antihypertensive drugs (109 out of 131, 83%) and similar rates of adherence  
197 (approximately 50%) were observed in those patients.

198

## 199 **Discussion**

200

201 Direct measurement of adherence in hypertensive patients by urine analysis using HP  
202 LC-MS/MS is a highly effective method of establishing whether patients are taking  
203 their blood pressure medications as prescribed. In the study by Tomaszewski *et al*  
204 making use of this method to analyse the urine of hypertensive patients at a specialist

205 hypertension clinic in Leicester, 25% of the 208 patients who underwent screening  
206 were found to be partially or completely non-adherent (9). However, they included all  
207 new referrals and follow-up patients. In our routine clinical practice, we are more  
208 selective in whom we test as the assay is mainly used to investigate for non-adherence  
209 in those most likely to be non-adherent i.e. those with uncontrolled hypertension  
210 apparently refractory to drug treatment. In this retrospective observational study,  
211 overall, we found that approximately half of the patients were taking their  
212 medications as prescribed (51%). Patients were not given any prior warning about the  
213 test, reducing the likelihood of the white coat adherence phenomenon confounding the  
214 results, a strength of this study. This study confirms that poor adherence with  
215 prescribed treatment remains one of the most important causes of failing to achieve  
216 target blood pressure. A significant proportion of patients were not taking any of their  
217 antihypertensive medications (16%). This is a high figure due to the selectivity of  
218 patients in whom the test is used as a screening method and does not reflect the true  
219 prevalence of complete non-adherence in the clinic. The most extreme case included  
220 one patient who was referred to the clinic having been prescribed ten antihypertensive  
221 medications under the care of a cardiologist, none of which were detected in his urine.  
222 When analysing only the patients with uncontrolled hypertension prescribed three or  
223 more drugs (usually including a diuretic), 55% were found to be partially or  
224 completely non-adherent. This finding is very similar to a previous study using a  
225 similar methodology, which found approximately half (53%) of patients with apparent  
226 resistant hypertension were non-adherent (10). In light of this finding, our view is that  
227 urine adherence testing should become routine when managing patients with apparent  
228 resistant hypertension because patients with true resistance warrant meticulous  
229 investigation for secondary causes. Such investigations are expensive, time-

230 consuming and potentially involve radiation exposure. In patients with confirmed  
231 poor adherence, such tests may be completely unnecessary and the focus can be  
232 shifted towards optimising adherence.

233

234 Previous studies using urine analysis to measure adherence have not looked at how  
235 such patients react when they are informed of the results, or the reasons given for not  
236 taking their medications. It was noted from the present study that when informed of  
237 the results of their urine tests, patients acted in different ways. Despite the objective  
238 nature of the test, and explanation to the patient of its high sensitivity, about 30% of  
239 non-adherent patients denied that they were not taking their medications. Whether this  
240 represents a refusal to admit the truth, a false negative test result or simply a  
241 misunderstanding is not known. However, anecdotal evidence suggests that even  
242 when patients disputed the result, they were usually open to the suggestion of starting  
243 treatment afresh with a single BP agent, indicating that there was actually an issue  
244 with the number of medications they were prescribed. When a patient did admit to  
245 non-adherence, treatment could then be tailored to that particular individual with an  
246 emphasis on ways to improve adherence. It is important not to appear judgemental in  
247 this situation. Good relationships between healthcare providers and their patients are  
248 essential for good adherence. Some of the most important attributes that have  
249 previously been shown to be determinants of adherence in patients include an  
250 empathetic and non-judgemental attitude, ready availability and good quality of  
251 communication (11).

252

253 A multitude of different factors have been shown to contribute to poor adherence.

254 Two important features specific to hypertension include the asymptomatic and

255 lifelong nature of the disease itself. In keeping with this, the most common  
256 explanations given for non-adherence in the present study were adverse effects and  
257 forgetfulness. Memory and recall are well-known obstacles to good adherence.  
258 Simply forgetting to take the medicine at the right time, or poor recall of prescription  
259 instructions are both common (5). A study in 1979 by Anderson *et al* showed that  
260 patients could recall less than 50% of prescription instructions (12), and memory  
261 performance has subsequently been found to correlate with reduced adherence across  
262 a number of chronic diseases (13). There are other well-recognised issues relating to  
263 the drug therapy of hypertension, including drug tolerability, treatment duration, drug  
264 costs and complexity of the treatment regimen (11, 14). Regimen complexity is an  
265 important cause of non-adherence. Number of doses per day has been shown in a  
266 systematic review to be inversely related to adherence; adherence was significantly  
267 higher for once-daily compared with multiple-daily dosing (15). Because regimen  
268 complexity is a barrier that tends to reduce adherence, use of once-daily long-acting  
269 substances can improve adherence (15). However, the pharmacokinetics of a twice-  
270 daily dosing regimen actually confers better maintenance of drug action despite a  
271 higher percentage of omitted doses (8). A Cochrane review on interventions for  
272 improving adherence to treatment in patients with high blood pressure in ambulatory  
273 settings showed that simplification of dosing regimens increased adherence in seven  
274 out of nine studies (16), although only one study reported an increase in adherence  
275 together with a reduction in blood pressure (17). Fixed-dose combinations have been  
276 frequently proposed as a strategy for improving adherence in patients with  
277 cardiovascular disease. There are obvious advantages in reducing the pill burden but  
278 drawbacks too. For example, missing one dose means several drugs are omitted, doses  
279 cannot be easily titrated, combinations are fixed and they are more expensive. In the

280 UMPIRE randomised controlled trial, use of a fixed dose combination of aspirin,  
281 simvastatin and two blood pressure lowering drugs did result in improved adherence  
282 compared with the usual care group (86% vs 65%; relative risk of being adherent,  
283 1.33 95% CI, 1.26-1.41;  $p < 0.001$ ), but this did not translate into a reduction in  
284 cardiovascular events or serious adverse events (18). Although the effect of dosing  
285 frequency on adherence was not analysed in our study, we were able to establish a  
286 trend towards decreasing adherence rates with the higher number of drugs prescribed.  
287 This did not reach statistical significance ( $p=0.115$ ) because most patients in our study  
288 were prescribed 3-5 antihypertensive drugs, with only a minority of patients  
289 prescribed fewer than three antihypertensive drugs or greater than five. Our study did  
290 show that new referrals were less likely to be fully adherent and more likely to be  
291 completely non-adherent to their medications than follow-up patients. Reasons for the  
292 better rates of adherence shown in the follow-up patients are multifactorial but likely  
293 to be significantly contributed to by the closer attention to adherence these patients  
294 receive in the hypertension clinic.

295

296 Patients' beliefs and perceptions are also very important when it comes to adherence.  
297 Studies involving patients with a wide range of medical conditions have found that  
298 high rates of non-adherence are related to doubts about personal need for medication  
299 and concerns about potential side effects (5, 19, 20). Beliefs about the illness,  
300 perceptions of pharmaceuticals, expectations and experiences of symptoms all  
301 influence patients' behaviour with regard to medicine taking (5). These beliefs may  
302 change over time. Patients often 'test' their need for the medication by altering the  
303 dose or taking a 'drug holiday' and monitoring the effects (21). Such drug holidays  
304 may or may not be detected with urine testing, depending on the timing of events.

305 Although the urine test can be affected by white coat adherence, it is unlikely that any  
306 of the patients were aware of the test when it was first performed, prior to attending  
307 the clinic. Subsequent testing may be affected by this phenomenon as patients became  
308 wise to the test and this is an area that offers the opportunity for further research.

309

310 When looking at the most commonly prescribed classes of antihypertensive drugs,  
311 adherence rates for thiazide/thiazide-like diuretics (53.95%) and the aldosterone  
312 antagonist spironolactone (47.83%) were substantially lower than for other classes of  
313 antihypertensive drugs, which were all around 70%. This observation is consistent  
314 with a large observational study which showed that patients initiating treatment with  
315 angiotensin receptor blockers had a dramatically lower likelihood of early non-  
316 persistence (stopping the medication) compared with patients initiated on diuretics  
317 (22). Diuretics are highly effective antihypertensive drugs and patients with resistant  
318 hypertension often benefit from intensification of diuretic therapy, including the  
319 addition of an aldosterone antagonist. However, adverse effects may lead to non-  
320 adherence so it is important to encourage patients to be open and honest if they are  
321 experiencing intolerable side effects. Direct questioning about commonly experienced  
322 adverse effects are encouraged and substitutions made if an issue is highlighted.

323

324 In our clinic, no patients have so far refused to have the test performed. However, six  
325 patients who were found to be non-adherent did not attend their follow-up  
326 appointment, and speculatively, this could be because they feared the doctor's  
327 response or felt guilty about not taking their tablets. The test may have been the  
328 reason for the patient not attending but this is not known and it was only a small  
329 minority of patients. Further research is required into what implications this assay

330 might have on the patient-clinician relationship and we intend to explore this in  
331 subsequent projects using quantitative and qualitative methodologies.

332

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339 Health.

340

### 341 **Conflicts of Interest**

342 There are no conflicts of interest.

343

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412  
413

414 **Figure legends**

415

416 Figure 1: Box-and-whisker plot comparing the median number of antihypertensive  
417 medications prescribed with the median number detected in the urine in this group of  
418 patients with uncontrolled hypertension.

419

420 Figure 2: Pie-chart showing percentage of patients in this cohort who were adherent,  
421 partially adherent, and completely non-adherent with their antihypertensive  
422 medication.

423

424 Table 1: Table showing non-adherent patients' reactions when presented with their  
425 urine test results.

426

427 Table 2: Table showing patients' explanations for non-adherence.

428

429 Table 3: Adherence rates with the seven most commonly prescribed antihypertensive  
430 drug classes in the clinic. ACE = angiotensin converting enzyme; ARB = angiotensin  
431 receptor blocker; CCB = calcium channel blocker.

432

433 Figure 3: Graph showing percentage of patients who were fully adherent according to  
434 the number of antihypertensive drugs they were prescribed.

435