Evaluation of Adherence Should Become an Integral Part of Assessment of Patients With Apparently Treatment-Resistant Hypertension

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Online Data Supplement

Renal Denervation: An Eye Opener
Since the publication of the first Symplicity studies in 2009 to 2010, renal sympathetic denervation gained acceptance as a novel treatment of drug-resistant hypertension. The latter has been defined as a blood pressure (BP) >140/90 mm Hg, despite appropriate lifestyle measures plus a diuretic and 2 other antihypertensive drugs belonging to different classes at adequate doses.1 According to the US definition, patients with controlled BP on ≥4 antihypertensive drugs are also considered as resistant hypertensives.2 However, a substantial proportion of patients with apparently resistant hypertension are in fact poorly adherents to drug treatment. The highly variable BP response to renal denervation (RDN)3-4 prompted to a more rigorous evaluation of eligible patients, with the goal to exclude false resistant hypertension, because of poor adherence to drug treatment.5-6 In particular, several publications documented a high proportion of low drug adherence in patients with apparently resistant hypertension (23%–66%) baseline drug adherence, in terms of both BP control and regression of target organ damage.22 Therefore, from a public health and pharmacoeconomic perspective, diagnosis and management of poor drug adherence in patients with apparently resistant hypertension23 is a priority.

Furthermore, RDN studies shed the light on the dynamic character of drug adherence. Inclusion in RDN trials may influence drug adherence in various, unpredictable directions.6 In some patients, close follow-up and massive attention devoted to them may lead to improved adherence to lifestyle measures and drug treatment, particularly in the RDN arm (Hawthorne effect). Other patients may stop their medications after RDN according to their perception that the intervention cured their hypertension. On the other hand, patients from the control group may have not taken their medications properly to keep their BP high, in the hope that this will make them eligible for crossover to the RDN group.

Overall, RDN trials confirm (1) that poor drug adherence is a frequent cause of apparently resistant and difficult-to-treat hypertension, (2) that drug adherence is a dynamic phenomenon influenced by complex psychosocial determinants and cannot be captured by any single assessment, (3) and that changes in drug adherence are a major potential confounder in trials assessing new treatment modalities of resistant hypertension.

Although the prevalence of resistant hypertension has been estimated to be 10% to 30%,19,20 it may decrease to <2% when patients with low drug adherence estimated by pharmacy refill are excluded.21 Furthermore, even in those patients with truly resistant hypertension, the benefits of antihypertensive treatment are predominantly present in patients with acceptable (>80%) baseline drug adherence, in terms of both BP control and regression of target organ damage.21 Therefore, from a public health and pharmacoeconomic perspective, diagnosis and management of poor drug adherence in patients with apparently resistant hypertension23 is a priority.

Identification of poorly adherent patients among those with apparently resistant hypertension will avoid unnecessary and potentially harmful treatment intensification and allow implementation of strategies to improve drug adherence.14,24 This approach would be expected to result in a more cost-effective allocation of health resources. Unfortunately, healthcare providers underestimate the size of the problem of poor adherence to drug treatment.
drug adherence. Assessment of adherence is not part of routine clinical practice and is seldom performed in studies, even those testing drugs or interventions in patients with resistant hypertension. The finding of persistent tachycardia in a patient on β-blockers suggests a poor adherence or may orient toward a secondary form of hypertension. However, intuitive assessment of adherence by physicians is specific (most patients identified as nonadherent by their physician are indeed so), but lacks sensitivity (24%–62% depending on the definition of adherence).25 Moreover, unsubstantiated suspicion of poor adherence in difficult-to-treat patients with resistant hypertension contributes to medical skepticism and therapeutic inertia. Knowing which of their patients do not achieve BP control despite demonstrated good adherence, physicians would feel more motivated and responsible for the optimization of their antihypertensive regimen.

The authors of this review article make a plea for a more widespread, systematic, and standardized use of assessment of drug adherence in patients with apparently resistant hypertension, both in clinical practice and for evaluation of novel drug and interventional strategies, with particular emphasis on drug monitoring its advantages and limitations.

### Drug Adherence in Resistant Hypertension

Drug adherence is a major concern in hypertensive patients at large, and poor adherence has a demonstrated impact on cardiovascular prognosis (see online-only Data Supplement). Not unexpectedly, poor adherence is particularly frequent in apparently resistant hypertensive patients. Nine recent studies totaling 747 patients from 5 countries10–18 evaluated the level of adherence in outpatients with resistant or difficult-to-control hypertension using high-performance liquid chromatography coupled with mass spectrometry in urine and plasma. Overall, clinical characteristics, BP values, and average of prescribed drugs per day were similar10–18 (Table 1). The percentage of poor and full nonadherence to drug regimens in these 9 studies

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<tbody>
<tr>
<td>Resistant hypertensive</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Number of patients</td>
<td>84</td>
<td>76</td>
<td>163</td>
<td>66</td>
<td>17</td>
<td>56</td>
<td>100</td>
<td>24</td>
<td>82</td>
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<tr>
<td>Mean age, y</td>
<td>55</td>
<td>58</td>
<td>54</td>
<td>57</td>
<td>63</td>
<td>NR</td>
<td>63</td>
<td>65</td>
<td>NR</td>
</tr>
<tr>
<td>Male, %</td>
<td>60</td>
<td>58</td>
<td>56</td>
<td>42</td>
<td>47</td>
<td>NR</td>
<td>67</td>
<td>62</td>
<td>NR</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>NR</td>
<td>NR</td>
<td>32.3</td>
<td>31.6*</td>
<td>31.9*</td>
<td>NR</td>
<td>30.8</td>
<td>33.0</td>
<td>NR</td>
</tr>
<tr>
<td>Number of drugs</td>
<td>5.0±1.2</td>
<td>5</td>
<td>5.2±1.3</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>5.2±1.4</td>
<td>3.3±1.7</td>
<td>NR</td>
</tr>
<tr>
<td>Office BP, mm Hg</td>
<td>172/97</td>
<td>NR</td>
<td>175/100</td>
<td>168/95*</td>
<td>168/94*</td>
<td>168/94</td>
<td>167/88</td>
<td>172/92</td>
<td>158/88</td>
</tr>
<tr>
<td>24-h ambulatory BP, mm Hg</td>
<td>NR</td>
<td>NR</td>
<td>156/91</td>
<td>160/91*</td>
<td>160/89*</td>
<td>NR</td>
<td>154/86</td>
<td>162/88</td>
<td>NR</td>
</tr>
<tr>
<td>HPLC-MS</td>
<td>blood</td>
<td>urine</td>
<td>blood</td>
<td>urine</td>
<td>urine</td>
<td>blood</td>
<td>blood/urine</td>
<td>urine</td>
<td>urine</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; BP, blood pressure; HPLC-MS, high-performance liquid chromatography coupled with mass spectrometry; and NR, not reported.

*Not available for all patients.
ranged from 13% to 46% and from 2% to 35%, respectively (Figure 1).

However, it should be kept in mind that these measurements give only a snapshot of evaluation of adherence. In view of the known phenomenon of white coat adherence or toothbrush effect (increased adherence during the few days preceding a medical contact), daily-life drug adherence between 2 visits may be overestimated. Unfortunately, most of these studies have important limitations: (1) no rigorous definition of resistant hypertension or of partial adherence was provided; (2) details on the antihypertensive regimen were not reported; (3) patients included were not always on optimal antihypertensive therapy and did not always meet strict criteria of drug resistance; (4) details on methodology of drug dosage were not reported; (5) the timing of the samplings after the last drug intake was not clearly defined; (6) the possible influence of preanalytical errors and pharmacokinetics on the level of drugs detected was not discussed; (7) it was not clearly explained whether patients gave informed consent to have their adherence assessed and when; and (8) predictors of poor adherence were not analyzed.

**Methods to Evaluate Drug Adherence**

Over time, adherence has been studied using increasingly reliable and sophisticated methods. According to the method used, assessment of drug adherence can take place at different steps of the patient’s pathway (physician’s office, pharmacy, home; Figure 2). These different approaches to assess drug adherence can be divided into 2 categories: indirect and direct methods. Indirect methods include assessment by the clinician, self-assessment by the patient (interviews/questionnaires), measurement of pharmacodynamics parameters (heart rate for β-blockers, lack of rise of plasma renin for renin–angiotensin inhibitors, which may be also due to undetected primary aldosteronism, as well as acetyl-SDKP measurements for angiotensin-converting enzyme inhibitors), pill counts, and prescription refill. Direct methods include witnessed drug intake, Medication Event Monitoring System (MEMS), telemonitoring, and drug monitoring in body fluids.

The choice to use a method rather than another depends on multiple factors, including reliability, sensitivity to white-coat adherence, educational value, local facilities, long-term feasibility, patient profile, and financial resources (Table 2). All methods have limitations, and ideally, accurate evaluation of adherence should involve a combination of several approaches.

Bobrie et al evaluated adherence in a cohort of 164 resistant hypertensive patients on a standardized triple antihypertensive therapy, which were randomized to 2 different treatment strategies (sequential nephron blockade versus renin–angiotensin system blockade). Subsequently, the same group evaluated the influence of adherence on the efficacy of these 2 approaches. The authors used 2 indirect and 2 direct methods to assess adherence, assigning one point to each drug adherence measurement to calculate a global score. The superiority of sequential nephron blockade over renin–angiotensin system blockade in terms of BP control and regression of target organ damage (arterial stiffness and left ventricular mass) was significant only in adherent patients. Along similar lines, in a cohort of >240,000 newly treated hypertensive patients from the Italian Lombardy region, followed for 6 years, patients with a drug coverage ≥75% (24% of the cohort) had a 25% lower risk of cardiovascular events compared with those with a coverage <25% (22% of the cohort).

Indirect methods are simple, inexpensive, and time-efficient, and they imply a reasonable workload. On the other hand, the sensitivity of these methods is poor; they are heavily dependent on patient behavior, affected by social desirability and recall biases, and fail to provide information about the timing of doses, which is an essential
aspect of adherence.\textsuperscript{48} Accordingly, they are poorly correlated with direct methods such as MEMS and drug dosage in body fluids.\textsuperscript{35,37,42,44,45,47} In particular, in a sample of 47 patients with apparently resistant hypertension, poor adherence was grossly underestimated by the Morisky Medication Adherence Scale-8 (26\%), compared with drug monitoring (51\%).\textsuperscript{57} Compared with the latter, the sensitivity of Morisky Medication Adherence Scale-8 was found to be 26\%, specificity 75\%, positive predictive value 50\%, and negative predictive value 51\%.

Direct methods are more accurate and reliable\textsuperscript{49} than indirect methods, but also more expensive and demanding in terms of human resources.\textsuperscript{44,50}

Witnessed drug intake combined with ambulatory BP measurement might appear as a gold standard but cannot give information about persistence. Its application requires a hospital environment and the involvement of dedicated, trained healthcare professionals. The strength of this method is to provide an immediate proof that the prescribed medication in the prescribed doses is effective, if taken. On the other hand, witnessed drug intake raises ethical issues. Its use is justified only within the framework of clinical studies.\textsuperscript{9,52}

Telemonitoring allows obtaining a higher number of BP measures and improves the patient–physician communication. Furthermore, it improves patient compliance and hence BP control.\textsuperscript{51–55} Moreover, nowadays, the use of memory-equipped BP monitors allows overcoming problems related to the reliability of reports by patients.\textsuperscript{56} However, telemonitoring involves a high workload for the healthcare professionals, which limits its applicability in clinical practice.\textsuperscript{57,58}

The MEMS system provides detailed information about the timing of drug intake and missing doses.\textsuperscript{40,59} It can be used long term, favors patient empowerment, and has a demonstrated educational value.\textsuperscript{60,61} Accordingly, it has been associated with improved drug adherence.\textsuperscript{57,58,60–62} Nevertheless, electronic monitoring has an important limitation: it does not allow detecting patients who willingly open the box without swallowing the pill. Such behavior may be observed in the subgroup of difficult-to-treat patients referred for RDN.\textsuperscript{63,64} This intrinsic disadvantage can be overcome by the use of an ingestible sensor\textsuperscript{65,66} but the latter is expensive, is invasive, has not been validated on a large scale, and is not free from possible side effects, such as skin allergies caused by the patch and possible gut retention of its metal components.

The alternative is measuring drug/metabolite levels in body fluids. In hypertensive patients, the most widely used matrices for drug measurements are blood and urine.\textsuperscript{10–18} High-performance liquid chromatography coupled with a sensitive detector such as mass spectrometry is considered the reference analytic technique.\textsuperscript{67} Although widely used for drug monitoring, blood has the disadvantage to require invasive sampling and relatively accurate blood drawing time, especially for drugs with higher clearance. Even though urine provides a larger detection window as compared with blood, none of these matrices are able to assess if the treatment is rigorously followed between medical visits. Possible alternative approaches and matrices for drug monitoring are discussed in the online-only Data Supplement.

Drug monitoring is objective in detecting in a semiquantitative manner the presence or not of drugs in body fluids, but cannot give precise quantitative information, such as whether the patient is at his/her maximal tolerated dose.\textsuperscript{45,59} In contrast to electronic drug monitoring, it allows to test adherence for all drugs, which is not a trivial asset in view of the known differences in adherence according to drug class.\textsuperscript{68–70} Nevertheless, drug monitoring provides no information on the timing of drug intake or on the persistence on treatment. Furthermore, in contrast with MEMS,\textsuperscript{40,61} the educational value of repeated drug monitoring has not been studied in depth. Still, in a cohort

### Table 2. Advantages and Disadvantages of Different Methods to Assess Drug Adherence

<table>
<thead>
<tr>
<th>Advantages and Disadvantages</th>
<th>Indirect Methods</th>
<th>Direct Methods</th>
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</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Assessment by Clinician</td>
<td>Questionnaires</td>
</tr>
<tr>
<td>Objectivity</td>
<td>↓↓↓↓</td>
<td>↓↓</td>
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<tr>
<td>Accuracy</td>
<td>↓↓↓↓</td>
<td>↓↓</td>
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<tr>
<td>Feasibility</td>
<td>↑↑↑↑</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Educational value</td>
<td>↓↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>Cost/workload</td>
<td>↓↓↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>White coat effect</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Social desirability bias</td>
<td>↓↓↓↓</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Manipulability</td>
<td>↓↓↓↓</td>
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Social desirability bias: people respond to questioning in ways that make them seem more appealing to others or to healthcare providers. Manipulability: patients willingly manipulate the results of the assessment.
of 56 patients with apparently resistant hypertension, Brinker et al documented a sustained BP decrease (−46±10/−26±14 mm Hg; P<0.01) after information about the undetectable level of prescribed drugs, focused discussion and counseling, in the absence of drug treatment adjustment.14

Drug monitoring is sensitive to white-coat adherence, especially if the patient has been informed in advance.46 Nevertheless, this disadvantage can be partly overcome if drug monitoring is performed at short notice (ie, the day the patient provides his informed consent) or chronically at irregular intervals (the patient knows that adherence will be regularly checked but does not know when). Finally, to avoid misclassification of patients as adherent or nonadherent, the interpretation of drug monitoring results requires a good knowledge of the influence of pharmacokinetics, pharmacogenetics, and pharmacological interactions on the level of drugs in body fluids. This may be particularly relevant in patients with resistant hypertension who are often obese, on complex drug regimens, or have altered renal function.20 These aspects, as well as the advantages and disadvantages of different body fluids for drug measurement, will be discussed in the following sections.

**Influence of Pharmacokinetics and Preanalytical Errors on Drug Monitoring**

The clinician should be aware that blood concentration of drugs may be influenced by factors other than treatment adherence (Figure 3). In particular, pharmacokinetics may be highly variable for some drugs, resulting in high or on the contrary low or even undetectable blood or urine levels, depending on the sensitivity of the analytical method. The most frequent causes of variability in drug concentration include comedication with enzymatic inducers or inhibitors, diarrhea, malabsorption, obesity,71,72 food interference, salt intake,73 edema, ascites, as well as hepatic and renal impairment.

Polyorphism of genes involved in drug metabolism or distribution is another important source of variability in pharmacokinetics (fast metabolizers, increased efflux transport protein expression, etc). For example, torasemide is metabolized by CYP2C9, which has been described to be polymorphic, with ethnicity being involved.74 The majority of β-blockers (metoprolol, nebivolol, timolol, and to a lesser extent, propranolol, carvedilol, and bisoprolol) are metabolized by CYP2D6. Notably, the variable number of functional copies of the CYP2D6 gene (from 0 to 13) may have a substantial influence on the plasma concentration of the corresponding drugs.75 The frequency of fast or even ultrarapid metabolizers again may vary according to the ethnicity (1%–29%), leading to lower through concentrations.76–78 Some angiotensin type I receptors blockers (losartan, irbesartan, candesartan) are metabolized by the polymorphic CYP2C9.79 Finally, calcium antagonists are mainly substrates for highly polymorphic CYP3A4 3A5 enzymes.80–82 Table 3 summarizes the pharmacokinetic characteristics of the most frequently used antihypertensive drugs belonging to the 5 main classes.83–93

Drug monitoring may also be influenced by preanalytical errors. False-negative results might be because of nonspecific drug adsorption on the plastic tube or separator gel used or to drug instability at higher temperature or sensitivity to light as described for nifedipine.94 Moreover, P-glycoprotein and CYP3A4 inhibitors such as itraconazole markedly raise plasma concentrations of aliskiren and enhance its renin-inhibiting effect. The interaction is probably mainly explained by inhibition of the P-glycoprotein-mediated efflux of aliskiren in the small intestine, with a minor contribution from inhibition of CYP3A4.95

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**Figure 3.** Flow chart summarizing the different causes of low drug levels in plasma/urine to be considered before labeling a patient as poorly adherent.
Table 3. Pharmacokinetic Characteristics of the 5 Major Classes of Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Bioavailability, %</th>
<th>T1/2, h</th>
<th>Vd, L/kg</th>
<th>CLp, mL/min/kg</th>
<th>Protein Binding, %</th>
<th>Main Route of Elimination</th>
<th>Metabolism</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Diuretics</td>
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<tr>
<td>Hydrochlorothiazide</td>
<td>60–80</td>
<td>2.5</td>
<td>0.83</td>
<td>NA</td>
<td>60</td>
<td>Not known</td>
<td>Renal (≥65% unchanged)</td>
<td>Laurence et al(^{83})</td>
</tr>
<tr>
<td>Indapamide</td>
<td>100</td>
<td>14–16</td>
<td>21</td>
<td>NA</td>
<td>80</td>
<td>Hepatic (CYP3A4, hydroxylase)</td>
<td>Renal (70%) (&lt;7% unchanged)</td>
<td>Chaffman et al(^{84})</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>60–90</td>
<td>1.3</td>
<td>NA</td>
<td>NA</td>
<td>≥90</td>
<td>Hepatic</td>
<td>Renal [25%–55%] (mainly as metabolites)</td>
<td>Laurence et al(^{83})</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>54–74</td>
<td>25–69</td>
<td>0.14</td>
<td>0.04</td>
<td>75</td>
<td>Renal</td>
<td>[60%–70%] (mainly unchanged)</td>
<td>Laurence et al(^{83})</td>
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<tr>
<td>Beta blockers</td>
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<tr>
<td>Lipophilic (carvedilol, labetalol, metoprolol)</td>
<td>10–80</td>
<td>3–7</td>
<td>1.5–4</td>
<td>10–25</td>
<td>50–98 (10 for met.)</td>
<td>Hepatic (CYP1A2, 2D6, 3A4, 2C9, 2E1, some active metabolites)</td>
<td>Renal [60%–90%] (&lt;10% unchanged)</td>
<td>Laurence et al(^{83}), McNeil and Louis(^{85})</td>
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<td>Hydrophilic (atenolol)</td>
<td>30–50</td>
<td>4–24</td>
<td>0.5–2</td>
<td>1–3</td>
<td>≤5–30</td>
<td>Minimal hepatic metabolism</td>
<td>Renal [30%–80%] (almost entirely unchanged)</td>
<td>Laurence et al(^{83})</td>
</tr>
<tr>
<td>Intermediate (bisoprolol)</td>
<td>50–90</td>
<td>2–22</td>
<td>1–5</td>
<td>5–10</td>
<td>30–50</td>
<td>Hepatic (CYP2D6, 3A4)</td>
<td>Renal [20%–70%] (20%–50% unchanged)</td>
<td>Johns et al(^{88}), Kendall(^{89})</td>
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<tr>
<td>Calcium antagonists</td>
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<tr>
<td>Amlodipine</td>
<td>60–65</td>
<td>30–50</td>
<td>12–20</td>
<td>4–8</td>
<td>≥90</td>
<td>Hepatic (probably CYP3A4)</td>
<td>Renal (70%) (&lt;10% unchanged)</td>
<td>Laurence et al(^{83})</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>30–50</td>
<td>3–7</td>
<td>3.3</td>
<td>12–21</td>
<td>80</td>
<td>Hepatic (CYP3A4-5)</td>
<td>Renal [50%] (2%–4% unchanged)</td>
<td>Laurence et al(^{83})</td>
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<td>ACE inhibitors</td>
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<tr>
<td>Captopril</td>
<td>65–75</td>
<td>1–2</td>
<td>0.7</td>
<td>13</td>
<td>30</td>
<td>Hepatic</td>
<td>Renal [80%] (40%–50% unchanged)</td>
<td>Romankiewicz et al(^{81})</td>
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<tr>
<td>Lisinopril</td>
<td>25–50</td>
<td>12</td>
<td>1–3</td>
<td>1–3</td>
<td>31</td>
<td>None</td>
<td>Renal [35%] (totally unchanged)</td>
<td>Laurence et al(^{83})</td>
</tr>
<tr>
<td>ARB</td>
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<tr>
<td>Olmesartan</td>
<td>26</td>
<td>9–18</td>
<td>0.36</td>
<td>0.31</td>
<td>99</td>
<td>Gastrointestinal tract</td>
<td>Renal (35%–50% unchanged)</td>
<td>Laurence et al(^{83})</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>60–80</td>
<td>11–15</td>
<td>59–96</td>
<td>0.87</td>
<td>90</td>
<td>Hydrolysis Hepatic (CYP2C9)</td>
<td>Renal [50%] (&lt;2% unchanged)</td>
<td>Ruliepe(^{82})</td>
</tr>
<tr>
<td>Candesartan</td>
<td>15–40</td>
<td>4–9</td>
<td>0.13</td>
<td>0.37</td>
<td>&gt;99</td>
<td>Minor hepatic metabolism</td>
<td>Renal (20%–30% unchanged)</td>
<td>Gleiter et al(^{83})</td>
</tr>
</tbody>
</table>

\(^{ACE}\) indicates angiotensin-converting enzyme; \(^{ARB}\), angiotensin receptor blockers; \(^{CL_p}\), plasmatic clearance; \(^{met}\), metoprolol; \(^{NA}\), not available; \(^{NS}\), not significant; \(^{T_{1/2}}\), half-life; and \(^{Vd}\), volume of distribution.

**Psychology and Ethics**

Evaluation of adherence raises several ethical issues. First, before suspecting a problem of poor adherence, physicians should make sure that the diagnosis is correctly established and therapy is of known efficacy and appropriate for the patient’s attitudes and cultural beliefs.\(^{96}\) The importance of drug adherence should be discussed with patients, and unless there is an imminent necessity, assessment of adherence should not be performed without informing patients. Appropriate discussion of results of drug monitoring with the patient may improve patient–physician relationship, favor patient’s empowerment, and lead to improved drug adherence and subsequent BP control.\(^{14}\) Nevertheless, labeling a patient as poorly or nonadherent should be made with caution because adherence is a dynamic phenomenon (a patient may be adherent today, not tomorrow), and low drug dosages obtained by drug
monitoring may reflect technical artifacts or pharmacokinetic effects (Figure 3). Another important aspect is the way of communication between patient and physician: stigmatization of poorly adherent patients should be avoided and physicians should be empathic rather than inquisitive. Physicians must not forget that attempts to improve patient’s adherence by threatening are unethical, and there are no evidences of their effectiveness in the literature. Instead, there are other means of demonstrated efficacy to improve adherence with long-term treatments: simplifying the regimens and counseling about it using educational materials, such as reminders for medications and appointments, implementing medical visits, and involving family members.96

Cost-Effectiveness of Drug Monitoring
The high prevalence of poor adherence in patients with apparently resistant hypertension raises the issue of cost-effectiveness of drug monitoring. In the German Healthcare System, the cost for the high-performance liquid chromatography coupled with mass spectrometry is €60 per test.11 This may seem a lot, but it is necessary to compare this investment with the global cost of managing resistant hypertensive patients. This includes ruling out secondary hypertension, costs of additional antihypertensive drugs, and in some cases, the cost of new device-based therapies, such as RDN or baroreflex activation therapies. The cost for the screening of a secondary form of arterial hypertension is €250 per patient, and the yield is expected to be low. Furthermore, it is estimated that additional drugs, 1 or 2 pills per patient, for a period of only 6 to 12 weeks cost as much as liquid chromatography–mass spectrometry.97

More recently, using a Markov model to evaluate the incremental cost-effectiveness ratio, Chung et al demonstrated that optimal management of resistant hypertension, including drug monitoring, is cost-effective in a wide age range (30–90 years) compared with optimal management without drug monitoring.23 Notably, although the model assumed an overall 20 mm Hg drug monitoring–related reduction in systolic BP over the patients’ lifetime, drug monitoring remains cost-effective if systolic BP remains at the initial level in 50% of patients. Even more so, the use of drug monitoring to control for adherence before considering invasive procedures, such as renal sympathetic denervation or baroreflex activation therapy, is likely to be highly cost-effective. Indeed, the direct interventional cost for renal sympathetic denervation is already at €400098 and a baroreflex activation therapy costs as much as €20000.99 Hypothesizing a population of 100 patients with apparently resistant hypertension and assuming that all patients will undergo RDN or baroreflex activation therapy, the cost will be €400000 for RDN and €2000000 for baroreflex activation therapy. If detection of nonadherence by drug monitoring allows decreasing by 50% the number of patients eligible for RDN or baroreflex stimulation, the global saving will be of €1 200 000.11

Conclusions
The authors make a plea for a better study and wider use of direct methods to evaluate drug adherence in patients with difficult-to-treat and apparently resistant hypertension.

The main priorities for the next 5 years are the following:

- Better information of healthcare professionals, patients, and the lay public on the importance of a good drug adherence.
- Generalization of the use of validated adherence questionnaires (such as Morisky questionnaire)28 in patients with hypertension.
- Routine use of direct evaluation of drug adherence before considering complex or costly diagnostic procedures,100 further treatment intensification, or the use of invasive, expensive nondrug treatments (RDN, baroreflex stimulation) in patients on 4 drugs or more.
- Identification of the most adequate target population, for which direct methods of assessment of adherence are cost-effective and should be implemented.
- Determination of the best method or combination of methods to assess adherence in the long term in this target group. Drug monitoring is a good candidate, especially for the initial evaluation of adherence, if possible associated with other methods such as MEMS, for long-term follow-up and improvement of adherence.
- Standardization of the definition of partial and total adherence.
- Standardization of the methods of drug monitoring and assessment of the contribution of pharmacokinetic factors versus poor adherence on low drugs dosage in body fluids.
- Establishment of registries of adherence in the specific population of patients with apparently resistant hypertension, allowing further identification of predictors of poor adherence and, conversely, the barriers to a good adherence.
- Identification of distinct profiles of poor or nonadherent patients (careless, absent-minded, or badly organized patients, nonbelievers in the efficacy of drugs or having adverse events versus psychiatric patients who willingly do not take drugs).
- Study of the most efficient approaches to improve long-term drug adherence in these different types of patients.24

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References
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Evaluation of Adherence Should Become an Integral Part of Assessment of Patients With
Apparently Treatment-Resistant Hypertension

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Online Supplement

EVALUATION OF ADHERENCE SHOULD BECOME AN INTEGRAL PART OF ASSESSMENT OF PATIENTS WITH APPARENTLY TREATMENT-RESISTANT HYPERTENSION

Short title: drug monitoring in patients with resistant hypertension

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Drug adherence in the general hypertensive population

Adherence is a complex and dynamic phenomenon. It is defined as the intake of the correct drug at the correct dose at the correct time\(^1\,\,\,^2\). Furthermore, drug adherence also includes persistence, which is the continuous use of medications for the specified treatment time period\(^3\,\,\,^4\). Two types of non-adherence have been identified: intentional non-adherence and non-intentional non-adherence\(^5\).

Self-reported reasons for intentional non-adherence include: absence of symptoms, the belief that stress reduction may allow controlling blood pressure without drugs, fear of addiction, tolerance or side effects and preference for alternative medicine. In contrast, non-intentional poor adherence may be due to forgetfulness, problems of organization, cost of drugs and medical visits and difficulties in accessing health insurance\(^5\).

Adherence is a major health problem in chronic diseases. This is particularly true for a usually asymptomatic disease -or risk factor- such as hypertension\(^3\). In a population of 18.806 newly diagnosed hypertensive patients, followed by 400 Italian primary care physicians, the proportion of days covered by therapy during a mean of six months of follow-up was ≤40% in 51% of patients\(^6\). Similar results have been found in 82.824 newly-treated hypertensive elderly patients, of which only 51% were persistent with therapy for one full year\(^7\). Even using self-reporting questionnaires, which are likely to overestimate adherence\(^8\), the rate of adherence still remains at 53%\(^9\). Along the same lines, in a longitudinal database including 4783 hypertensive patients using electronic monitoring for 30 to 330 days, as much as 10% of the prescribed doses were omitted every day\(^10\).

In particular, 42% of patients forgot to take their therapy for one day only, 15% for one or two days and 43% for three or more days. In 13% of patients, “drug holidays” of two months or more were observed\(^10\).

Predictive factors of a poor drug adherence in the general hypertensive population include young age, sex\(^9\,\,\,^{11}\,\,\,^{12}\), comorbidities, pill burden, high number of daily intakes, number and nature of drugs\(^9\,\,\,^{13}\,\,\,^{14}\,\,\,^{15}\), the presence of side effects\(^13\,\,\,^{16}\), socio-cultural level, health service access and poor patient-physician interaction\(^17\). Other predictors of adherence include: depression, cognitive impairment, inadequate follow-up, cost of medication, patient’s lack of belief in benefit of treatment and patient’s poor insight into the illness\(^3\).

Impact of poor adherence on cardiovascular risk

Evidence is growing that patients with a poor level of adherence are at increased risk of cardiovascular events compared to adherent patients. In a cohort study of 18.806 newly diagnosed hypertensive patients, Mazzaglia et al. observed a significantly increased risk of acute cardiovascular events in patients with low level of adherence (≤ 40%) compared with highly adherent patients (≥80%) (hazard ratio: 1.61; p = 0.032)\(^6\). Similarly, in a retrospective analysis, hypertensive patients with low (< 60%) and moderate (60%-79%) adherence were more likely to be hospitalized for a cardiovascular event (odds ratio 1.33 and 1.28, respectively; p < 0.001) than adherent patients (≥ 80%)\(^18\). Along the same lines, in a population-based retrospective study including 31.306 newly treated hypertensive patients, the risk of all-cause death, stroke, or acute myocardial infarction was higher in patients with poor adherence (≤ 40%) compared to patients with good (61% to 80%) or excellent adherence levels (> 80%) (hazard ratio: 1.45 and 1.89 respectively, p = 0.001)\(^19\). Finally, Kim et al. evaluated the effect of antihypertensive medication adherence on incidence of ischemic heart disease, cerebral haemorrhage, and cerebral infarction in a population of about 34,000 hypertensive subjects for a period of five years. Drug adherence was assessed using a cumulative medication adherence scale based on pharmacy claims data. Patients with poor medication adherence (< 50%) had a higher mortality from ischemic heart disease (hazard ratio, 1.64; p= 0.005), cerebral haemorrhage (hazard ratio, 2.19; p =0.004), and cerebral infarction (hazard ratio, 1.92; p = 0.003) compared to those with good adherence (≥ 80%)\(^20\).
Alternative approaches for drug monitoring

The emerging technology of dried blood spot (DBS) sampling offers new possibilities. DBS capillary blood is obtained from a finger prick with a lancet by the patient himself. The DBS sampling technique is minimally invasive and therefore ideal for routine clinical testing. Sample storage and shipment is easy with a reduced biological hazard. After drying, the paper with the blood spot sample is mailed to the analytical laboratory. The laboratory punches out a disk from the blood spot before extraction of target drug(s). The size of the paper disk provides a volumetric measurement similar to liquid measurement devices. The advantages of DBS-based methods coupled with improved analytical instrumental capability have led to an increasing interest in this methodology for various applications including drug monitoring, toxicology and pharmacokinetic studies. This emerging technology has been used for bisoprolol and ramipril, but, to our knowledge, has not been validated for other antihypertensive drugs. The risk to have false negatives is higher with DBS than with blood or urine samples. This is because of the small amount of blood/urine compared to a blood or urine sample. Future implementation of DBS needs further investigations and will require highly sensitive assays. Finally, in the future, the DBS-sampling technique could be replaced by point-of-care-testing (POCT). POCT has the advantage to avoid shipping of samples and to allow evaluation of adherence and discussion of the results with the patient at the same consultation. Nowadays, POCT has been already successfully used for detection of drugs of abuse in urine or saliva and determination of plasma levels of glycated haemoglobin, total cholesterol, triglycerides and albumin-creatinine ratio. In addition to blood and urines, the use of alternative matrices such as saliva and hair may be considered in the future. Saliva has been used for monitoring patient compliance with psychiatric medications, anti-epileptic drugs, some anti-cancer drugs and antiretroviral agonists in HIV carriers patients. Collection of saliva does not require needle, lancet or technical expertise and is totally non-invasive, resulting generally in a better acceptance. A preliminary assessment and validation of the relation between drug concentrations in saliva/hair and blood is of course mandatory. Another aspect to take into consideration is the fact that, in contrast to blood, in the saliva most of the drugs will be present as unbound fraction. The presence of a drug in the saliva will be influenced by its physico-chemical properties, its interaction with the cells and tissues of the salivary glands as well as by extravascular drug metabolism. Therefore, this approach may not be appropriate for all drugs. Finally, as the concentration of drugs in hair reflects uptake from the systemic circulation over an extended time window (weeks to months), hair analysis may provide advantages over plasma or saliva monitoring in assessing average drug exposure over a longer period of time. This approach has been recently explored in anticancer and anti-HIV medications. Furthermore, unlike phlebotomy, hair collection is not invasive and does not require particular skills, refrigeration, or sterile equipment.
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