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CORRESPONDENCE

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Therapeutic Drug Monitoring Facilitates Blood Pressure Control in Resistant Hypertension

To the Editor: Adherence to medications is a major challenge clinicians often face in treating hypertension. An increasing number of studies show therapeutic drug monitoring (TDM) is reliable for detecting medication nonadherence in patients who seem to have resistant hypertension (RH) (1,2). In the United States, TDM assays for most antihypertensive drugs are available in clinical practice, including thiazide diuretics, beta-blockers, calcium channel blockers, and spironolactone (Fig. 1A) but not angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or direct renin inhibitors. The impact of TDM in optimizing blood pressure (BP) control in RH patients has not been determined.

We reviewed the medical records of all patients evaluated at our hypertension clinic from 2009 to 2012 who met the definition of RH (3). The TDM was performed in 56 subjects in whom all antihypertensive drugs prescribed were titrated to the maximal or near-maximal doses at the time of evaluation. The remaining 127

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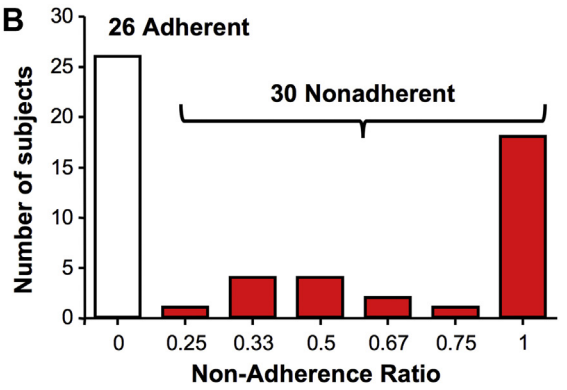
Drug Name	CPT codes	Price $	Method of Analysis
Beta Blocker Panel	83789	$171	LC-MS/MS
Hydrochlorothiazide	80299	$110	HPLC
Chlorthalidone	80299	$94	HPLC
Amlodipine	82491	$185	HPLC
Diltiazem	82491	$139	HPLC
Triamterene	83789	$299	LC-MS/MS
Spironolactone	80299	$94	Spectro-fluorometry
Furosemide	83789	$93	LC-MS/MS
Clonidine	83789	$136	LC-MS/MS
Guanfacine	83789	$182	LC-MS/MS
Doxazosin	82491	$235	HPLC
Minoxidil	83789	$240	LC-MS/MS
Hydralazine	82542	$453	GC
Angiotensin-Converting Enzyme Inhibitors	NA		
Angiotensin Receptor Blockers	NA		
Direct Renin Inhibitors	NA		



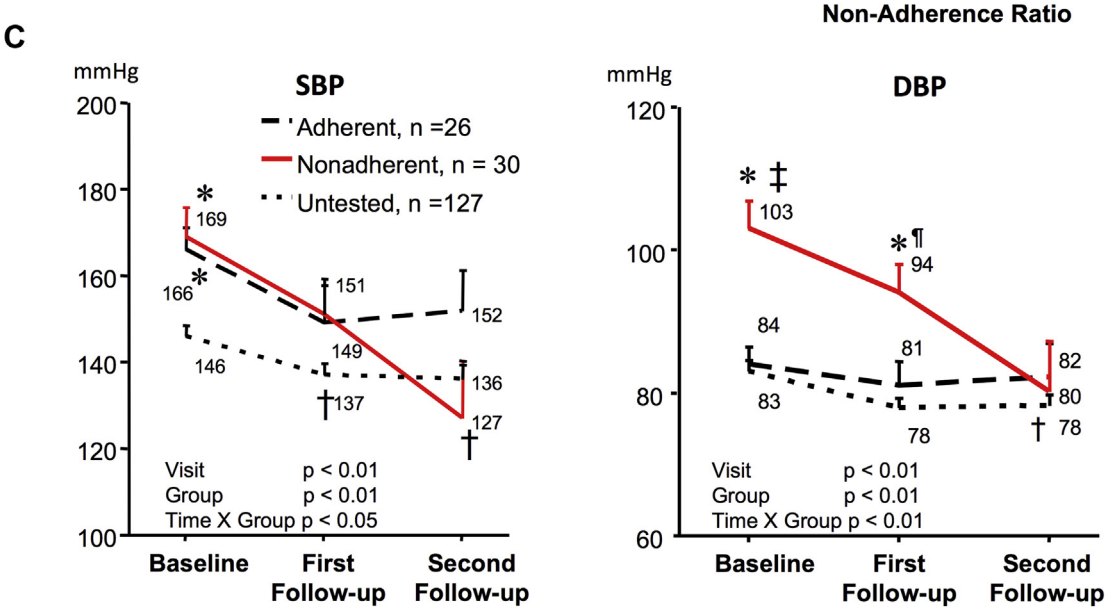


Figure 1 Frequency Distribution of Medication Nonadherence and Changes in BP During Follow-Up in Resistant Hypertension

(A) List of serum/plasma assays of commonly used antihypertensive drugs available for clinical testing. **(B)** Distribution of nonadherence ratio (the ratio of numbers of undetectable antihypertensive drugs to the total number of antihypertensive drugs tested) among subjects undergoing therapeutic drug monitoring. **(C)** Changes in systolic (SBP) and diastolic blood pressure (DBP) for the adherent, nonadherent, and untested groups. (*$p < 0.05$ vs. untested; †$p < 0.05$ vs. baseline; ‡$p < 0.01$ vs. adherent; ¶$p < 0.05$ vs. adherent). CPT = Current Procedural Terminology; GC = gas chromatography; HPLC = high-performance liquid chromatography; LC = liquid chromatography; MS = mass spectrometry.

patients did not undergo TDM, because of submaximal dosages of ≥1 of the antihypertensive drugs. Subjects with serum levels of at least 1 prescribed antihypertensive drug below the minimal detection limit were considered to be nonadherent. Nonadherent patients were younger (age 49 ± 2 years vs. 56 ± 2 years, $p < 0.05$) and had higher baseline diastolic BP (103 ± 4 mm Hg vs. 84 ± 2 mm Hg, $p < 0.05$) and heart rate (83 ± 3 beats/min vs. 71 ± 3 beats/min, $p < 0.05$) than adherent patients. Systolic blood pressure (SBP) was similar between the 2 groups (169 ± 7 mm Hg vs. 166 ± 5 mm Hg, p = NS).

Over one-half (54%) of patients who underwent TDM were found to be nonadherent to treatment. Specifically, 18 (32%) had undetectable levels of all drugs (Fig. 1B), whereas 12 (22%) had at least 1 undetectable drug. All 30 nonadherent patients initially denied missing any doses of their antihypertensive medications in the 24 h before TDM.

After the initial visit, 16 subjects in the nonadherent group, 16 in the adherent group, and 87 in the untested group completed follow-up visits. When the 16 patients in the nonadherent group were provided with TDM results, 2 attributed their nonadherence to memory loss, 3 described debilitating fatigue not previously reported during the first encounter, and 5 reported drug cost as a major barrier to nonadherence. Additional counseling of methods to overcome barriers to adherence was provided to the patients during the first follow-up visit, and BP reduced from the initial visit to the second follow-up visit by 46 ± 10/26 ± 14 mm Hg in the nonadherent group, compared with 12 ± 17/7 ± 7 mm Hg in the adherent group and 11 ± 4/4 ± 2 mm Hg in the untested group ($p < 0.01$ for both SBP and diastolic BP) (Fig. 1C). No differences in the number of antihypertensive medications were found during the second follow-up visit among the 3 groups (5.3 ± 0.7 vs. 4.2 ± 0.4 vs. 3.7 ± 0.2 drugs, respectively, $p > 0.05$).

The median cost of TDM in the nonadherent group was $301.00 ($224.00 to $544.00)/subject, which was not significantly different from $277.00 ($140.00 to $375.00)/subject in the adherent group (p = 0.2). The incremental cost associated with TDM in the tested group (regardless of TDM result) was $4.90 ($3.80 to $5.90)/mm Hg-reduction in SBP. Long-term results were available in a subset of 5 RH patients who were initially nonadherent to treatment. The TDM-guided adherence counseling led to sustained reduction in BP (from 200 ± 13/121 ± 8 mm Hg to 117 ± 13/75 ± 6 mm Hg) over an average of 25 ± 4 months of follow-up. This improvement in BP was achieved without increasing the number of antihypertensive drugs prescribed (5.6 ± 0.4 drugs vs. 4.6 ± 0.7 drugs). Repeated TDM in 9 initially undetectable drugs in these 5 patients revealed therapeutic serum levels in all drugs.

Nonadherence to antihypertensive medications is a major cause of cardiovascular morbidity and mortality. However, practical methods of adherence detection are not well-developed, and methods to modify nonadherent behavior have so far been unsatisfactory. Many physicians might not be aware that TDM of antihypertensive drug levels is available for clinical use and is covered by most health insurance plans. The advantage of this technique is ease of use without requiring additional time spent tracking the pharmacy refill rates or pill counts.

More importantly, when patients were informed of their undetectable serum drug levels and provided additional counseling, BP control was markedly improved without increasing treatment intensity. We found the incremental cost of TDM testing/mm Hg-reduction in SBP to be under $5.00/mm Hg-reduction in BP, far less than the cost associated with device therapies such as renal sympathetic denervation (RDN). The cost of RDN in European countries was estimated to be €4,500.00 or approximately $185.00/mm Hg-reduction in SBP at current exchange rates assuming an average reduction in SBP of 33 mm Hg with RDN (4).

Our study is limited by retrospective design and small sample size, which might, for example, explain our inability to demonstrate a statistically significant difference in SBP between adherent and nonadherent groups at baseline. Nonetheless, our data suggest TDM is a useful and practical tool in both monitoring adherence and in facilitating BP control in patients with apparently resistant hypertension at a favorable incremental cost. Further large prospective studies with long-term follow-up are still needed to confirm the benefit effect of TDM on BP control in RH.

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