Non-adherence in Resistant Hypertension

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No conflicts of interest
Objectives

To review:

- Measurement of non-adherence
- Effectiveness of interventions to improve adherence
- Prevalence of non-adherence in treated hypertensives
- Role of non-adherence in resistant hypertension
How to measure adherence

- Clinician impression
- Direct question
- Pill count
- Self-report instrument eg. “Morisky”
- Refill records
- Electronic bottle cap monitoring
- Blood or urine levels
Can you change adherence?

Cochrane Database Systematic Review (2008)
Haynes RB et al

“Current methods of improving adherence for chronic health problems are mostly complex and not very effective.”
Can you change adherence?

Annals of Internal Medicine (2012)
Viswanathan M et al.: Interventions to Improve Adherence to Self-administered Medications for Chronic Diseases in the United States: A systematic review

Reduced out-of-pocket expenses, case management, and patient education with behavioral support all improved medication adherence for more than 1 condition. Evidence is limited on whether these approaches are broadly applicable or affect long-term medication adherence and health outcomes.
Adherence in population of treated hypertensives
Dropouts from BP Treatment Hard to Find in Population Studies

- Harris poll
  91% of aware hypertensives on medication
  
  Moser M, J Clin Hypertension 2007

- NHANES 2003-2004
  94% of persons who ever took any BP med still take one

- Houston Population Survey
  87% aware hypertensives on medicine; of those not, ½ told to stop by doctor

  Hyman, Am J Public Health 1998
Adherence and Blood Pressure Control in 13 Managed Care Organizations 1999-2002:

<table>
<thead>
<tr>
<th>Adherence Level</th>
<th>Percent Treated Population</th>
<th>Percent Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Adherence (&gt; 80% of doses)</td>
<td>75%</td>
<td>43%</td>
</tr>
<tr>
<td>Medium adherence (50-79% of doses)</td>
<td>20%</td>
<td>34%</td>
</tr>
<tr>
<td>Low adherence (&lt; 50% of doses)</td>
<td>5%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Bramley TJ, et. al. J Managed Care Pharmacy 2006
Is it the Doctor or the Patient?

Inadequate regimen: 72%
Non-compliance: 13%

Rose, J Clin Htn 2007
How much of resistant hypertension is due to non-adherence?
Non-adherence in resistant hypertension: what do we know from the device studies?

- **Symplicity-HTN 1**
  
  *Method:* no published comment

- **Symplicity-HTN 2**
  
  *Method:* 2 week run in period with home BP and “compliance documentation”
  
  *Results:* 36/190 ineligible 2\textsuperscript{nd} to decline in BP no comment on adherence

- **Symplicity-HTN 3**
  
  *Method:* similar to Symplicity-HTN 2
  
  *Results:* results not yet reported

- **Enlig-HTN 1**
  
  *Method:* >14 days medical regimen monitoring,
  
  *Results:* 6/67 BP declined below threshold, no comment on adherence
### Referral Clinic Populations

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Non-adherent</th>
<th>Psychological cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Haven (Yale) 1991</td>
<td>91</td>
<td>9.9%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Chicago (Rush) 2005</td>
<td>141</td>
<td>16.0%</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

Method of adherence measurement: patient report

*Yakovlevitch M, Black HR: Arch Intern Med 1991*
*Garg JP,..., Black HR: Am J Hypertension 2005*

Subjects: 41 patients with elevated BP on 3 drugs, BP 156/106 not stated how sample was selected

Intervention: patients told they would be monitored for adherence and placed on electronic bottle caps for 2 months

Result: BP of group dropped to 147/97, 1/3 controlled to < 140/90 during 2 month monitoring:
- mean adherence: 93%
- 80% had > 90% adherence
- bottom tertile of adherence had worst BP
- of the 2/3 not controlled, 70% were adherent

Implication: Up to 50% non-adherent at baseline
Setting: London, special clinic set up to observe patients take medications

Patients: 37 patients referred to this clinic for uncontrolled hypertension

Assessment: patients took their meds at clinic, followed that day, some then got 24 ABPM attached, then f/u in clinic

Result: ? 60% controlled after tablet feed and/or ABPM
Difficult-to-control arterial hypertension or uncooperative patients? The assessment of serum antihypertensive drug levels to differentiate non-responsiveness from non-adherence to recommended therapy. 
Ceral J et al., *Hypertension Research* 2011

Setting: Hypertension clinic in Prague

Patients: 84 out of 524 patients followed who were “suspected of non-adherence” (not clear if this was everyone uncontrolled on 3 drugs)

Adherence Assessment: Serum drug levels

Results: All tested drugs found 34.5%
No drugs found 34.5%
At least one drug found but not all 31.0%
Resistant hypertension? Assessment of adherence by toxicological Urine analysis.
Jung O et Al., J Hypertension 2013

Setting: Hypertension referral clinic, Frankfurt, Germany

Patients: All patients still uncontrolled after r/o white coat and 4 drug therapy n= 76

Assessment: Urine gas-chromatography- mass spectrometry

Results:
- No drug detected 16%
- All drugs detected 47%
- < 50% of drugs detected 24%
- > 50% but not all detected 13%
Therapeutic Drug Monitoring Facilitates BP Control In Resistant Hypertension
Brinker SK et al., Abstract ASH 2013

Setting: Hypertension clinic at UT Southwestern, Dallas, TX

Patients: 40/111 who met criteria for RH had a total of 76 drugs measured

Assessment: Serum levels

Results: 17 (42.5%) took no drug
6 (15.0%) took some drug
17 (42.5%) took all drugs

Patients who were found non-adherent and counseled improved more with follow up
Renal Sympathetic Denervation in Patients with Treatment-Resistant Hypertension after Witnessed Intake of Medication Before Qualifying Ambulatory Blood Pressure  
Elmula F, et al., *Hypertension* 2013

Setting: Patients with presumed RH referred for device therapy screening protocol included 24hr ABPM after witnessed drug intake

Result: 5 out of 18 patients excluded for normal ABPM  
3/5 of ?? had prior abnormal ABPM  
implication: 3 to 5 of 18 non-adherent
Characteristics of Resistant Hypertension in a Large Ethnically Diverse Hypertension Population of an Integrated Health System


Setting:   Kaiser System,  Southern California

Subjects:  470,386 patients with dx HTN, 60,327 w resistant

Adherence measure:   Pharmacy data

Result:   Resistant Hypertensives:   age 69, blood pressure 143/74

Adherence in prior 6 months:   93%

Adherence in non resistant hypertensives:   89%
Longitudinal Evaluation of Medication Adherence in a Resistant Hypertension Population
Sim JJ et al., Abstract ASH 2013

Setting: Kaiser Permanente Southern California

Subjects: 60,359 persons on 3 drugs with BP>139 or 89 or 4+ drugs

Adherence assessment: refill data - Proportion of Days Covered (PDC) a year after identification:

<table>
<thead>
<tr>
<th>Results</th>
<th>PDC</th>
<th>Proportion of patients</th>
<th>BP baseline</th>
<th>BP change over year</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80%</td>
<td></td>
<td>39.7%</td>
<td>140/73</td>
<td>-7.1</td>
</tr>
<tr>
<td>60-79%</td>
<td></td>
<td>35.3%</td>
<td>142/74</td>
<td>-7.7</td>
</tr>
<tr>
<td>40-59%</td>
<td></td>
<td>18.7%</td>
<td>146/76</td>
<td>-8.5</td>
</tr>
<tr>
<td>&lt; 40%</td>
<td></td>
<td>6.3%</td>
<td>146/78</td>
<td>-8.2</td>
</tr>
</tbody>
</table>
Characteristics, drug combinations and dosages of primary care patients with uncontrolled ambulatory BP and high medication adherence.
Grigoryan L, Pavlik VN, Hyman DJ. J Am Soc Hypertension 2013 (epub ahead of print)

Setting: 2 health systems in Houston, TX with primary care clinics

Patients: Patients with uncontrolled office HTN that were recruited to a trial of methods to reduce therapeutic inertia. A subsample had baseline 24-hr ABPM and 30 day electronic bottle cap monitoring of up to 3 BP medications.

Analysis: Adherence was calculated in patients with uncontrolled 24-hour ABPM on 3 or more anti-hypertensives. Treatment regimens were evaluated for appropriateness.
Results

uncontrolled office BP (n=140)

- < 3 drugs
  - potential inertia
    - N=71
  - 24 APBM controlled
    - n=15 (22%)
  - MEMS non-adherent
    - n=20 (37%)
  - on optimal regimen 0%

- > 3 drugs
  - potential RH
    - N=69
  - 24 APBM uncontrolled
    - n=54 (78%)
  - MEMS adherent
    - n=34 (63%)
Prevalence of non-adherence in “Apparently Resistant Hypertension”:

- Data are limited
  - Variations in measurement of adherence
  - Mostly small, heterogeneous samples
  - Many samples likely unrepresentative of general RH population

- Non-adherence estimates are highly variable (7%-66%)
- Excluding the baseline Kaiser sample and self report studies estimates about 35-66%
- When assessed with biomarkers or monitoring, partial non-adherence is more common than complete non-adherence
More research on prevalence of non-adherence in RH and effective adherence interventions needed.

Assessment of non-adherence and intervention if present should be considered before device therapy.

Aside: would be nice to know if device therapy beneficial to the high risk hypertensive who will likely always remain non-adherent.