Caution: Contents Under Pressure
Identifying Drug-Induced Hypertension

Melanie Claborn, Pharm.D., BCACP
Assistant Professor of Pharmacy Practice
Southwestern Oklahoma State University College of Pharmacy
Clinical Pharmacy Specialist-Oklahoma City Indian Clinic
Oklahoma City, OK

Disclosure

• Under guidelines established by the Accreditation Council for Pharmacy Education, disclosure must be made regarding financial relationships with commercial interests within the last 12 months.

• I have no relevant financial relationships or affiliations with commercial interests to disclose.
Learning Objectives

At the completion of this activity, pharmacists will be able to:

• Describe the complications of untreated hypertension

• List drugs/supplements associated with secondary hypertension

Pre-Assessment Question:
What is the leading cause of death in the United States?

a. Heart disease
b. Cancer
c. Accidents
d. Influenza
Pre-Assessment Question:
A patient has blood pressure readings in the clinic that are consistently 136/82. How would you classify his blood pressure?

a. Normal  
b. Elevated  
c. Stage 1 HTN  
d. Stage 2 HTN

Pre-Assessment Question:
Which of these medications can be associated with increasing blood pressure?

a. Cyclosporine  
b. Erythropoietin  
c. Indomethacin  
d. All of the above
Why talk about the same old thing...

Nearly half of all adults in the US have cardiovascular disease

Dishonorable Awards

Heart disease is the leading cause of death in the US

Ischemic heart disease and stroke lead worldwide

Image: http://clipart-library.com/medal-clips.html
CVD and other major causes of death for American Indians or Alaska Natives United States, 2016

Percentage of Deaths Attributable to Cardiovascular Disease (United States: 2016)

Heart Failure, 9.3%
Coronary Heart Disease, 43.2%
Stroke, 16.9%
High Blood Pressure, 9.8%
Diseases of the Arteries, 3.0%
Other, 17.7%
5/21/2019

CVD Risk Factors

- Hypertension
- Diabetes Mellitus
- Overweight/Obesity
- Cigarette smoking
- Physical inactivity
- Dyslipidemia
- Microalbuminuria (or GFR < 60 mL/min)
- Age
- Family History of Premature CVD


Snapshot of Hypertension in the US

116.4 million, or 46% of US adults are estimated to have hypertension. These are findings related to the new 2017 Hypertension Clinical Practice Guidelines.

On average, 1 in 5 adults, or 22.5% of American adults, reported achieving adequate leisure-time aerobic and muscle-strengthening activities to meet the physical activity guidelines, based on 2016 data.

Prevalence of hypertension in adults ≥20 years of age by sex and age (NHANES, 2013–2016)

**BP Control in the US**

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Aware</td>
<td>51%</td>
<td>73%</td>
<td>68%</td>
<td>70%</td>
<td>83%</td>
</tr>
<tr>
<td>Treated</td>
<td>31%</td>
<td>55%</td>
<td>54%</td>
<td>59%</td>
<td>77%</td>
</tr>
<tr>
<td>Controlled</td>
<td>10%</td>
<td>29%</td>
<td>27%</td>
<td>34%</td>
<td>54%</td>
</tr>
</tbody>
</table>

1 SBP <140 mm Hg and DBP <90 mm Hg.
2 Age 18 to 74 years with SBP 140 mm Hg or DBP 90 mm Hg or taking antihypertensive medication.

JNC VII. JAMA 2003; 289:2560-2572
Extent of awareness, treatment, and control of high blood pressure by age NHANES, 2013–2016

Why Blood Pressure Control Matters

On average, someone dies of CVD every 38 seconds
About 2,303 deaths from CVD each day, based on 2016 data.

On average, someone in the US has a stroke every 40 seconds
About 795,000 new or recurrent stroke each year, based on 2015 data.

On average, someone dies of a stroke every 3.70 minutes
About 389.4 deaths from stroke each day, based on 2016 data.

Target Organ Damage

Hypertension

- Hemorrhage, stroke, dementia
- LVH, CHD, HF
- Retinopathy
- Peripheral vascular disease
- Renal failure

Reducing average population systolic blood pressure by only 12-13 mmHg could reduce:

- Stroke: 37%
- Coronary heart disease: 21%
- Death from cardiovascular cause: 25%
- Death from all causes: 13%

# Categories of Blood Pressure in Adults

<table>
<thead>
<tr>
<th>BP Category</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120 mm Hg</td>
<td>AND &lt;80 mm Hg</td>
</tr>
<tr>
<td>Elevated</td>
<td>120-129 mm Hg</td>
<td>AND &lt;80 mm Hg</td>
</tr>
</tbody>
</table>

**Hypertension**

<table>
<thead>
<tr>
<th>Stage</th>
<th>SBP</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>130–139 mm Hg</td>
<td>80–89 mm Hg</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥140 mm Hg</td>
<td>≥90 mm Hg</td>
</tr>
</tbody>
</table>

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category*

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# Blood Pressure Goals

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated HTN</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Diabetes</td>
<td>&lt;130/80</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>CVD</td>
<td>&lt;140/90</td>
<td>--</td>
<td>&lt;140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>CKD</td>
<td>&lt;130/80</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Elderly</td>
<td>Not specified</td>
<td>&lt;150/90 (≥60 years)</td>
<td>&lt;150/90 (≥80 years)</td>
<td>&lt;130 (SBP)</td>
</tr>
</tbody>
</table>


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![MAKE CONTROL YOUR GOAL, EVERY DAY](http://www.cdc.gov/bloodpressure/infographic.htm)
### Nonpharmacological Interventions for Prevention and Treatment of Hypertension

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Approximate Impact on SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>-5 mm Hg</td>
</tr>
<tr>
<td>Best goal is ideal body weight. Expect about 1 mm Hg for every 1-kg reduction in body weight.</td>
<td></td>
</tr>
<tr>
<td>Healthy diet</td>
<td>-11 mm Hg</td>
</tr>
<tr>
<td>Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.</td>
<td></td>
</tr>
<tr>
<td>Reduced intake of dietary sodium</td>
<td>-5/6 mm Hg</td>
</tr>
<tr>
<td>Optimal goal is &lt;1500 mg/d, but aim for at least a 1000-mg/d reduction in most adults.</td>
<td></td>
</tr>
<tr>
<td>Enhanced intake of dietary potassium</td>
<td>-4/5 mm Hg</td>
</tr>
<tr>
<td>Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium.</td>
<td></td>
</tr>
<tr>
<td>Physical activity (aerobic)</td>
<td>-5/8 mm Hg</td>
</tr>
<tr>
<td>● 90–150 min/wk</td>
<td></td>
</tr>
<tr>
<td>● 65%–75% heart rate reserve</td>
<td></td>
</tr>
<tr>
<td>Physical activity (dynamic resistance)</td>
<td>-4 mm Hg</td>
</tr>
<tr>
<td>● 90–150 min/wk</td>
<td></td>
</tr>
<tr>
<td>● 50%–80% 1 rep maximum</td>
<td></td>
</tr>
<tr>
<td>● 6 exercises, 3 sets/exercise, 10 repetitions/set</td>
<td></td>
</tr>
<tr>
<td>Moderation of alcohol intake</td>
<td>-4 mm Hg</td>
</tr>
<tr>
<td>In individuals who drink alcohol, reduce alcohol to:</td>
<td></td>
</tr>
<tr>
<td>● Men: ≤2 drinks daily; Women: ≤1 drink daily</td>
<td></td>
</tr>
</tbody>
</table>


### Screening for Secondary Hypertension

**Conditions**
- Drug-resistant/induced hypertension
- Abrupt onset of hypertension
- Onset of hypertension at <30 y
- Exacerbation of previously controlled hypertension
- Disproportionate TID for degree of hypertension
- Accelerated/malignant hypertension
- Onset of diastolic hypertension in older adults (≥65 y)
- Unprovoked or excessive hypokalemia

**Screen for secondary hypertension (Class I)**
(see Table 13)

**Positive screening test**

Identifiable Causes of Hypertension

A • Accuracy  
• Apnea  
• Aldosteronism

B • Bruits (renovascular disease)  
• Bad kidneys

C • Catecholamines  
• Coarctation  
• Cushing’s syndrome

D • DRUGS  
• Diet

E • Erythropoietin  
• Endocrine disorders

Secondary Causes

Renal parenchymal disease • 1-2%
Renovascular disease • 5-34%
Primary aldosteronism • 8-20%
Obstructive sleep apnea • 25-50%
Pheochromocyctoma, Cushings, Thyroid, Aortic coarctation, Hyperparathyroidism, Adrenal hyperplasia, Acromegaly • Less than 1%
Accuracy of Blood Pressure Measurement

- Equipment inspected
- Trained operator
- Patient properly positioned
- Caffeine, exercise, and smoking should be avoided for at least 30 minutes before
- Appropriately sized cuff
- Two measurements

Definition of Drug-Induced Hypertension

High blood pressure caused by a response to using, or stopping the use of, a chemical substance, drug, or medication.

— U.S. National Library of Medicine/National Institutes of Health

Risk Factors for Drug-induced Hypertension

- History of elevated blood pressure
- Decreased GFR
- Metabolic syndrome
- Advanced age
- Persistent use
Drugs Associated with Increases in BP

- Amphetamines
- Bevacizumab
- Buspirone
- Caffeine
- Cocaine
- Corticosteroids
- Cyclosporine
- Erythropoietin Stimulating Agents
- Estrogen-containing oral contraceptives
- Herbals
- Licorice
- Monoamine Oxidase Inhibitors
- NSAIDS
- Phenylephrine/Pseudoephedrine
- Protease Inhibitors
- Sibutramine (off market)
- Sorafenib/Sunitinib
- Tacrolimus
- Venlafaxine

Mechanism for Increasing BP

- **Volume retention**
  - Glucocorticoids/mineralocorticoids
  - Hormones
  - NSAIDS
- **Activation of the sympathetic nervous system**
  - Decongestants
  - Stimulants
- **Direct vasoconstriction**
  - Cyclosporine
  - Tacrolimus
- **Combined**
  - Erythropoietin
  - Alcohol
  - VEGF
- **Unknown**
Steroids/Glucocorticoids

- Occurs in at least 20% of patients
  - More in elderly and with family history
- Dose dependent
- Oral cortisol doses of 80-200 mg/day can increase systolic BP up to 15 mmHg in 24 hours
  - At low doses cortisol has less effect
- Cessation usually results in normalization of BP
- Management
  - Use short term or non-systemic options
  - Consider diuretic if long term therapy needed

Licorice

- Main ingredient- glycyrrhizic acid
- Excess mineralocorticoid
- Dose dependent
- Can have a sustained increase in BP

References:
- Image: http://www.candyfavorites.com/candy-flavors/black-licorice
**Estrogens (Oral Contraceptives)**

- Oral contraceptives induce HTN in ~5% of users
  - 50 mcg of estrogen and 1-4 mg of progestin
- Usually minimal but can be severe, even malignant HTN
- Risk decreases with cessation of oral contraceptive
- Postmenopausal HRT has minimal effect on BP in normotensive women—may even reduce
- If BP not controlled—may consider progestin only or IUD


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**Nonsteroidal Anti-Inflammatory Drugs**

**Cox-2 Inhibitors**

- Ibuprofen, naproxen, piroxicam
- Celecoxib
- Implicated in increasing BP and CVD risk
- Can antagonize effects of some BP agents
- NSAIDS inhibit PG → vasoconstriction and volume retention
- Recommended
  - Lifestyle changes and nonpharmacologic therapies for pain
  - Use lowest effective NSAID dose
  - Modifying antihypertensive therapy and diuretic management

Change of BP in Hypertensives and Normotensives

<table>
<thead>
<tr>
<th></th>
<th>Hypertensive patients (mmHg)</th>
<th>Normotensive individuals (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIIDs (pooled)</td>
<td>3.6–5.4</td>
<td>1.0–1.1</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>4.8–6.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Naproxen</td>
<td>3.1–6.1</td>
<td>ND</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>2.9–6.2</td>
<td>ND</td>
</tr>
<tr>
<td>Sulindac</td>
<td>−1.6 to 2.2</td>
<td>−1.6</td>
</tr>
<tr>
<td>Aspirin</td>
<td>−1.8 to 1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>COXIBs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>2.6–4.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>−0.4</td>
<td>4.3</td>
</tr>
</tbody>
</table>


Atypical Antipsychotics

- Linked to metabolic syndrome and weight gain
- More likely with clozapine and olanzapine
- Management
  - Lower dose
  - Consider alternative agent and behavioral therapy

Stimulants

• Nicotine, amphetamines
• Unpredictable
• Methylphenidate, amphetamines usually only cause modest increases
  – BP: 2-5/1-3 mmHg
  – HR: 3-6 bpm
• Some can experience significant increases in BP or HR
• Management
  – Consider behavioral therapy


Cocaine, Anesthetics, Narcotics

• Cocaine
  – Abuse causes adrenergic overactivity
  – Acute increases in BP, but not usually chronic increases
  – Problematic when used while taking beta blockers
• Ketamine
• Naloxone
  – Hypertensive responses seen in reversal of narcotics
  – Can acutely reverse antihypertensive effects of clonidine

Decongestants

- Pseudoephedrine, phenylephrine, epinephrine, oxymetazoline
- Mainly due to activation of the sympathetic nervous system
- Counteract pharmacological treatment
- Sympathomimetics with beta-blockers may increase BP due to unopposed alpha vasoconstriction
- Management
  - Consider alternative therapies (nasal saline, intranasal corticosteroids, antihistamines)


Caffeine

- Potential activation of the sympathetic nervous system
- More pronounced in males and African-Americans
- Caffeine in 2-3 cups of coffee can raise as much as 10 mmHg (average is 3-5 mmHg)
- Tolerance usually develops
- Caffeine content in drinks vary

Image: http://www.theprospect.net/a-users-guide-to-caffeine-11237
Antidepressants

- Venlafaxine-SNRI-3-13%
  - Meta-analysis showed increase
    - Dose dependent
    - Older patients
    - Men
  - Elevated diastolic BP (>90 mmHg) was statistically at doses > 300 mg/day
- Monoamine oxidase inhibitors-selegiline
- Thioridazine-in overdose

Immunosuppressive Agents

- Cyclosporine-BLACK BOX WARNING
  - Can be mild to severe and up to 80%
  - 1 year after renal transplant 32.7-81.6%
  - Bone marrow transplants 57% incidence of HTn vs. 4% with methotrexate
  - Cardiac transplant-may be up to 100%
- Tacrolimus-associated much less than cyclosporine
Recombinant Human Erythropoietin

- Dose-related
- Reported to develop (or worsen) in 20-30% of patients
- May appear as early as 2 weeks and as late as 4 months
- Increase risk
  - Pre-existing HTN, genetic predisposition, rapid rise in hematocrit
- Can be controlled with dialysis and antihypertensives


Alcohol

- Excessive intake can raise BP and resistance to antihypertensives
- Increase in prevalence of 7-11%
- Prospective cohort study
  - ~4,000 Japanese men
  - Greater in those who consume > 300 g/week
- Also can see HTN with disulfiram

Anti-vascular Endothelial Growth Factor (VEGF)

- **Bevacizumab**
  - Dose related
  - Severe HTN (>200/100) >3-5-fold higher
  - Up to 32%
  - More pronounced in elderly, preexisting HTN, renal cell carcinoma

- **Sorafenib**
  - Study using 24-hour ambulatory BP monitoring, 400 mg twice a day increased systolic BP by 8.2 mm Hg, and diastolic BP by 6.5 mm Hg within 24 hours of treatment

- **Sunitinib**
  - Increased risk of severe HTN-relative risk 22.7, 95% CI 4.48-115.29 (p= 0.001) in comparison to controls


Adverse effects of VEGF inhibitors

Antiretroviral therapy-Protease Inhibitors

- May increase more than 10 mmHg (systolic or diastolic)
- Elevations more likely in elderly, higher baseline systolic BP, higher cholesterol, low CD4 count
- Usually seen more with the therapy that causes metabolic changes
  - Highest risk with lopinavir/ritonavir
- Drug interaction with calcium channel blockers


Herbal Products

- Yohimbine
  - Increases norepinephrine and sympathetic activation
  - Interacts with clonidine
- Ginseng
  - Information to suggest increase or decrease
- Ma huang/ephedra
  - Many case reports involving young adults
- St John’s Wort

Patient Case

• 76 year old female presents to the pharmacy with a new prescription for clonidine. When talking with the patient, she reports “my doctor put me on another new medication to help control my high blood pressure”

• Current medications: hydrochlorothiazide 25 mg daily, losartan 100 mg daily, metoprolol 50 mg twice daily, amlodipine 10 mg daily

• She reports that her blood pressures at home are in the “150s on the top”
Patient Case (continued)

• When you question her about any medications that she takes OTC or supplements—she reports that she takes ibuprofen 3 tabs daily for her arthritis and ginger to help with her nausea.
• You also verify how (and if) she is taking all of her medications.
• What medications might be worsening her blood pressure?

Strategies to Help with Adherence

S | • Simplify the regimen
I | • Impart knowledge
M | • Modify patients’ beliefs and behavior
P | • Provide communications and trust
L | • Leave the bias
E | • Evaluate adherence

Millionhearts.hhs.gov
Conclusion

• Hypertension affects many Americans
• Controlling hypertension can help prevent complications
• In most cases, the cause of hypertension is unknown
• Identifying agents that can increase blood pressure can help patients to improve control
• All patients should follow lifestyle modifications

Contact Information

• Melanie.Claborn@swosu.edu
• Melanie.c@okcic.com
• 405-948-4900
  extension 494
References


References

- Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2019. American Diabetes Association. Diabetes Care Jan 2019, 42 (Supplement 1) S103 S123; DOI: 10.2337/dc19-S010
Self-Check

You may have high blood pressure if you are...

- A smoker
- Dealing with sleep apnea
- Physically inactive
- Older than 50 years
- Overweight or obese
- Dealing with diabetes or kidney disease
- Taking more than 2 grams of sodium per day
- African American, Hispanic or Latino/Latina
- A man who drinks more than 1 ounce of alcohol per day
- A woman who drinks more than half an ounce of alcohol per day
- A person whose mother or father has hypertension

Post-Assessment Question:
What is the leading cause of death in the United States?

a. Heart disease
b. Cancer
c. Accidents
d. Influenza
Post-Assessment Question:
A patient has blood pressure readings in the clinic that are consistently 136/82. How would you classify his blood pressure?

a. Normal  
b. Elevated  
c. Stage 1 HTN  
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Post-Assessment Question:
Which of these medications can be associated with increasing blood pressure?

a. Cyclosporine  
b. Erythropoietin  
c. Indomethacin  
d. All of the above
Stress-Does it increase BP?

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Identifying Drug-Induced Hypertension

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Southwestern Oklahoma State University College of Pharmacy
Clinical Pharmacy Specialist-Okahoma City Indian Clinic
Oklahoma City, OK