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Caution: Contents Under Pressure Identifying Drug-Induced Hypertension

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Caution: Contents Under Pressure
Identifying Drug-Induced Hypertension

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Learning Objectives

Pharmacists
• Identify common challenges to achieving optimal blood pressure control
• Describe the complications of untreated hypertension
• Discuss the potential mechanisms of drug-induced hypertension
• List drugs-supplements associated with secondary hypertension
• Given a patient case with hypertension, be able to recognize which medication is a potential causative agent

Technicians
• Describe the complications of untreated hypertension
• List drugs-supplements associated with secondary hypertension

Why talk about the same old thing...

Percentage of Deaths Attributable to Cardiovascular Disease (United States: 2011)

- Coronary Heart Disease, 47.7%
- Heart Failure, 7.4%
- Stroke, 16.4%
- High Blood Pressure, 8.1%
- Diseases of the Arteries, 3.3%
- Other, 16.9%

Adapted from Mozaffarian et al. Circulation. 2015;131:e29-e322


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

A SNAPSHOT: BLOOD PRESSURE IN THE U.S.

Make Control Your Goal

67 MILLION American adults have high blood pressure

1 IN 3

High blood pressure contributes to

~1,000 DEATHS/DAY

CDC

http://www.cdc.gov/bloodpressure/infographic.htm

Prevalence of high blood pressure in adults ≥20 years of age by age and sex (NHANES: 2007–2012)

Prevalence of Hypertension, 2011
U.S. Adults Ages 20 and Older (Percentage)

Why Blood Pressure Control Matters

When your blood pressure is high:

You're 4x more likely to die from a stroke
You're 3x more likely to die from heart disease

69% of people who have a first heart attack
77% of people who have a first stroke
74% of people with chronic heart failure

HAVE HIGH BLOOD PRESSURE

Annual estimated costs associated with high blood pressure:

$51 BILLION

$47.5 BILLION in direct medical expenses

http://www.cdc.gov/bloodpressure/infographic.htm

BP Control in the US

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

SBP <140 mm Hg and DBP <90 mm Hg.
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
Mozaffarian et al. Circulation. 2015;131:e29-e322

Only about half of patients with high blood pressure are controlled
Extent of awareness, treatment, and control of high blood pressure by age (NHANES: 2007–2012)

Extent of awareness, treatment, and control of high blood pressure by race/ethnicity (NHANES: 2007–2012)

Target Organ Damage

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%

Audience Question:
A patient has blood pressure readings in the clinic that are consistently 136/84. How would you classify his blood pressure?

a. Normal
b. Pre-hypertension
c. Stage 1 HTN
d. Stage 2 HTN
JNC VII Classification

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>&gt;160</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>


Audience Question:
For the general population aged 60 years or older, the JNC 8 panel recommends initiating pharmacologic treatment to lower BP at a diastolic blood pressure of:

a. 80
b. 90
c. 140
d. 150

Blood Pressure Goals

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Diabetes</td>
<td>&lt;130/80</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>CVD</td>
<td>&lt;140/90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>&lt;130/80</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>Elderly (Not specified)</td>
<td>&lt;140/90</td>
<td>&lt;150/90</td>
<td></td>
</tr>
<tr>
<td>Elderly (&gt;60 years)</td>
<td>&lt;150/90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly (&gt;80 years)</td>
<td></td>
<td>&lt;150/90</td>
<td></td>
</tr>
</tbody>
</table>

JNC 8: JAMA. 2014;311(5):507-520

Lifestyle Modifications

<table>
<thead>
<tr>
<th>Modification</th>
<th>Approximate SBP reduction (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>5-20 mmHg/10 kg weight loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium restriction</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>4-9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>

Identifiable Causes of Hypertension

- A: Acute
- B: BPH
- C: Cushing's syndrome
- D: Drug
- E: Endocrine disorders
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


Medication Adherence by the Numbers

For every 100 prescriptions written...
- 50-70 go to a pharmacy
- 48-66 come out of the pharmacy
- 25-30 are taken properly
- 15-20 are refilled as prescribed

Risk Factors for Drug-induced Hypertension

- History of elevated blood pressure
- Decreased GFR
- Metabolic syndrome
- Advanced age
- Persistent use of high dose NSAID therapy

Audience Question:
Which of these medications is associated with increasing blood pressure?

- a. Cyclosporine
- b. Erythropoietin
- c. Indomethacin
- d. All of the above

Drugs Associated with Increases in BP

- Amphetamines
- Bevacizumab
- Bluevone
- Caffeine
- Celecoxib
- Cocaine
- Corticosteroids
- Cyclosporine
- Erythropoietin
- Estrogen-containing oral contraceptives
- Herbals
- Herbs
- Licorice
- Licorice
- Monamine Oxidase Inhibitors
- NSAIDs
- Phenylephrine/Pseudoephedrine
- Sibutramine (off market)
- Sorafenib/Sunitinib
- Tacrolimus
- Testosterone
- Venlafaxine
Mechanisms for Increasing BP

**Volume retention**
- Glucocorticoids
- Hormones
- NSAIDS

**Activation of the sympathetic nervous system**
- Decongestants
- Stimulants
- Catecholamines

**Direct vasoconstriction**
- Cyclosporine
- Tacrolimus

**Combined**
- Erythropoietin
- Alcohol
- VEGF

**Unknown**

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**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
- Consider diuretic if long term steroid therapy needed

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

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**Estrogens (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—may even reduce
- If BP not controlled—may consider alternative contraceptive

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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
  - Monitor BP, renal function, and edema
  - Lifestyle changes and nonpharmacologic therapies for pain
  - Use lowest effective NSAID dose
  - Modifying antihypertensive therapy and diuretic management

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**Change of BP in Hypertensives and Normotensives**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hypertensive patients (mmHg)</th>
<th>Normotensive individuals (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID</td>
<td>3.5-5.4</td>
<td>1.0-1.1</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>4.8-6.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Naproxen</td>
<td>3.1-6.1</td>
<td>ND</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>2.6-6.3</td>
<td>ND</td>
</tr>
<tr>
<td>Sulindac</td>
<td>-1.6 to 2.3</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>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>

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Image: [Licorice](http://www.candyfavorites.com/candy-flavors/black-licorice)
### Stimulants
- Nicotine, amphetamines
- Unpredictable
- Methylphenidate, amphetamines usually only cause modest increases
  - BP: 2-4 mmHg
  - HR: 3-6 bpm
- Some can experience significant increases in BP or HR

### Cocaine, Aesthetics, Narcotics
- Cocaine
  - Abuse causes adrenergic overactivity
  - Acute increases in BP, but not usually chronic increases
  - Problematic when used while taking beta blockers
- Ketamine
- Naloxone
  - Can acutely reverse antihypertensive effects of clonidine

### Decongestants
- Pseudoephedrine, phenylephrine, epinephrine, oxymetazoline, ephedra alkaloids
- Phenylpropanolamine-taken off market
- Mainly due to activation of the sympathetic nervous system
- Sympathomimetics with beta-blockers may increase BP due to unopposed alpha vasoconstriction

### Caffeine
- Potentially due to activation of the sympathetic nervous system
- More pronounced in males and African-Americans
- Tolerance usually develops

### Antidepressants
- Venlafaxine-SNRI-3-13%
  - Meta-analysis-more pronounced
    - Dose dependent
    - Older patients
    - Men
- Monoamine oxidase inhibitors-selegiline
- Thioridazine-in overdose

### Caffeine
- Phenylpropanolamine-taken off market
- Mainly due to activation of the sympathetic nervous system
- Sympathomimetics with beta-blockers may increase BP due to unopposed alpha vasoconstriction

### Immunosuppressive Agents
- Cyclosporine-BLACK BOX WARNING
  - Can be up to 30-80%
  - Can be mild to severe
  - Dose dependent
- Tacrolimus-associated much less than cyclosporine
Recombinant Human Erythropoietin
- Reported to develop (or worsen) in 20-30% of patients
- May appear as early as 2 weeks and as late as 4 months
- Dose-related
- Increased risk
  - Pre-existing HTN, genetic predisposition, rapid risk in hematocrit

Alcohol
- Excessive intake can raise BP
- Excessive alcohol can cause resistance to antihypertensives
- Studies find 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) Signaling
- Bevacizumab
  - 8-18%
  - Dose related
  - More pronounced in elderly, preexisting HTN, renal cell carcinoma
- Sorafenib
- Sunitinib

HAART
- May increase more than 10 mmHg (systolic or diastolic)
- Usually seen more with the therapy that causes metabolic changes (protease inhibitors)
  - Highest risk with lopinavir/ritonavir
  - Lower with atazanavir (rec in naive patients)

Other 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
- Ginger
  - Seen with abuse of this agent
- St John’s Wort
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

Patient Case

- 76 year old female presents to the pharmacy with a new prescription for clonidine. She states “my doctor put me on another new medication to help control my 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

QUESTIONS?

Contact Information

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- 405-948-4900 extension 494