UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

Resistant Hypertension in Primary Care

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Disclosure

- Relevant Financial Conflicts of Interest
  - CE Presenter, Abbey Smith: none
  - CE Mentor, Karen Gunning: none
- Off Label Uses of Medications
  - Loop diuretics: furosemide, bumetanide, torsemide – hypertension

Learning Objectives – Pharmacists

At the conclusion of this activity, participants should be able to successfully:

1. Recognize resistant hypertension and clinical inertia
2. Outline the diagnostic criteria for resistant hypertension
3. Evaluate specific agents to treat resistant hypertension using current guidelines and evidence-based practices
4. Develop a therapeutic treatment plan for resistant hypertension considering patient-specific factors

Learning Objectives – Technicians

At the conclusion of this activity, participants should be able to successfully:

1. Recognize the correct way to measure blood pressure
2. Identify technical issues that may contribute to falsely elevated blood pressure readings
3. Assess adherence to antihypertensive medications

Patient Case

JS is a 71-year-old male with hypertension, obesity, diabetes, and obstructive sleep apnea who was referred to clinical pharmacy for hypertension management.

- Pertinent labs and vitals
  - Clinic average BP 172/89 mm Hg and HR 65 bpm
  - Weight 114 kg, BMI 36.2 kg/m2
  - SCr 0.96 mg/dL, CrCl (adjusted body weight) 101 mL/min
  - K^+ 3.7 mEq/L and other labs are within normal limits
- Medications
  - Metformin 1 g 2x daily, insulin glargine 30 units daily
  - Valsartan 160 mg daily, hydrochlorothiazide (HCTZ) 25 mg daily, amlodipine 10 mg daily

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Background

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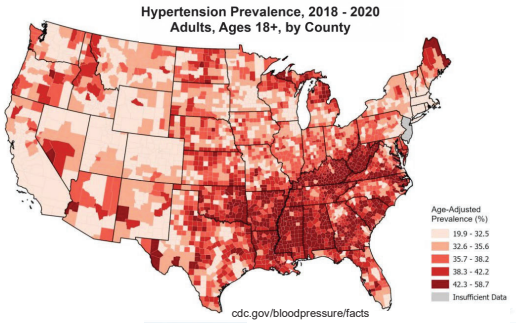
Hypertension

Hypertension (HTN) is the leading risk factor for CVD, stroke, disability, and death

48% of Americans have HTN

76% are uncontrolled



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Resistant Hypertension

18% of patients with HTN have resistant hypertension (RH)

RH increases the risk of target organ damage, morbidity, and mortality

Outcome	Increased risk
Death, MI, HF, CKD, stroke	47%
Heart failure	46%
Development of ESRD	32%
Ischemic heart events	24%
Stroke	14%
Death	6%

Hypertension. 2018 Nov;72(5):e53-e90.

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Resistant Hypertension

Resistant hypertension

Above goal blood pressure (BP) despite concurrent use of 3 antihypertensive agents in different classes at maximally tolerated dose

OR

Controlled HTN achieved with ≥ 4 antihypertensive agents

BP goal <130/80 mm Hg

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Patient Characteristics

Demographics

- Older age
- Male sex
- Non-Hispanic black race (56%)

Social Determinants of Health

- Education
- Healthcare access
- Insurance coverage

CDC.gov; health.gov/healthypeople
Hypertension. 2018 Nov;72(5):e53-e90.
Am J Hypertens. 2021 Aug 9;34(7):707-717.

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Comorbidities

- Obesity
- Diabetes
- Chronic kidney disease
- Obstructive sleep apnea
- Primary aldosteronism

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Diagnosis

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Refining Resistant Hypertension

True Resistant Hypertension (tRH)

Pseudoresistant Hypertension (pRH)

Meet criteria for RH but lack of control may be contributed to other factors

Apparent Treatment Resistant Hypertension (aTRH)

pRH has not been ruled out

Hypertension. 2018 Nov;72(5):e53-e90.

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White-Coat Hypertension

- Elevated BP in the office with controlled/lower BP outside of the office
- Present in 28-39% of patients with aTRH
- Identified by 24-hour ambulatory BP monitoring (ABPM)
- Alternative is self-monitoring blood pressure (SMBP) with a validated monitor

Wikimedia

Hypertension. 2018 Nov;72(5):e53-e90.

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Proper BP Measurement

Patient Preparation	Effect on BP
Sitting	3-10 mm Hg
Uncrossed legs	5-8 mm Hg
Cuff placed on bare arm	5-50 mm Hg
Support arm	10 mm Hg
Empty bladder	10 mm Hg
Remain still and silent	10 mm Hg

Hypertension. 2019 May;73(5):e35-e66.

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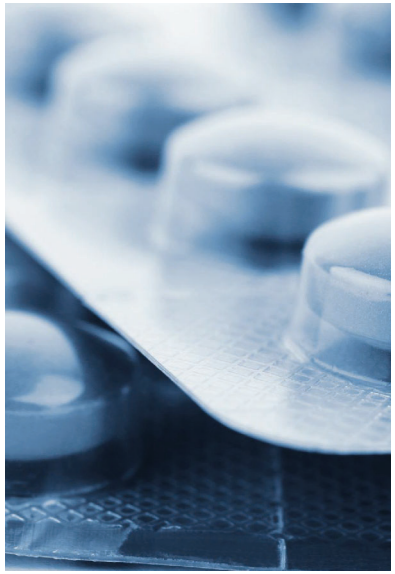

Adherence

Antihypertensive adherence goal >80%

- 50-80% of patients are not adherent
- 12% of patients never fill their prescription
- 30-80% are not persistent within 1 year

Hypertension. 2018 Nov;72(5):e53-e90.
Hypertension. 2022 Jan;79(1):e1-e14.

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Assessing Adherence

- Patient report
- Pharmacy fill history
- Multidomain questionnaire
- Direct observation
- Electronic drug monitoring
- Digital sensors
- Drug levels

Hypertension. 2022 Jan;79(1):e1-e14.

Patient Case

JS endorses missing his medication ~2 times a week. He is currently uninsured and endorses high pill burden.

- Pharmacy fill history
  - Valsartan 160 mg daily – last filled 6 weeks ago #30
  - HCTZ 25 mg daily – last filled 8 weeks ago #30
  - Amlodipine 10 mg daily – last filled 6.5 weeks ago #30
- Social history
  - Immigrated to Utah 2 years ago and requires an interpreter
  - Works as an Uber driver and has an unpredictable schedule

What could be contributing to JS's poor adherence?

Predictors of Nonadherence

Socioeconomic	Providers	Patient	Medication
• Language barrier • Health literacy • Lack of support • Homelessness • Uninsured • Financial barriers • Access	• Patient relationship • Knowledge gaps • Low care continuity • Limited capacity • Long wait times	• Impairments • Beliefs • Fear • Motivation • Comorbid diseases • Lack of perceived benefit	• Complex regimens • Frequent changes • Side effects • Lifestyle interference • Duration of therapy

Hypertension. 2022 Jan;79(1):e1-e14.

Addressing Nonadherence

Hypertension. 2022 Jan;79(1):e1-e14.

Patient Case

JS reports taking several nonprescription medications including:

- Ibuprofen 800 mg 2-3 x daily
- Multivitamin 1 tablet daily
- Loratadine 10 mg daily
- Turmeric 1 capsule daily

He asks you if these are safe to take considering he has hypertension

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Medications that Increase BP

NSAIDs	Steroids	High dose oral estrogen	Stimulants
Cocaine	Cyclosporine and tacrolimus	Antidepressants (MAOI, TCA)	VEGF inhibitors

MAOI= Monoamine oxidase inhibitor; TCA = tricyclic antidepressant
VEGF = Vascular endothelial growth factor

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Management

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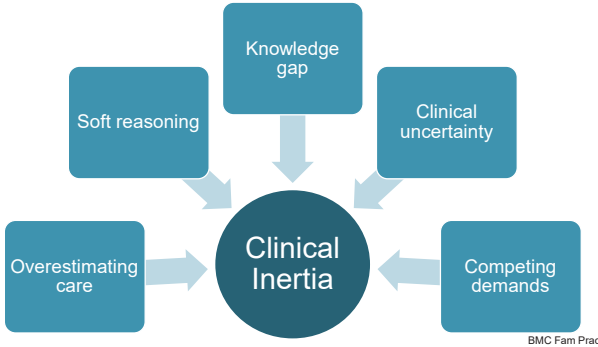
Clinical Inertia

Recognizing a patient's BP is not at goal, but not adjusting or adding medications



BMC Fam Pract. 2014 Jul 2;15:130.

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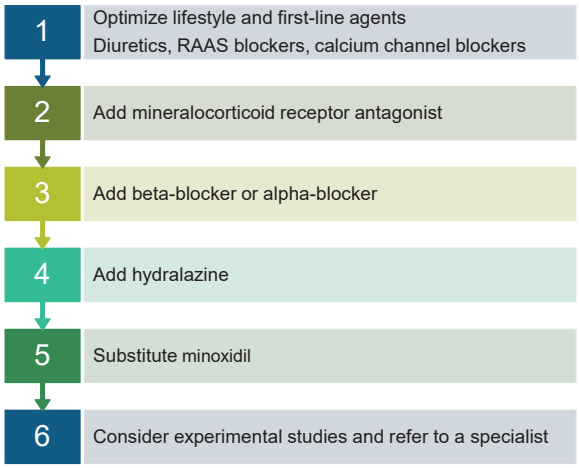
American Heart Association 2018 Guidelines



Hypertension. 2018 Nov;72(5):e53-e90.

Patient Case

JS returns to clinic and reports his adherence has improved. His BP has trended down but remains elevated with an average home BP of 145/84 mm Hg and average clinic BP of 150/87 mm Hg.

He is interested in lifestyle interventions to further reduce his BP. He reports eating fast food daily and does not regularly exercise. His BMI is 36.2 kg/m2.

What lifestyle modifications would you recommend?

Lifestyle Interventions 1

Modification	Recommendation	Approximate SBP
Low sodium diet	<2,400 mg/day or <1500 mg/day	5-6 mm Hg
DASH diet	Rich in fruits, vegetables, whole grains, and low-fat dairy foods	11 mm Hg
Moderate alcohol consumption	<2 drinks/day for men <1 drink/day for women	4 mm Hg
Weight reduction	5-10% of body weight	5 mm Hg
Physical activity	150 minutes/week of aerobic exercise	5-8 mm Hg

Hypertension. 2018 Nov;72(5):e53-e90.
Ann Intern Med. 2018 Mar 6;168(5):351-358.

Diuretics 1

Thiazides

- Greatest evidence for ↓ CVD outcomes
- Substitute HCTZ for chlorthalidone or indapamide for greater BP reductions

Loop diuretics

- Preferred if eGFR < 30 mL/min or for edema
- Not FDA approved for HTN

Side effects

- ↓ K^+, Mg^{2+}, Na^{2+}
- ↑ Ca, uric acid, LDL, TG, BG

Class	Drug	Dose
Thiazide	HCTZ	12.5-50 mg daily
	Indapamide	1.25-5 mg daily
	Chlorthalidone	12.5-25* mg daily
Loop	Furosemide	20-80 mg 2x daily
	Bumetanide	0.5-2 mg 2x daily
	Torsemide	5-10 mg daily

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Ann Intern Med. 2018 Mar 6;168(5):351-358
Hypertension. 2018 Nov;72(5):e53-e90.

RAAS Inhibitors 1

No difference between CVD outcomes between classes

Side effects

- Angioedema
- Cough
- ↑ K, SCr
- Headache
- Teratogenic

Class	Drug	Dose	Considerations
ACE Inhibitors	Lisinopril	10-40 mg daily	More side effects
	Benazepril	10-40 mg daily	
ARBs	Losartan	50-100 mg 1-2 x daily	May decrease risk of cognitive impairment
	Valsartan	80-320 mg daily	
	Telmisartan	20-80 mg daily	
Direct Renin Inhibitors	Aliskiren	150-300 mg daily	High cost

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Hypertension. 2021 Sep;78(3):591-603.
Hypertension. 2018 Nov;72(5):e53-e90.
Ann Intern Med. 2018 Mar 6;168(5):351-358

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Calcium Channel Blockers 1

Dihydropyridines have the most evidence in HTN

Avoid use in heart failure with reduced ejection fraction (HFrEF)

Class	Drug	Side Effects
Dihydropyridine	Amlodipine 2.5-10 mg daily	Pedal edema Flushing Palpitations
	Nifedipine SR 60-120 mg daily	
Nondihydropyridine	Diltiazem ER 120-360 mg daily	Bradycardia
	Verapamil ER 100-300 mg daily	

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Ann Intern Med. 2018 Mar 6;168(5):351-358

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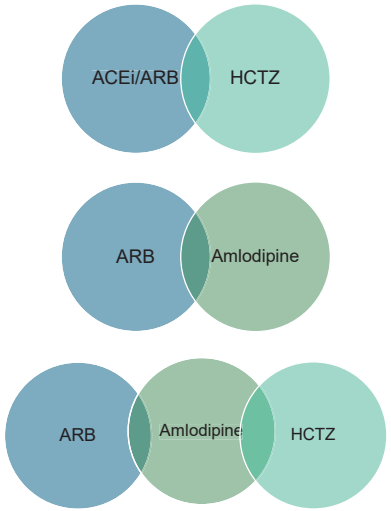
Combination Products



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Mineralocorticoid Receptor Antagonists (MRA) 2

Can decrease BP by an additional 8 mm Hg

Avoid if: eGFR < 30 mL/min or K > 5.0

Side effects: ↑ K^+, ↑SCr, dizziness

Drug	Dose	Considerations
Spironolactone	12.5-100 mg daily	Endocrine side effects
Eplerenone	50-100 mg 2x daily	Short half-life Major CYP3A4 substrate High cost

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Ann Intern Med. 2018 Mar 6;168(5):351-358

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Beta Blockers 3

Consider 1st line
- Heart failure
- Coronary artery disease

Preferred 4th agent
- HR > 80 bpm
- Coarctation of aorta

Avoid
- HR < 70 bpm*
- AV heart block
- Chronic aortic insufficiency
- Carvedilol: severe hepatic impairment

Drug	Dose
Atenolol	25-100 mg 2x daily
Metoprolol tartrate	100-200 mg 2x daily
Metoprolol succinate	50-200 mg daily
Carvedilol*	12.5-50 mg 2x daily

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Ann Intern Med. 2018 Mar 6;168(5):351-358

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Alpha-2 Agonists 3

Consider if beta blockers are contraindicated and HR >80 bpm

Be cautious of rebound hypertension - taper to discontinue

Avoid in heart failure

Side effects:
- Somnolence, fatigue, dizziness, headache
- Dry mouth, constipation
- Bradycardia
- Behavioral changes

Drug	Dose
Clonidine patch	0.1-0.3 mg weekly
Guanfacine	0.5-2 mg daily

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Ann Intern Med. 2018 Mar 6;168(5):351-358

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Direct Vasodilators 4 5

Cause sodium and water retention and reflex tachycardia

Must be used with beta blocker and diuretic

Drug	Dose	Avoid Use	Side Effects
Hydralazine	10-50 mg 3-4 x daily Max 150 mg/day	Rheumatic heart disease Coronary artery disease	Peripheral edema Headache Flushing Nausea, vomiting Drug-induced lupus
Minoxidil	5-40 mg BID Max 100 mg/day	Pheochromocytoma	Hair growth Pericardial effusion

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Hypertension. 2018 Nov;72(5):e53-e90.
Ann Intern Med. 2018 Mar 6;168(5):351-358

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Surgery and Procedures

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- Carotid Baroreceptor Stimulation
- Renal Denervation
- Endovascular Ultrasound Renal Denervation
- Central Iliac Arteriovenous Anastomosis

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In the Pipeline

Aprocitentan 25 mg by mouth daily

- Dual endothelin antagonist
- Phase 3 trials completed; perusing FDA approval
- Difference vs placebo at 4 weeks: SBP -3.8 mm Hg

Baxdrostat 2 mg by mouth daily

- Selective aldosterone synthase inhibitor
- Phase 2 trial completed
- Difference vs placebo at 12 weeks: SBP -11.0 mm Hg

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