Resistant Hypertension: A Pharmacist’s Role

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Disclosure

- I have no relevant information to disclose

Objectives

- Describe the evaluation and diagnosis of resistant hypertension.
- Discuss medication nonadherence in the treatment of hypertension
- Identify treatment options in the management of resistant hypertension
- Discuss the role of the pharmacist in the management of resistant hypertension
Hypertension

• 1 in 3 adults in the US have high blood pressure
• Hypertension contributes to risk of:
  • Stroke
  • Heart attack
  • Heart failure
  • Death
• “Silent Killer”
• Hypertension cost the US almost $77 billion in health care services, medications, and missed days of work

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

Treatment Goals

• Goal BP – <140/90 mm Hg
  • <150/90 in age ≥ 60 years (<140/90 with DM or CKD)
• Implement lifestyle modifications
• In the general population with no CKD initiate therapy
  • Black – Thiazide or CCB
  • Nonblack – Thiazide, CCB or ACEi/ARB
• Follow-up in 2-3 weeks
Hypertension

- 78 million Americans have hypertension
- 82% of patients have been diagnosed as having hypertension
- 75% of patients are using antihypertensive medications
- Only 53% of patients have their blood pressure controlled
- In ALLHAT, ~50% of patients would need 3 or more medications to control their blood pressure

Case #1

A 55 y.o. AAF returns to the MTM clinic for follow-up of hypertension. She has no other significant PMH and no other complaints today. BP today in clinic is 170/108 and pulse is 70. Medications include:

lisinopril 40mg daily, HCTZ 25mg daily, and amlodipine 10mg daily. Last BMP was normal (GFR of 60ml/min, K+ - 4.2 meq/L) BMI – 33. What is the next step that you would recommend:

a) Increase lisinopril to 80mg daily
b) Add clonidine 0.1 mg TID
c) Add losartan 25mg QHS
d) Obtain serum catecholamines
e) None of the above

Resistant Hypertension

- Defined as a blood pressure (BP) that remains elevated (above 140/90 despite:
  - Concomitant use of 3 optimally dosed antihypertensive agents
  - One of these agents must be an appropriate and optimally dosed diuretic

- A patient whose blood pressure is controlled but requires 4 or more meds is also resistant
Patient Characteristics

- Patient characteristics associated with resistant hypertension
  - Older age
  - High baseline BP
  - Obesity
  - Excessive dietary salt
  - Chronic Kidney Disease (CKD)
  - Diabetes
  - Left ventricular hypertrophy (LVH)
  - Black race
  - Female sex
  - Resident of southeastern US

Diagnosis

- Prior to classifying a patient as having resistant hypertension it is important to assess several issues:
  - BP measurement
  - Hypertensive regimen
  - White coat hypertension
  - Drug-related causes
  - Lifestyle factors
  - Secondary Hypertension
  - Medication adherence

Blood Pressure Measurement

- Mistakes in measuring blood pressure may lead to inaccurate BP classification
  - This may lead to inaccurate classification as resistant

  - Two most common mistakes:
    - Failing to let the patient sit quietly for several minutes prior to measurement
    - Wrong size cuff
Blood Pressure Measurement

• Appropriate technique:
  • Have patient sit quietly in a chair with back supported for 5 minutes
  • Ensure correct cuff size
    • Bladder encircling at least 80% of the arm
  • Support arm at heart level during measurement
  • Take a minimum of 2 readings
    • 1 minute apart
    • Use the average

White Coat Hypertension

• Clinic BP is persistently elevated while BP out-of-clinic is normal or lower
• Prevalence – 20-30% of hypertensive patients
• These patients have:
  • Significantly less cardiovascular risk
  • Less severe target organ damage

A Lesson From Europe

• Out-of-office blood pressure monitoring
• Ambulatory Blood Pressure Monitoring (ABPM)
• Home (Non-office BP)
• Consider ambulatory BP monitoring in suspected patients
Hypertensive Regimen

- Suboptimal therapy represents a common cause for uncontrolled blood pressure
- Review the patient's medication regimen
  - Optimize the dose of prescribed medications
    - Adjust for renal function and weight
  - Consider time intervals/frequency of dosing
- Consider having patient take at least 1 medication at night
  - Also consider twice daily dosing

Drug-Related Causes

- Several classes of medications can increase blood pressure
- Common medications that can affect BP
  - NSAIDs
  - Steroids
  - Decongestants
  - Weight-loss drugs (diet pills)
  - Stimulants
  - Oral contraceptives
  - Illicit drugs

Lifestyle Factors

- Obesity
  - Commonly associated with resistant hypertension
- Excessive dietary salt intake
  - Directly increases BP
  - Blunts effect of most antihypertensive agents
- Alcohol
  - Associated with increased risk of hypertension and resistant hypertension
Secondary Hypertension

- Common in patients with resistant hypertension and should be identified if present
- Causes of secondary hypertension
  - Primary hyperaldosteronism
  - Chronic kidney disease
  - Obstructive sleep apnea
  - Renal artery stenosis
  - Pheochromocytoma
  - Cushing’s disease
  - Thyroid disease

Still Not at Goal?

- What about patients who are negative for these issues yet BP is still uncontrolled?
- Many efficacious medical treatments exist in our current healthcare system for hypertension
- A gap exists between current treatment success rates in practice and those believed to be achievable in the literature
- What contributes to this gap?
The Medication Adherence Problem

“Drugs don’t work in patients who don’t take them.”
-C. Everett Koop, M.D

The Problem - Medication Nonadherence

- Poor medication adherence is common
- 20-30% of prescriptions are never filled
- 50% of medications for chronic disease are not taken as prescribed
- At one year, only ~50% of patients persist in taking their antihypertensive medications

Question 1

- At one year after initial prescription, how many patients continue to adhere(persist) taking chronic hypertensive medications?
  A. 10%
  B. 25%
  C. 40%
  D. 50%
  E. 75%
The Problem - Medication Nonadherence

• Lack of adherence to prescribed medications has negative effects on health outcomes
• Nonadherence is estimated to contribute to:
  • At least 10% of all hospitalizations
  • 33-69% of all medication-related hospital admissions
  • Substantial increase in morbidity and mortality
  • Approximately 125,000 deaths per year in the US
• The estimated cost of nonadherence in the US - $100 and $289 Billion annually

The Problem – Definitions

• Compliance – the extent to which the patient’s behavior coincides with the clinical prescription
• Adherence – the extent to which a person’s behavior corresponds with agreed recommendations from a health care provider
  • Complex relationship between patient, provider, and healthcare system
• Persistence – length of time patient is adherent

http://www.who.int/chp/knowledge/publications/adherence_Section1.pdf
Adherence Further Defined

- Nonfulfillment (primary nonadherence) - prescription is written but never filled
- Nonpersistence - patients stop taking a medication after starting it
  - Can happen at any point in time
- Nonconforming – medications are not taken as prescribed
  - Ex: Skipping doses, incorrect timing, incorrect doses, etc

Adherence – Key Points

- In order for a medication to work it must be appropriately prescribed, filled, initiated, continued, and taken appropriately as intended
- Failure at any one step above can negatively affect a patient’s health
- What is considered significant nonadherence to one medication may not be significant for another
- A variety of factors influence medication adherence

Adherence Further Defined

- Unintentional nonadherence
  - Ex: forgetting to take medications

- Intentional nonadherence
  - Based on patients’ beliefs regarding their medications or disease
**Question 2**

- **True or False:** The majority of patients who are nonadherent experience unintentional nonadherence (ex: forgetfulness).

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**Adherence Further Defined**

- Over 2/3 of non-adherence has been found to be intentional
  - Based on patients’ beliefs regarding their medications or disease
- Most interventions target unintentional non-adherence
  - Can include:
    - Refill reminders
    - Pill box

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**Factors That Affect Adherence**

- Adherence involves a complex interaction of variables between: patient, health care team and system, social/economic, and family support
- Many barriers to medication adherence have been identified
  - There are many ways to organize these barriers
  - Some are controlled by the patient while others are influenced by the healthcare system or provider/team
  - **Disease state factors, pharmacotherapy factors, and patient/lifestyle factors**
Interventions to Improve Adherence

• All potential barriers should be considered
• Multiple interventions have been shown to increase medication adherence
• These interventions often have varying effects on clinical outcomes
• Most literature involves multifaceted interventions and it is difficult to determine which individual components are most effective
• Decreasing cost as well as decreasing dosing frequency have proven to be effective

Interventions to Improve Adherence

• Outpatient interventions by physicians, nurses and pharmacists have been shown to be effective
• Many interventions are too time-intensive or burdensome for routine clinic visits and may be difficult to sustain
• A coordinated or collaborative effort may provide the best opportunity to improve adherence and clinical outcomes

Medication Adherence Summary

• Major cause of uncontrolled BP
  • 40% of patients will discontinue their medications during the first year of treatment
  • Next 5-10 years – less than 40% persist with prescribed therapy
  • For an antihypertensive regimen to fail the patient must adhere to it and take it correctly
  • Consider non-adherence in patients not reaching goals
  • Consider a collaborative effort to improve BP
Hypertension Treatment

- Lifestyle Modifications
  - Can expect a modest but clinically important reduction in blood pressure
  - Reduce sodium intake
    - DASH diet
  - Lose weight
  - Moderate exercise
  - Reduce alcohol intake
- Patients should be routinely reminded and encouraged to make these changes

Treatment Options

- Little data exists to guide the choice of medications when BP remains uncontrolled
- Treat with combination therapy
- Combination therapy with agents from different classes improves efficacy and improves tolerability
- How to choose combination therapy
  - Inhibit different pathogenic mechanisms
  - Combine drugs to compensate for changes induced by other medications

Proven Combinations

- ACE inhibitor (ACEi)/ARB/DRI + Thiazide Diuretic
  - Reduce hypokalemia seen with diuretics
- ACEi/ARB + Calcium Channel Blocker (CCB)
  - Reduce tachycardia and edema seen with CCB
- ARB + CCB
  - Results better than monotherapy with either
- ACEi/ARB + CCB + Diuretic
Treatment - Diuretics

• Mainstay of treatment
  ◦ Volume overload is common amongst these patients
• HCTZ – Most common diuretic
  ◦ Consider increased dosages (50mg) or increased frequency (BID)
  ◦ Consider switch to Chlorthalidone
• Agent should be optimized based on renal function
  ◦ Avoid thiazides with low GFR – switch to a loop
  ◦ Consider dose and frequency of loop diuretics

Chlorthalidone

• Thiazide diuretic
• More potent than HCTZ
  ◦ 25mg = 37.5mg – 50mg of HCTZ
• Longer duration of action
  ◦ Benefit in non-adherent patients?
  ◦ Benefit in resistant patients?
• Dosage forms
  ◦ Available in 25mg, 50mg, and 100mg tabs
  ◦ May require patient to take ½ tab (12.5mg)
  ◦ Monitor K+

Additional Therapy

• Beta-blocker
  ◦ Preferably an agent with dual effects
    ◦ Additional alpha blockade
      ◦ Carvedilol, labetalol
      ◦ Nebivolol
    ◦ Consider comorbid conditions (CAD, CHF)
    ◦ ADRs/efficacy may limit use
• CCB + CCB
  ◦ Example: Verapamil + amlodipine
Additional Therapy

- Last line of therapy
  - Clonodine
    - Consider weekly patch
  - Vasodilators
    - Hydralazine, minoxidil
  - These agents are effective but use is limited by:
    - ADRs
    - Frequent dosing
    - Lack of outcome data
- Dual RAAS agents
  - Spironolactone

Renin-Angiotensin Aldosterone System

- The renin-angiotensin aldosterone system regulates BP and fluid homeostasis
- Angiotensin II is responsible for vasoconstriction both directly and indirectly
- Angiotensin II also regulates BP by:
  - Affecting sodium and water reabsorption
  - Stimulating the release of aldosterone
- Aldosterone regulates sodium and potassium balance as well as extracellular volume

Renin-Angiotensin Aldosterone System Diagram:

- Angiotensinogen
- Renin
- Angiotensin I
- ACE
- Angiotensin II
- Vasoconstrictor
- Aldosterone
- Arginine Vasopressin (ADH)
- Na & Water Retention
- Vasodilator
- Water Retention

Renin-Angiotensin Aldosterone System

- ACE inhibitors, ARBs, and aldosterone antagonists are effective in the blockade of the RAAS and result in decreased blood pressure
- Is monotherapy effective?
- “Escape phenomenon”
  - Secondary increase in Renin
  - Increase in aldosterone levels

RAAS – Dual Blockade

- Novel approach
- Simultaneously taking 2 agents
  - ACE inhibitor + ARB
  - ACE inhibitor/ARB + Renin inhibitor
  - ACE inhibitor/ARB + Aldosterone antagonist

RAAS – Dual Blockade

- ACE inhibitor + ARB
  - Little additional effects on BP
  - Increase in ADRs

  - Renin Inhibitor + ACE inhibitor/ARB
    - Combination now contraindicated in patients with diabetes and/or kidney disease

  - ACE inhibitor/ARB + spironolactone
Aldosterone Antagonists

• Spironolactone, Eplerenone

• Mechanism of action
  • Aldosterone receptor blockers
    • Increases diuresis and removal of sodium while retaining potassium
    • Hypothesized to decrease sympathetic tone and produce changes and/or reductions in vascular tone and stiffness

Spironolactone

• Effective add-on for resistant hypertension due to its effectiveness as an aldosterone receptor blocker
  • There is a correlation between increased aldosterone (primary hyperaldosteronism) and increased BP levels in patients with resistant hypertension
  • Shown to be effective in both patients with and those without increased aldosterone/renin ratios

• Doses of 12.5mg – 50 mg daily are effective
  • Added to existing multidrug regimens
Spironolactone

- Adding spironolactone to an ACEi/ARB
  - May provide an additional 25 and 12 mm Hg reduction in SBP and DBP respectively
  - When compared with ACEi+ARB dual therapy, spironolactone + ACEi/ARB results in a greater reduction in BP
    - 32mm Hg/ 11 mmHG reduction
  - Additional studies have evaluated spironolactone as an add-on to an optimal regimen

Evidence Supporting Spironolactone - Results

- Adding spironolactone to baseline refractory hypertension treatment improves BP control
  - Increase in number of patients controlled
  - Decrease in number of medications per patient
  - Similar results regardless of baseline aldosterone
    - Primary hyperaldosteronism = higher dose
  - No differences in BP reduction based on race
  - No significant differences between 3 dosages (25, 50, 100mg)

Other Aldosterone Antagonists

- Amiloride
  - Also effective in reducing BP
  - Has not shown to be as effective as spironolactone in reducing BP in resistant patients
- Eplerenone
  - Has not been studied specifically in patients with resistant hypertension
  - May be considered if spironolactone cannot be tolerated
Summary

• The goal of evaluating and treating resistant hypertension is:
  • Correct contributing factors
  • Identify and treat nonadherence
  • Optimize pharmacologic therapy

• Spironolactone is a preferred add-on therapy for patients with resistant hypertension
  • May also be effective in patients with underlying CKD and OSA
  • Use with caution in patients on ACEi/ARBs and/or with CKD

The Pharmacist’s Role

• Pharmacists can help identify patients with resistant hypertension
• Pharmacists can refer patients to their physician for workup of secondary causes
• Pharmacists can provide counseling on lifestyle factors and home measurement of BP
• Pharmacists can collaboratively assist with improving adherence to medications
• Pharmacists can collaboratively assist with optimization of the medication regimen

Case #1 - Review

• A 55 y.o. AAF returns to the MTM clinic for follow-up of hypertension. She has no other significant PMH and no other complaints today. BP today in clinic is 170/108 and pulse is 70. Medications include: lisinopril 40mg daily, HCTZ 25mg daily, and amlodipine 10mg daily. Last BMP was normal (GFR of 60ml/min, K+ - 4.2 meq/L) BMI - 33. Which of the following would you recommend:
  a) Measure and counsel on medication adherence
  b) Counsel the patient on diet and lifestyle modifications
  c) Measure the blood pressure again
  d) Add spironolactone 25 mg daily
  e) All of the above
Management of Resistant Hypertension

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