

## Hypertension and Antihypertensive Agents

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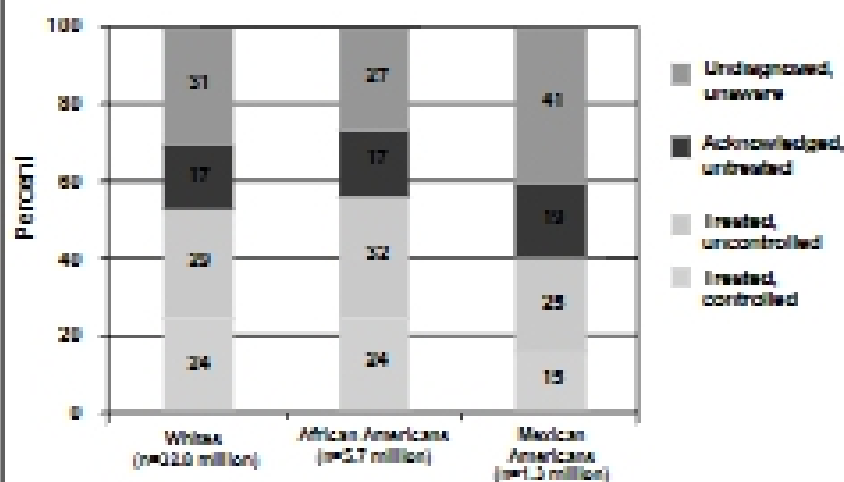


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## Blood Pressure Classification – JNC VII

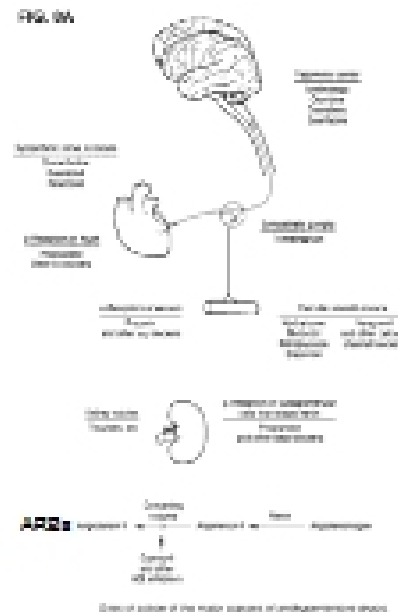
BP Classification	SBP mmHg		DBP mmHg
Normal	<120	and	<80
Pre-hypertension	120–139	or	80–89
Stage 1 Hypertension	140–159	or	90–99
Stage 2 Hypertension	≥160	or	≥100

## Hypertension Is Largely Uncontrolled



Awareness, Treatment, Control of Hypertension in Whites, African Americans, and Hispanics (Mexican Americans) Fleck et al. *J Clin Hypertens*. 2005;2(suppl 1):S-11.

FIG. 9A



### Sites of Action of Antihypertensive Agents

#### Main classes ('frontline agents')

Beta-blockers  
 Diuretics  
 Calcium blockers  
 ACE inhibitors / ARBs

## Antihypertensive Agents (JNC VII, 2003)

- |                                     |                                |
|-------------------------------------|--------------------------------|
| 1. Diuretics                        | eg. hydrochlorothiazide        |
| 2. Renin / Angiotensin (ACEI, ARBs) | eg. lisinopril, losartan       |
| 3. Beta-antagonists                 | eg. propranolol                |
| 4. Calcium-antagonists              | eg. nifedipine, verapamil      |
| 6. Alpha-antagonists                | eg. prazosin                   |
| 8. Potassium sparing                | eg. spironolactone             |
| 7. Vasodilators                     | eg. hydralazine, nitroprusside |
| 8. Central acting alpha2-agonists:  | eg. clonidine, α-methyl dopa   |
| 8. Inhibit/reduce NE release        | eg. guanethidine, reserpine    |
| 10. Ganglionic blockers             | eg. mecamylamine               |

## Antihypertensive Usage (ACC, 2001)

For untreated patients patients with BP of 140-159/90-99 mmHg and no other risk factors, indicate which class(es) of medications you would use:

	% Selecting each class	
	Cardiologist	GP/FP
ACE inhibitor / ARB	71.6	57.5
Beta-blocker	57.9	50.2
Ca-blocker	51.5	35.6
Diuretics	48.8	54.5
Alpha-blocker	16.4	17.2
Other class	4.4	5.1
None (life-style)	8.4	15.3

## Diuretics

Frontline class (1<sup>st</sup> among equals)

- ↓ BP by body depletion of Na<sup>+</sup> and reducing blood volume (BV)
- High clinical value as antihypertensive
- Effective in older patients (less β-blockers, ACEI)
- Less effective in lean individuals
- Used also in treatment of Congestive Heart Failure
- Often used in combination with β-blockers or vasodilators
- Effective when GFR > 30 ml/min (normal: 125 ml/min)

## Diuretics - Mechanism of action

Initial:

↓ body Na<sup>+</sup> → ↓ BV → ↓ CO → ↓ BP (↑TPR, reflex)

Chronic:

CO unchanged, ↓ TPR, ↓ NE → ↓ [Ca<sup>2+</sup>]<sub>i</sub> → ↓ vascular tone

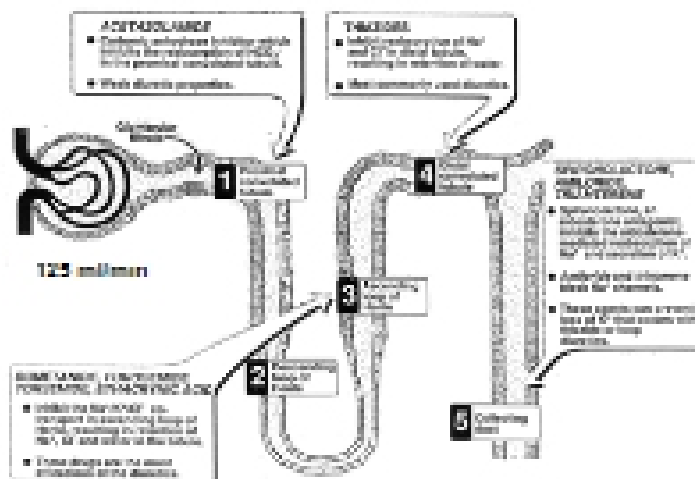
Direct vasodilation effect:

probably by opening K<sup>+</sup> channels

**Thiazides:** - eg. hydrochlorothiazide  
- act on early distal tubule  
- inhibit Na<sup>+</sup> reabsorption

**Loop Diuretics:** - eg. furosemide  
- act on loop of Henle  
- most potent

## Nephron



## Diuretics - Adverse effects (Thiazide & Loop)

- potassium depletion → hypokalemia: hazardous in persons taking digitalis → arrhythmia
- magnesium depletion → arrhythmia
- photosensitivity
- impair glucose tolerance → diabetes
- increase serum lipids (usually returns to normal)
- increase serum uric acid concentration → gout

## Potassium Sparing Diuretic Agents

- eg. Spironolactone
- aldosterone antagonist
- act on late distal tubule (collecting duct) to inhibit Na<sup>+</sup> reabsorption and K<sup>+</sup> secretion
- weak action
- hyperkalemia
- commonly used in combination therapy with other antihypertensive agents

## Centrally acting sympatholytic agents

Useful class

- Act on central α<sub>2</sub>-receptors → ↓ sympathetic outflow
- Good clinical value as antihypertensives.

Clonidine, Guanfacine

α-Methyldopa (converted to α-methyl-NE)

- do not interfere with exercise tolerance
- no metabolic effects

Adverse effects:

- sedation, mental depression, lactation, dry mouth
- withdrawal effect: rebound HT (can be very serious)

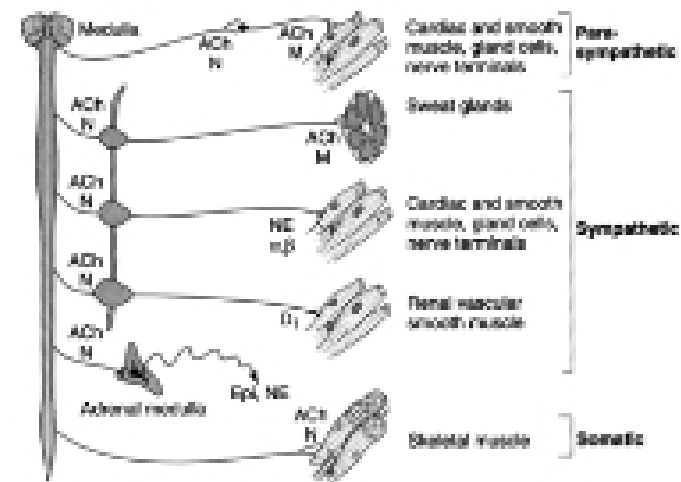
### Ganglion-Blocking Agents

- block ganglionic nicotinic receptors (SNS, PNS)
- first effective antihypertensive class
- currently not used for chronic HT

#### Adverse effects (significant):

- Sympathoplegia:
  - excessive orthostatic hypotension, sexual dysfunction
- Parasympathoplegia:
  - constipation, ↓urine, blurred vision, dry mouth
- Trimethaphan
  - Iv. injection, rapid, short half life (precise titration)
  - hypertensive crisis (CNS-mediated), controlled hypotension during surgery
- Mecamylamine: effective orally

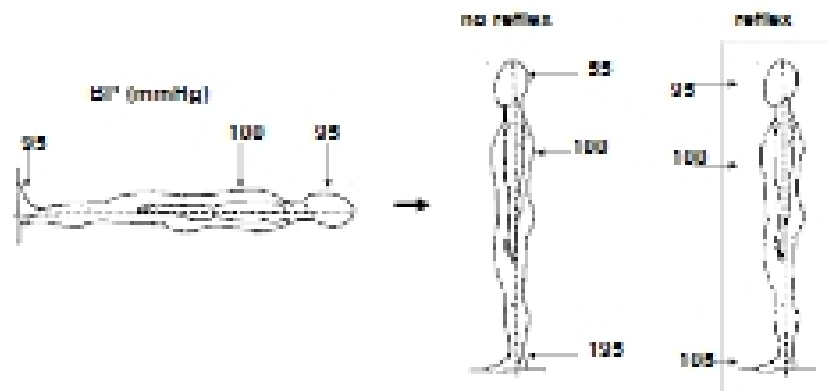
### Neurons of the ANS



### Postural (Orthostatic) Hypotension

- Venous return falls
- Blood pressure falls

- Sympathetic activity increases
    - ↳ Constriction of great veins
    - ↳ Constriction of arteries (↑ BP)
    - ↳ Increase in heart rate
- reflex mediated



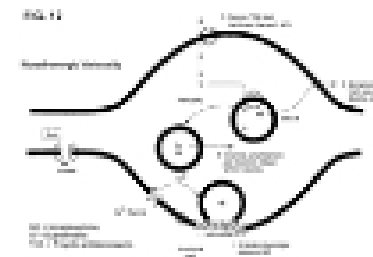
### Adrenergic Neuron-Blocking Agents

Clinical value as antihypertensive is low

Guaneethidine (last resort), bretylium

- inhibits release of NE from nerve terminals
- gradual depletion of NE stores
- neuronal uptake (uptake 1) is essential for action
- tricyclic antidepressants, cocaine decrease effectiveness

- Adverse effects:
- marked postural hypotension
  - diarrhea, impaired ejaculation



### Reserpine

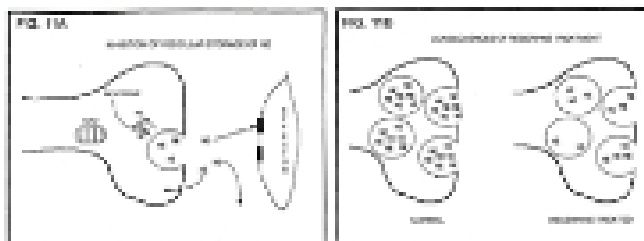
Clinical value as antihypertensive is low

Reserpine (last resort)

- inhibit uptake of NE into storage vesicle (also DA, 5-HT)
- leads to depletion of transmitter stores (peripheral & CNS action)

#### Adverse effects:

- sedation, mental depression, Parkinsonism syndrome
- increases gastric acid secretion - ulcer



### Alpha-Adrenoceptor Antagonists

Use low, but constant

Phenoxybenzamine (irreversible α1-receptor blocker)

- reflex tachycardia effect
- therapeutic value in pheochromocytoma, HT crisis

Prazosin (selective α1-receptor blocker)

- selective alpha1-receptor blocker in arterioles and venules (dilates both resistance and capacitance vessels)
- does not produce reflex tachycardia
- also used for benign prostatic hypertrophy

Phentolamine (non-selective α-receptor blocker)

- reflex tachycardia effect
- diagnostic and therapeutic value in pheochromocytoma

- Adverse effects:
- postural hypotension
  - salt and fluid retention
  - beneficial effect on plasma lipids