Antihypertensive Agents
Part-1

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Hypertension

Hypertension is defined as either a sustained systolic blood pressure of greater than 140 mmHg or a sustained diastolic blood pressure of greater than 90mmHg ,hypertension results from increased peripheral vascular arteriolar smooth muscle tone, which leads to increased arteriolar resistance and increased capacitance of venous system.

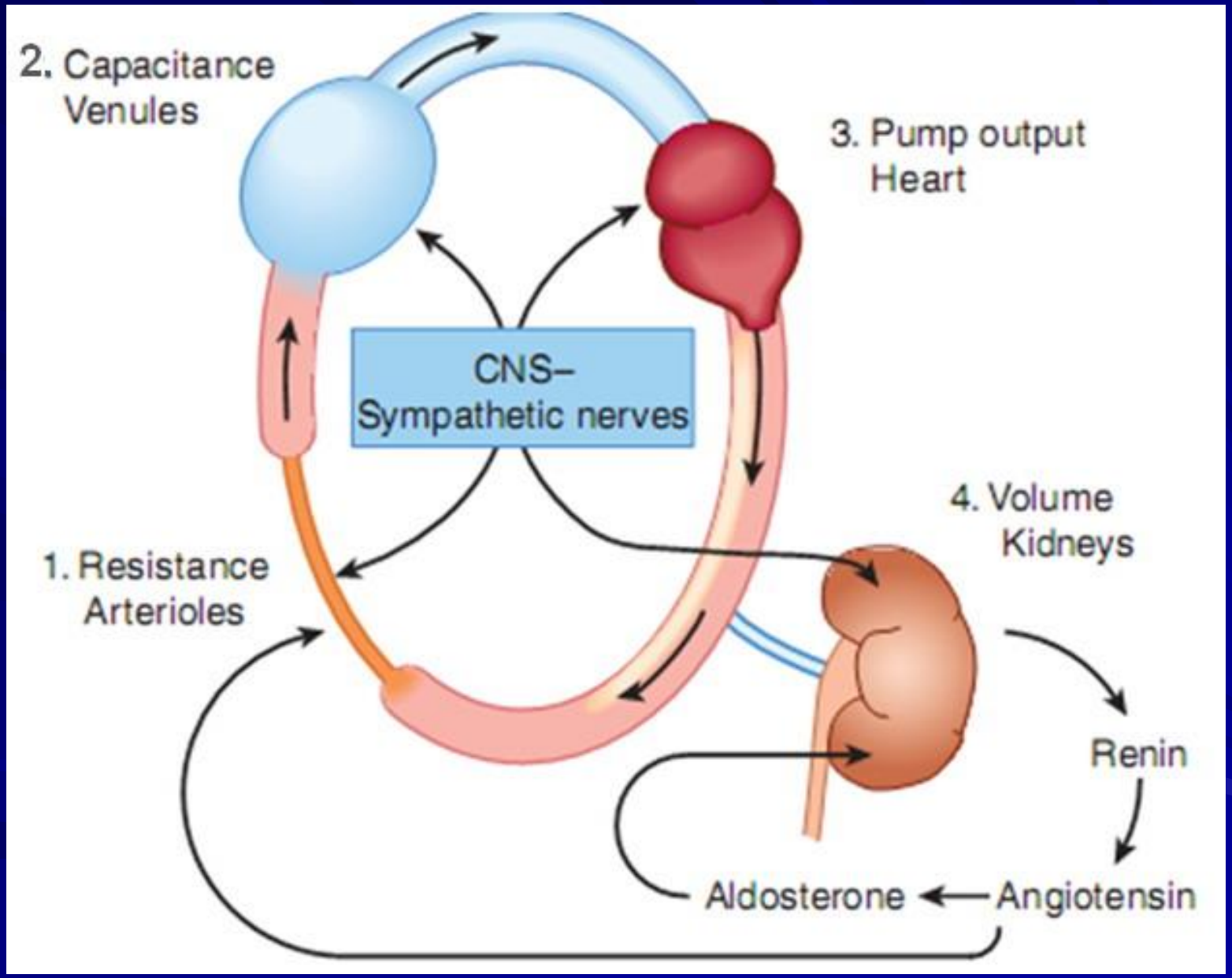
Hypertension damages blood vessels in kidney, heart, brain and increased incidence of renal failure, coronary disease, heart failure, stroke

Effective pharmacologic lowering of blood pressure prevent damage to blood vessels and reduce morbidity and mortality rates

Normal Regulation of Blood Pressure

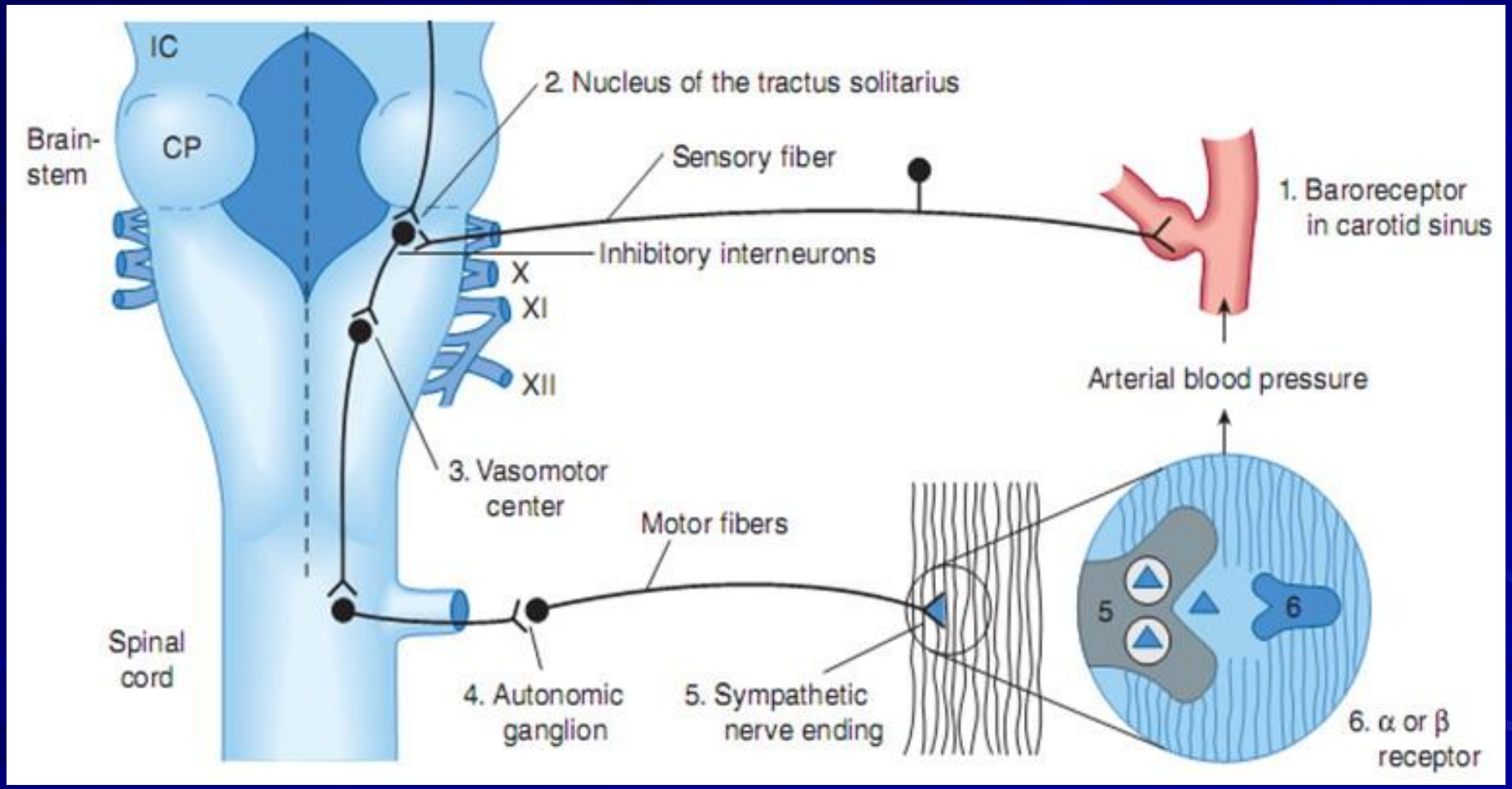
Arterial blood pressure (BP) is directly proportionate to the product of the blood flow (cardiac output, CO) and the resistance to passage of blood through precapillary arterioles (peripheral vascular resistance, PVR):

$BP = CO \times PVR$


2. Capacitance
Venules
3. Pump output
Heart
CNS–
Sympathetic nerves
4. Volume
Kidneys
1. Resistance
Arterioles
Renin
Aldosterone
Angiotensin

Postural Baroreflex

Baroreflexes are responsible for rapid, moment-to-moment adjustments in blood pressure, such as in transition from a reclining to an upright posture.


IC
CP
Brain-
stem
2. Nucleus of the tractus solitarius
Sensory fiber
1. Baroreceptor
in carotid sinus
Inhibitory interneurons
X
XI
XII
Arterial blood pressure
3. Vasomotor
center
Motor fibers
Spinal
cord
4. Autonomic
ganglion
5. Sympathetic
nerve ending
5
6
6. α or β
receptor

Renal Response to Decreased Blood Pressure

By controlling blood volume, the kidney is primarily responsible for long-term blood pressure control.

Etiology of Hypertension

- Essential primary hypertension: no specific cause of hypertension
- Secondary hypertension: Patients with a specific etiology.

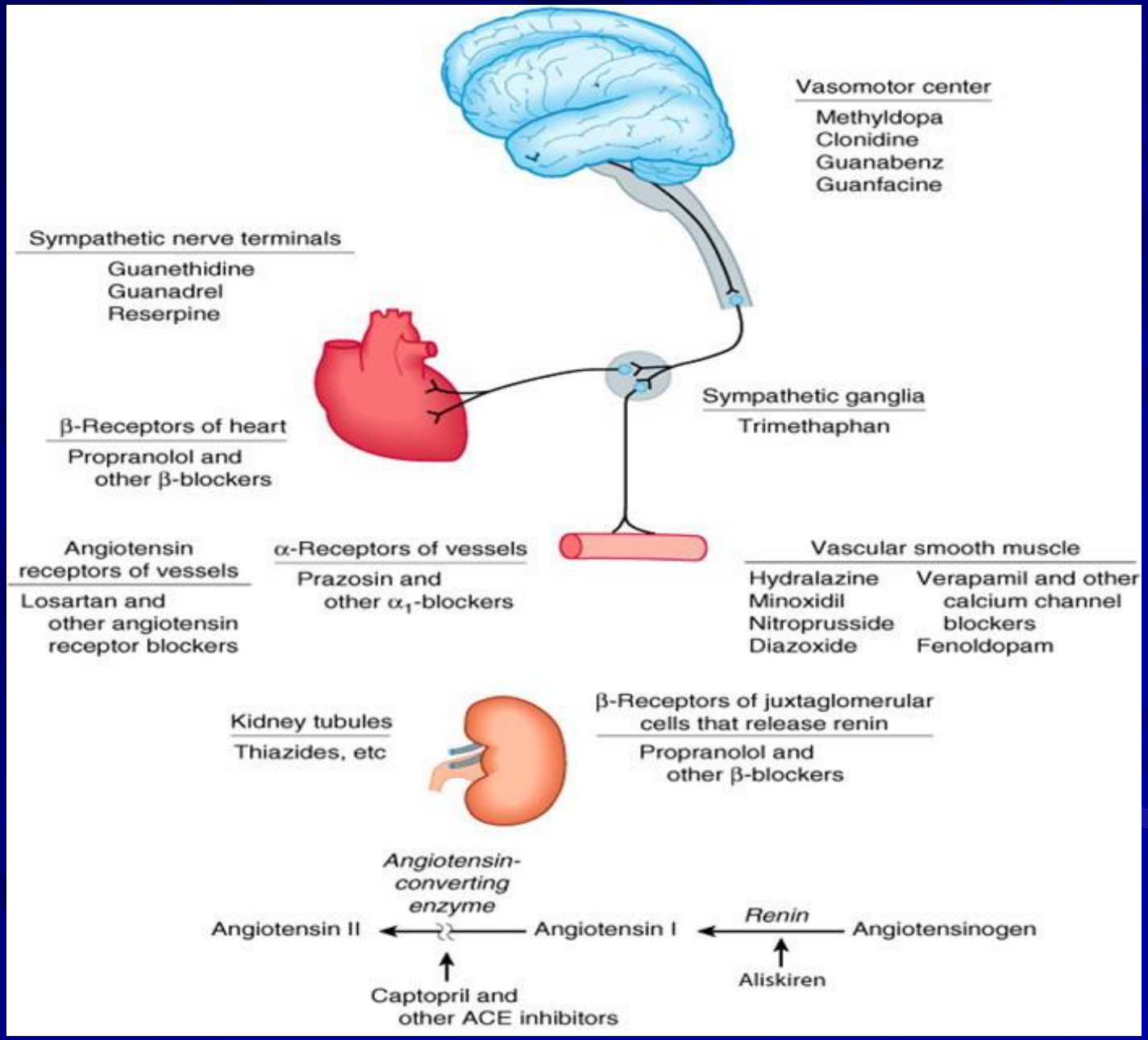
Definition of Hypertension

Category	systolic blood pressure (mmHg)	diastolic blood pressure (mmHg)
Blood pressure		
Optimal	<120	< 80
Normal	<130	<85
High normal	130-139	85-89
Hypertension		
Grade1(mild)	140-159	90-99
Grade2(moderatre)	160-179	100-109
Grade3(severe)	≥180	≥110
Isolated systolic hypertension		
Grade1	140-159	<90
Grade2	≥160	<90

Antihypertensive Agent

Antihypertensive drugs divided according to their primary site or mechanism of action.

- Diuretics
- Sympatholytic drugs (Sympathoplegic agents)
- Agents that block production or action of angiotensin
- Vasodilators


Vasomotor center
Methyldopa
Clonidine
Guanabenz
Guanfacine
Sympathetic nerve terminals
Guanethidine
Guanadrel
Reserpine
Sympathetic ganglia
Trimethaphan
β-Receptors of heart
Propranolol and other β-blockers
Angiotensin receptors of vessels
Losartan and other angiotensin receptor blockers
α-Receptors of vessels
Prazosin and other α1-blockers
Vascular smooth muscle
Hydralazine
Minoxidil
Nitroprusside
Diazoxide
Verapamil and other calcium channel blockers
Fenoldopam
Kidney tubules
Thiazides, etc
β-Receptors of juxtaglomerular cells that release renin
Propranolol and other β-blockers
Angiotensin-converting enzyme
Angiotensin II
Angiotensin I
Renin
Angiotensinogen
Captopril and other ACE inhibitors
Aliskiren

Diuretics

- Which lower blood pressure by depleting the body of sodium and reducing blood volume and perhaps by other mechanisms.
- In mild or moderate essential hypertension Diuretics alone are used.
- In more sever hypertension, diuretics are used in combination with sympathoplegic and vasodilator drugs

Diuretics

- Thiazides and related agents (hydrochlorthiazide).
- Loop diuretics (furosemide)
- Potassium sparing diuretics (amiloride, triamterine)

Sympatholytic Drugs (Sympathoplegic Agents)
which lower BP by reducing peripheral vascular resistance, inhibiting cardiac function and increasing venous pooling in capacitance vessels, these agents are subdivided into:

- Centrally acting agents (methyldopa, clonidine)
- Adrenergic neuron blocking agents (guanadrel, reserpine).
- Ganglion-blocking agents
- Adrenocepter antagonists which divided into:
  1. ß-adrenergic antagonists (metoprolol, atenolol, etc.).
  2. α-adrenergic antagonists (prazosin, terazosin, doxazosin, phenoxybenzamine and phentolamine).
  3. Mixed adrenergic antagonists (labetolol, carvedilol).
  4. Partial agonists with intrinsic sympathomimetic activity (Acebutolol, pindolol).

Sympathoplegic antihypertensive drugs are most effective when used concomitantly with a diuretic because it lead to retention of sodium by the kidney and expansion of blood volume

Centrally Acting Sympathoplegic Drugs

Centrally acting sympathoplegic drugs were once widely used in the treatment of hypertension, these drugs are rarely used today. Methyldopa used for hypertension during pregnancy.

Mechanisms of Action of Centrally Acting Sympathoplegic Drugs

These agents reduce sympathetic outflow from vasomotor centers in the brainstem but allow these centers to retain or even increase their sensitivity to baroreceptor control

Methyldopa

- Is an analog of L-dopa and is converted to α-methyldopamine and α-methylnorepinephrine false transmitter, α-methylnorepinephrine bind to alpha 2 recepter s at the nerve ending (on presympathetic adrenergic neurons)they stimulate the recepters and reduce norepinephrine release onto receptor sites

Methyldopa

- It is now used for hypertension during pregnancy.
- It lowers blood pressure chiefly by reducing peripheral vascular resistance, with a variable reduction in heart rate and cardiac output.

Adverse Effect of Methyldopa

- Sedation
- Impaired mental concentration.
- Nightmares, mental depression, vertigo
- Lactation, associated with increased prolactin secretion, can occur both in men and in women treated with methyldopa.
- Development of a positive Coombs test hemolytic anemia, hepatitis and drug fever.

Pharmacokinetics of Methyldopa

- The usual oral dose of methyldopa produces its maximal antihypertensive effect in 4-6 hours and the effect can persist for up to 24 hours

Clonidine

- It reduce cardiac output due to decreased heart rate as well as a reduction in peripheral vascular resistance.
- It decrease renal vascular resistance and maintain renal blood flow.

Pharmacokinetics of Clonidine

- It is lipid-soluble and rapidly enters the brain from the circulation.
- Oral clonidine must be given twice a day.
- A transdermal preparation of clonidine that reduces blood pressure for 7 days after a single application is also available.

Adverse Effect of Clonidine

- Dry mouth
- Sedation
- Mental depression
- Concomitant treatment with tricyclic antidepressants may block the antihypertensive effect of Clonidine
- Sever hypertensive crisis when clonidine is suddenly withdrawn

Adrenergic Neuron-Blocking Agents (Guanethidine , Reserpine)

These drugs lower blood pressure by preventing normal physiologic release of norepinephrine from postganglionic sympathetic neurons.

Guanethidine

Mechanism of Action of Guanethidine

It inhibits the release of norepinephrine from sympathetic nerve endings. Once guanethidine has entered the nerve, it is concentrated in transmitter vesicles, where it replaces norepinephrine. Because it replaces norepinephrine, the drug causes a gradual depletion of norepinephrine stores in the nerve ending.

Pharmacokinetics of Guanethidine

- Too polar to enter the central nervous system
- Because of guanethidine's long half-life (5 days), the onset of sympathoplegia is gradual (maximal effect in 1–2 weeks) and sympathoplegia persists for a comparable period after cessation of therapy.

Side Effects Guanethidine

- Postural hypotension
- Delayed or retrograde ejaculation (into the bladder)
- Diarrhea
- Hypertensive crisis by releasing catecholaminesin pateints with pheochromocytoma (paradoxical effect)

Drug Interaction of Guanethidine

- Sympathomimetic agents, at doses available in over-the counter cold preparations can produce hypertension in pateints taking Guanethidine
- Drugs that block the catecholamine uptake or displace amines from the nerve terminal attenuate of antihypertensive effect like tricyclic antidepressants, cocaine.

Adrenoceptor Antagonists

β- Adrenoceptor- Blocking Agents

- First-line drug therapy for hypertension when indicated-for example, with heart failure.
- The Beta-blockers reduce BP primarily by Decreasing cardiac output
- They may also decrease sympathetic outflow from CNS
- Inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and secretion of aldosterone.

Non Selective β-blocker

Propranolol

- Which acts at both β_1 and β_2 receptors. Propranolol is contraindicated in patient with asthma, due to its blockade of β_2-mediated bronchodilation.

Cardioselective β-blocker

metoprolol and atenolol (Selective blockers of β_1 receptors)

- The most commonly prescribed β-blockers.

Partial Agonists With Intrinsic Sympatomimetic Activity

Acebutolol, Pindolol

- They lower blood pressure less than other blockers(because of greater agonist than antagonist effect of β2 receptors

Therapeutic Uses of β-blockers

- Conditions that discourage the use of β-blockers (for example, severe chronic obstructive lung disease, chronic congestive heart failure, or severe symptomatic occlusive peripheral vascular disease) are more commonly found in the elderly and in diabetics.
- Hypertensive patients with concomitant diseases such as previous myocardial infarction, angina pectoris, chronic heart failure.

Pharmacokinetics

Orally active, take several weeks to develop their full effects.

Adverse Effects

Bradycardia, fatigue, lethargy, insomnia, hallucinations, hypotension, impotence sexual dysfunction, decrease HDL and increase plasma triacylglycerol, abrupt withdrawal may cause rebound hypertension

Antagonists of Both α and β adrenoceptor

Carvedilol

- It is useful in patients with both heart failure and hypertension

Labetalol

- Is given as an intravenous bolus or infusion in hypertensive emergencies

Alpha (α)-Adrenoceptor-blocking Agents

Prazosin, Doxazosin and Terazosin

- Decrease the peripheral vascular resistance and lower the arterial blood pressure by causing relaxation of both arterial and venous smooth muscle.
- These drugs cause only minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.
- Postural hypotension may occur in some individuals. Reflex tachycardia and first-dose syncope are almost universal adverse effects.
- Concomitant use of a beta-blocker may be necessary to blunt the short-term effect of reflex tachycardia.