GANGLIONIC BLOCKERS

They act at N\textsubscript{N} receptors of the autonomic ganglia (block both parasympathetic and sympathetic ganglia) and produce widespread complex effects (Fig. 3.16).

**Fig. 3.16** Site of action of ganglion blockers (GBs).
The ganglionic blockers have ‘atropine-like’ action on heart (palpitation and tachycardia), eye (mydriasis and cycloplegia), GIT (dryness of mouth and constipation), bladder (urinary retention), impotence in males and decreased sweat secretion. Blockade of sympathetic ganglia results in marked postural hypotension.

No selective ganglion blockers are available till now. Hence, they are rarely used in therapy.

**Nicotine** is obtained from tobacco leaves. It has initial stimulating and later a prolonged blocking effect on the autonomic ganglia. Tobacco smoking and chewing is a serious risk factor for oral, lung, heart and other diseases. Nicotine is of no value in clinical practice except in the form of transdermal patch and chewing gum for the treatment of tobacco addiction.

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**Key Points for Dentists**

- **Drugs causing dry mouth (Xerostomia):** All anticholinergic agents, tricyclic antidepressants, phenothiazines, first-generation H₁ blockers—due to their anticholinergic action; clonidine—central sympatholytic agent.
- Patient on anticholinergics should be advised to maintain good oral hygiene.
- Anticholinergic drugs should not be used in patients with glaucoma and elderly males with enlarged prostate.

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**ADRENERGIC AGONISTS (SYMPATHOMIMETIC AGENTS)**

Adrenergic agonists mimic the actions of sympathetic stimulation.

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**Adrenergic Transmission**

The transmitter in the sympathetic system is noradrenaline (NA; norepinephrine). Nerves that synthesize, store and release NA are called adrenergic (sympathetic) nerves.

Synthesis of catecholamines begins with the amino acid tyrosine, which is transported into the adrenergic neuron by active transport. In the neuronal cytosol, tyrosine is converted to DOPA by tyrosine hydroxylase and DOPA to dopamine (DA) by DOPA decarboxylase. Dopamine enters the storage vesicles of the nerve terminal by active transport, where it is converted to NA by the enzyme dopamine β-hydroxylase (this enzyme is present only in the storage vesicles); the NA formed gets stored in the vesicles. In the adrenal medulla, NA is further converted to adrenaline by N-methyltransferase. Small quantities of NA are released continuously into the synaptic cleft and large quantities during nerve stimulation (Fig. 3.18).

Three processes are involved in the termination of action of released NA in the synaptic cleft (fate of released NA in the synaptic cleft):

1. Most of the released NA is taken back into the adrenergic nerve terminals (neuronal reuptake), which is either stored in the vesicles or inactivated by mitochondrial monoamine oxidase (MAO) in the cytosol. Neuronal reuptake is the most important mechanism through which the termination of action of NA takes place in the synaptic cleft.
**Fig. 3.18** Synthesis and release of NA from the adrenergic neuron and various drugs affecting the pathway (Table 3.8). MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; TCAs, tricyclic antidepressants.

**Table 3.8 Drugs Affecting Adrenergic Transmission and Their Uses**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Response/Therapeutic Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metyrosine (α-methyl tyrosine)</td>
<td>Inhibits tyrosine hydroxylase enzyme</td>
<td>Blocks the synthesis of NA—useful in the treatment of selected cases of pheochromocytoma</td>
</tr>
<tr>
<td>α-Methyldopa</td>
<td>Replacement of NA by false transmitter (α-methyl-NA)</td>
<td>α-Methyl NA is an α₂-agonist, used in hypertension especially in pregnancy</td>
</tr>
<tr>
<td>Reserpine</td>
<td>Blocks vesicular uptake and storage of NA</td>
<td>Depletion of NA; destruction by mitochondrial MAO: used in hypertension</td>
</tr>
<tr>
<td>Cocaine, TCAs</td>
<td>Inhibit neuronal reuptake of NA (uptake-1)</td>
<td>Accumulation of NA at receptors</td>
</tr>
<tr>
<td>Adrenergic agonists</td>
<td>Mimic the effects of neurotransmitter at receptor</td>
<td>Sympathomimetic effects</td>
</tr>
<tr>
<td>Tyramine, ephedrine, amphetamine</td>
<td>Promote the release of NA from adrenergic nerve terminals</td>
<td>Tyramine, amphetamine (indirectly acting) and ephedrine (mixed acting) sympathomimetics</td>
</tr>
<tr>
<td>Adrenergic antagonists</td>
<td>Block the effects of neurotransmitter at receptors</td>
<td></td>
</tr>
</tbody>
</table>
2. Small amount of NA from the synaptic cleft diffuses into circulation and gets inactivated in liver by catechol-O-methyltransferase (COMT) and MAO.
3. Small quantity of NA is transported into other tissues (extraneuronal uptake).

- **Metabolism of Catecholamines**

  The main metabolite of catecholamines is vanillylmandelic acid (VMA). It is excreted in urine.

- **Types, Distribution and Functions of Adrenergic Receptors**

  Ahlquist divided adrenergic receptors into $\alpha$ and $\beta$ types, which are located on the cell membrane. They are further divided into various subtypes, which are as follows:

  \[
  \begin{align*}
  \alpha & \leftrightarrow \alpha_1 \\
  \alpha & \leftrightarrow \alpha_2 \\
  \beta & \leftrightarrow \beta_1 \\
  \beta & \leftrightarrow \beta_2 \\
  \beta & \leftrightarrow \beta_3
  \end{align*}
  \]

  Distribution of various adrenergic receptors is indicated in Figure 3.19.

  1. **Effect of activation of $\alpha_1$-receptors**
     - **Blood vessels**: Constriction.
     - **GI sphincter (anal)**: Increase in tone.
     - **Urinary sphincter**: Increase in tone.
     - **Radial muscle (iris)**: Contraction (mydriasis).
  2. **Effect of activation of presynaptic $\alpha_2$-receptors**
     - Mediate negative-feedback control on NA secretion (i.e. stimulation of $\alpha_2$-receptors decreases the release of NA from sympathetic nerve endings).
  3. **Effect of activation of postsynaptic vascular $\alpha_2$-receptors**
     - Mediate stimulatory effects: Vasoconstriction and venoconstriction.
  4. **Effect of activation of $\alpha_3$-receptors on various secretions**
     - **Beta cells of islets of Langerhans in pancreas**: Decrease in insulin secretion.
     - **Ciliary epithelium**: Reduction of aqueous humor secretion.
     - **Sympathetic nerve endings**: Decrease in NA release.
  5. **Effect of activation of $\beta_1$-receptors**
     - **Heart**: Cardiac stimulation.
     - **Kidney**: Promote renin release.
  6. **Stimulatory effects due to activation of $\beta_2$-receptors**
     - **Liver**: Stimulation of glycogenolysis.
     - **Skeletal muscle**: Contraction.
     - **Ciliary epithelium**: Increase in secretion of aqueous humor.
     - Uptake of $K^+$ into cells.
  7. **Inhibitory effects due to activation of $\beta_3$-receptors**
     - **Bronchial, uterine (pregnant), vascular, bladder smooth muscles**: Relaxation.
     - In GI smooth muscle, activation of both $\alpha$ and $\beta$ receptors cause relaxation.
  8. **Effect of activation of $\beta_3$-receptors**
     - **Adipose tissue**: Lipolysis.
Drugs Acting on Autonomic Nervous System

Adrenergic Drugs (Sympathomimetics)

The sympathomimetic drugs mimic the effects of sympathetic nerve stimulation (Fig. 3.20). They are also referred to as adrenergic agonists.

Classification of Sympathomimetics

1. On the basis of their chemical structure

![Catechol nucleus](image)
Drugs Acting on Autonomic Nervous System

1. **Catecholamines**: Sympathomimetics with catechol nucleus are called catecholamines, e.g. adrenaline, noradrenaline, dopamine, dobutamine, isoprenaline.

2. **Non-catecholamines**: Sympathomimetics that lack catechol nucleus are called non-catecholamines, e.g. tyramine, ephedrine, amphetamine, phenylephrine, salbutamol, etc.

2. **On the basis of their mechanism of action** (Table 3.9):
   a. **Direct acting**: They act directly by stimulating adrenergic receptors.
   b. **Indirect acting**: They act by releasing NA from adrenergic nerve endings.
   c. **Mixed acting**: These drugs act both directly and indirectly.

3. **On the basis of their therapeutic use**:
   a. **To raise the blood pressure in shock**: Dopamine, noradrenaline, ephedrine, phenylephrine, methoxamine, mephentermine.
   b. **As bronchodilator**: Salbutamol, terbutaline, salmeterol, formoterol.
   c. **As cardiac stimulant**: Adrenaline, isoprenaline, dobutamine.
   d. **As CNS stimulant**: Amphetamine, dextroamphetamine.
   e. **For local vasoconstrictor effect**: Adrenaline.

---

**Fig. 3.20** An angry man symbolizing sympathetic overactivity (Fight–Fright–Flight)—1: Anger, alert, aggressive; 2: Pupillary dilatation (mydriasis); 3: Increased muscle tone, tremors; 4: Palpitation–increased cardiac output–increased blood flow to the skeletal muscles; 5: Flushing of the face; 6: Tachypnoea, bronchodilatation; 7: Liver–glycogenolysis–more energy; 8: Adipose tissue–lipolysis–energy.
Table 3.9 Summary of Sympathomimetic Agents

<table>
<thead>
<tr>
<th>Adrenergic Agonists</th>
<th>Receptor Action</th>
<th>Therapeutic Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Directly acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Adrenaline</td>
<td>α₁, α₂, β₁, β₂ and β₃-agonist</td>
<td>Anaphylactic shock, Bronchial asthma (acute), Cardiac arrest, to prolong the Duration of local anaesthesia, to control Epistaxis and other capillary oozing (ABCDE)</td>
</tr>
<tr>
<td>• Noradrenaline</td>
<td>α₁, α₂ and β₁-agonist</td>
<td>Hypotensive states</td>
</tr>
<tr>
<td>• Isoprenaline</td>
<td>β₁ and β₂-agonist</td>
<td>Heart block, cardiac arrest</td>
</tr>
<tr>
<td>• Dobutamine</td>
<td>Relatively selective β₁-agonist</td>
<td>Cardiogenic shock due to acute myocardial infarction (MI), congestive cardiac failure (CCF) or cardiac surgery</td>
</tr>
<tr>
<td>• Salbutamol (Albuterol), Terbutaline, Salmeterol, Formoterol</td>
<td>Selective β₂-agonists</td>
<td>Bronchial asthma, to suppress premature labour (as uterine relaxant)</td>
</tr>
<tr>
<td>• Phenylephrine, Methoxamine</td>
<td>Selective α₁-agonists</td>
<td>Vasopressor agents, nasal decongestants, as mydriatic (phenylephrine), allergic or vasomotor rhinitis</td>
</tr>
<tr>
<td>• Naphazoline, Oxymetazoline, Xylometazoline</td>
<td>α₁ + α₂-agonists</td>
<td>Nasal decongestants (α₁-stimulation), Structural damage can occur due to intense vasoconstriction (α₂-stimulation)</td>
</tr>
<tr>
<td>• Clonidine, α-Methyldopa</td>
<td>α₂-agonists</td>
<td>Hypertension</td>
</tr>
<tr>
<td>• Apraclonidine, Brimonidine</td>
<td>α₂-agonists</td>
<td>Glaucoma (topical)</td>
</tr>
<tr>
<td>2. Indirectly acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Amphetamine, Methamphetamine, Methylphenidate</td>
<td>They act by releasing NA in the periphery; NA, DA and 5-hydroxytryptamine (5-HT) centrally</td>
<td>Narcolepsy, attention-deficit hyperkinetic disorder (ADHD)</td>
</tr>
<tr>
<td>3. Mixed acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Ephedrine</td>
<td>α₁, α₂, β₁ and β₂ (direct action) + releases NA (indirect action)</td>
<td>Intravenous ephedrine is used for the treatment of hypotension due to spinal anaesthesia</td>
</tr>
<tr>
<td>• Dopamine</td>
<td>α₁, α₂, β₁, and D₁ + releases NA</td>
<td>Cardiogenic shock, CCF with oliguria</td>
</tr>
</tbody>
</table>

f. As nasal decongestant: Phenylephrine, xylometazoline, pseudoephedrine, oxymetazoline, naphazoline.
g. For allergic reactions (anaphylactic shock): Adrenaline.
h. As anorexiant: Dextroamphetamine, mazindol, phentermine, sibutramine.
Direct-acting Sympathomimetics

Adrenaline (Epinephrine): $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$ and $\beta_3$-Agonist

It is a catecholamine, which is secreted mainly by adrenal medulla. Adrenaline is a direct acting nonselective adrenergic agonist.

Pharmacological actions
Adrenaline acts on $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$ and $\beta_3$-receptors.

1. Cardiovascular system
   a. Heart: Adrenaline is a powerful cardiac stimulant. It acts mainly by interacting with $\beta_1$-receptors and produces various effects. They are as follows:
      i. Increase in heart rate (positive chronotropic effect).
      ii. Increase in myocardial contractility (positive inotropic effect).
      iii. Increase in conduction velocity (positive dromotropic effect).
      iv. Increase in cardiac output.
      v. Increase in automaticity.
      vi. Cardiac work and its oxygen requirement is markedly increased.
      vii. Increase in the excitability and tendency to cause cardiac arrhythmias.
   b. Blood vessels and BP: Blood vessels of the skin and mucous membranes ($\alpha_1$-receptors) are constricted by adrenaline. It also constricts renal, mesenteric, pulmonary and splanchnic vessels, but dilates the blood vessels of skeletal muscle and coronary vessels ($\beta_2$). Intravenous administration of adrenaline in moderate doses produces biphasic effect. There is an initial rise in BP due to $\alpha_1$ (blood vessels) and $\beta_1$ (heart) actions, followed by a fall in BP due to $\beta_2$-mediated vasodilatation in skeletal muscle. Administration of adrenaline after $\alpha$-blocker produces only a fall in BP ($\beta_2$-action). This is referred to as vasomotor reversal.

2. Respiratory system: Adrenaline rapidly relaxes ($\beta_2$) bronchial smooth muscle. It is a potent bronchodilator but has a short duration of action. It inhibits the release of inflammatory mediators from mast cells ($\beta_2$). It also reduces secretions and relieves mucosal congestion by vasoconstrictor effect ($\alpha_1$).

3. GIT: It relaxes the smooth muscle of the gut ($\alpha_2$ and $\beta_2$). It reduces the intestinal tone and peristaltic movements. But the effects are transient.

4. Bladder: It relaxes the detrusor muscle ($\beta_3$) and contracts the sphincter ($\alpha_1$). As a result, it may cause difficulty in urination.

5. CNS: In therapeutic doses, adrenaline does not cross the BBB and hence CNS effects are very minimal. But in high doses, it may cause headache, restlessness and tremor.

6. Eye: Adrenaline has poor penetration through cornea when applied topically into the eye. Hence, it is administered as a prodrug

7. Metabolic effects:
   Adrenaline increases the blood glucose level by:
      i. Stimulating hepatic glycogenolysis ($\beta_2$), which is the predominant effect.
      ii. Reducing insulin secretion.
      iii. Decreasing the uptake of glucose by peripheral tissues.

8. Other effects
   It reduces plasma $K^+$ levels by promoting the uptake of $K^+$ into the cells, particularly into the skeletal muscle ($\beta_2$).
Pharmacokinetics
Adrenaline is not suitable for oral administration because of its rapid inactivation in the GI mucosa and liver. Adrenaline can be given subcutaneously (s.c.). In anaphylactic shock, the absorption of s.c. adrenaline is very poor, hence given intramuscularly. In cardiac arrest, it is given intravenously. It does not cross the BBB; is rapidly metabolized by COMT and MAO and the metabolites are excreted in urine.

Adverse effects and contraindications
The adverse effects of adrenaline are due to extension of its pharmacological actions. They are tachycardia, palpitation, headache, restlessness, tremor and rise in BP. The serious side effects are cerebral haemorrhage and cardiac arrhythmias. In high concentration, adrenaline may cause acute pulmonary oedema due to shift of blood from systemic to pulmonary circulation. Adrenaline is contraindicated in most of the cardiovascular diseases such as hypertension, angina, cardiac arrhythmias, CCF, etc. It should also be avoided in patients on β-blockers because it may cause hypertensive crisis and cerebral haemorrhage due to unopposed action on vascular α₁-receptors.

Therapeutic uses of adrenaline (ABCDE)

1. **Anaphylactic shock**: Adrenaline is the life-saving drug in anaphylactic shock. Adrenaline 0.3–0.5 mL of 1:1000 solution (1 mg/mL) is administered intramuscularly. It rapidly reverses the manifestations of severe allergic reactions

2. **Bronchial asthma**: Adrenaline is a powerful bronchodilator and has rapid onset but short duration of action. It is useful for acute attack. Its use has declined because of its dangerous cardiac-stimulant effect. The beneficial effects of adrenaline in bronchial asthma are shown in Figure 3.21. Adrenaline 0.3–0.5 mL of 1:1000 solution is given subcutaneously. It can be given by nebulization (as inhalation).

3. **Cardiac resuscitation**: In the treatment of cardiac arrest due to drowning or electrocution, adrenaline is injected intravenously in 1:10000 (0.1 mg/mL) concentration along with other supportive measures such as external cardiac massage, as a part of advanced life support (ALS).

4. **Prolongs the Duration of local anaesthesia**: Adrenaline (1:1,00,000) with lignocaine. Adrenaline, by its vasoconstrictor effect (α₁) delays absorption of local anaesthetic and prolongs the duration of local anaesthesia

---

**Fig. 3.21** Effects of adrenaline in bronchial asthma: LTs, leukotrienes; PGF₂α, prostaglandin F₂α; PAF, platelet activating factor.
5. **Controls Epistaxis and other capillary ooze.** Adrenaline is used as a local haemostatic to control bleeding following tooth extraction and during surgical procedures in nose, throat, larynx, etc. because of its vasoconstrictor effect.

6. **Glaucoma:** Adrenaline has poor penetration when applied locally into the eye; hence it is administered as a prodrug.

**Noradrenaline:** $\alpha_1$, $\alpha_2$, and $\beta_1$-Agonist (Table 3.10)

Noradrenaline is a catecholamine. It is the main neurotransmitter in adrenergic system. It acts on $\alpha_1$, $\alpha_2$, and $\beta_1$-adrenergic receptors; has negligible $\beta_2$ action. The main action of NA is on cardiovascular system. It has a direct cardiac-stimulant effect ($\beta_1$); also constricts all the blood vessels ($\alpha_1$) including those of the skin, mucous membrane, renal, mesenteric, pulmonary, skeletal muscle, etc. So the systolic, diastolic and pulse pressures are increased. There is reflex bradycardia. Noradrenaline, like adrenaline, is not effective orally. It is not suitable for s.c., i.m. or direct i.v. infusion because of necrosis and sloughing of the tissues at the site of injection. It is administered by i.v. infusion. It can be used to raise BP in hypotensive states; but it may decrease blood flow to vital organs by causing widespread vasoconstriction.

**Isoprenaline (Isoproterenol): $\beta_1$, $\beta_2$, and $\beta_3$-Agonist**

It is a synthetic, nonselective $\beta$-receptor agonist with a catechol nucleus. It has potent $\beta$ actions ($\beta_1 + \beta_2$) but no action at $\alpha$-receptors. Isoprenaline is a powerful cardiac stimulant. It has positive inotropic, chronotropic and dromotropic effects. It dilates renal, mesenteric and skeletal muscle blood vessels. Systolic BP is minimally changed but the diastolic and mean arterial pressures are reduced. It relaxes bronchial and GI smooth muscles. Isoprenaline is not effective orally because of extensive first-pass metabolism. It can be given parenterally or as an aerosol. It is metabolized by COMT. Isoprenaline

<table>
<thead>
<tr>
<th>Table 3.10 Comparative Features of Adrenaline and Noradrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adrenaline</strong></td>
</tr>
<tr>
<td>Catecholamine</td>
</tr>
<tr>
<td>Direct-acting sympathomimetic agent—$\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$-agonist</td>
</tr>
<tr>
<td>Administered by s.c., i.m. and slow i.v. routes</td>
</tr>
<tr>
<td>Powerful cardiac stimulant—increases heart rate and force of contraction</td>
</tr>
<tr>
<td>On i.v. administration, in moderate doses, it produces typical biphasic response—initial rise in BP ($\alpha_1$-blood vessels and $\beta_1$-heart action) followed by a fall in BP due to $\beta_2$-mediated vasodilatation in skeletal muscle</td>
</tr>
<tr>
<td>Increase in blood glucose</td>
</tr>
<tr>
<td>Powerful bronchodilator</td>
</tr>
</tbody>
</table>

**Uses:** Anaphylactic shock, Bronchial asthma (acute), Cardiac resuscitation to prolong the Duration of local anaesthetics, Control Epistaxis and bleeding following tooth extraction, etc.

**Uses:** To raise blood pressure in hypotensive states
Drugs Acting on Autonomic Nervous System

is used to increase the heart rate in heart block. In bronchial asthma, isoprenaline has been replaced by selective $\beta_2$-agonists. Side effects are tachycardia, palpitation, cardiac arrhythmias, etc. due to its powerful cardiac-stimulant effect.

**Dobutamine: Relatively Selective $\beta_1$-Agonist**

Dobutamine, a synthetic catecholamine, structurally resembles dopamine. It is a potent inotropic agent, but causes only slight increase in heart rate. Total peripheral resistance is not significantly affected. It is administered by i.v. infusion in patients with acute heart failure. The side effects are tachycardia, rise in BP, etc.

**Salbutamol, Terbutaline, Salmeterol, Formoterol: Selective $\beta_2$-Adrenergic Agonists**

The main adverse effects of nonselective $\beta$-agonists, e.g. adrenaline, isoprenaline, etc. are on the heart. They can cause tachycardia, palpitation, cardiac arrhythmias and may even precipitate angina or myocardial infarction. Use of isoprenaline is almost obsolete for the treatment of asthma. Selective $\beta_2$-agonists are the main drugs used in bronchial asthma, e.g. salbutamol, terbutaline, salmeterol, formoterol, etc.

**Pharmacological actions**

Pharmacological actions of selective $\beta_2$-agonists are depicted in Figure 3.22. They cause bronchodilatation, relaxation of pregnant uterus, dilatation of blood vessels supplying the skeletal muscles, promote hepatic glycogenolysis and uptake of $K^+$ into the cells.

**Therapeutic uses**

1. **Bronchial asthma**: Selective $\beta_2$-agonists are usually administered by aerosol. They produce prompt bronchodilatation (salbutamol and formoterol) with minimal systemic side effects.
2. **Premature labour**: On oral or parenteral administration, salbutamol and terbutaline relax pregnant uterus by interacting with $\beta_2$-receptors; hence they are used to delay premature labour.
3. **Hyperkalaemia**: Selective $\beta_2$-agonists are useful in hyperkalaemia as they promote the uptake of $K^+$ into cells, especially into skeletal muscles.

**Adverse effects of selective $\beta$-agonists**

1. **Tremor** is due to the stimulation of $\beta_2$-receptors of skeletal muscle. Tolerance develops to this effect on continued administration.

![Fig. 3.22 Pharmacological actions of selective $\beta_2$-agonists.](image)
2. **Tachycardia** and palpitation are due to stimulation of $\beta_1$-receptors of heart ($\beta_2$-selectivity is not absolute—may cause cardiac side effects).

3. **Hyperglycaemia** may occur in diabetics following parenteral administration of $\beta_2$-agonists.

4. **Hypokalaemia** is due to shift of $K^+$ into cells.

### Phenylephrine, Methoxamine, Mephetamine: Selective $\alpha_1$-Adrenergic Agonists

- Phenylephrine
- Methoxamine  
  Directly acting $\alpha_1$-agonists

- Mephetamine  
  Directly acting $\alpha_1$-agonist + releases NA (indirect action)

Cause vasoconstriction

- Increase peripheral vascular resistance (PVR)

- Increase in BP

Like ephedrine, mephetamine also has cardiac-stimulant effect. They are used parenterally to raise the BP in hypotensive states. Phenylephrine is also used topically as a mydriatic and a nasal decongestant.

### Nasal Decongestants

The commonly used $\alpha$-agonists as nasal decongestants are naphazoline, oxymetazoline, xylometazoline (topical); pseudoephedrine (oral) and phenylephrine (oral, topical). They are used in allergic rhinitis, common cold, sinusitis, etc. These drugs stimulate $\alpha$-receptors and cause vasoconstriction in the nasal mucous membrane, thus relieve nasal congestion. On prolonged use, they cause rebound congestion (after congestion). Atrophic rhinitis, anosmia and local irritation are the other adverse effects seen with topical decongestants. If systemically absorbed, these drugs may aggravate hypertension.

Pseudoephedrine and phenylephrine are the commonly used oral preparations. They are usually combined with antihistaminics in anticold preparations. These drugs cause less rebound phenomenon, but systemic side effects like hypertension and CNS stimulation are common. They should not be combined with MAO inhibitors because of risk of hypertensive crisis, which could be fatal. Phenylpropanolamine was used as a nasal decongestant. It has been banned because of increased incidence of stroke.

### Selective $\alpha_2$-Adrenergic Agonists

They include clonidine, $\alpha$-methyldopa and tizanidine. Apraclonidine, selective $\alpha_2$-agonist, is topically used in glaucoma.
Indirect-acting Sympathomimetics

Amphetamine

Amphetamine is an indirect-acting sympathomimetic agent and has a potent CNS-stimulant effect. It occurs in two isomers. The \(d\)-isomer has more potent CNS effects and the \(l\)-isomer on CVS. The side effects are restlessness, insomnia, confusion, fatigue, tremor, hallucinations and suicidal tendencies. The cardiac side effects are tachycardia, palpitation, hypertension, angina and cardiac arrhythmias.

Treatment of acute intoxication
1. Acidification of urine with ascorbic acid (vitamin C) promotes the excretion of amphetamine, which is a basic drug.
2. Sedatives are effective to control CNS symptoms and sodium nitroprusside for severe hypertension.

Uses
1. Narcolepsy: It is a sleep disorder characterized by recurrent episodes of uncontrollable desire for sleep. Amphetamine improves narcolepsy by its CNS-stimulant effect.
2. As an anorexiant: Amphetamine-like drugs reduce body weight by suppressing hypothalamic feeding centre. Tolerance to this effect develops rapidly.
3. Attention-deficit hyperkinetic disorder: Amphetamine acts paradoxically and controls the activity in children with hyperkinetic disorder. The main adverse effects are loss of appetite and insomnia. Methylphenidate and dextroamphetamine are also useful in this disorder.

Mixed-acting Sympathomimetics

Ephedrine: \(\alpha\) - and \(\beta\)-Agonist with NA Release

Ephedrine is a mixed-acting adrenergic agonist. It is an alkaloid, acts on \(\alpha_1\), \(\alpha_2\), \(\beta_1\), \(\beta_2\)-receptors and releases NA from sympathetic nerve endings.

Pharmacological actions

![Pharmacological actions diagram]

Uses
Intravenous ephedrine is the drug of choice to treat hypotension due to spinal anaesthesia as it increases peripheral vascular resistance, heart rate, cardiac output and thus BP. It was used in heart block, narcolepsy and more frequently in bronchial asthma. Now, it has been replaced by more selective drugs. The side effects are due to the extension of its pharmacological actions. They are insomnia, hypertension, tachycardia, palpitation, difficulty in urination; tachyphylaxis occurs on repeated administration.
Dopamine: $\alpha_1$, $\alpha_2$, $\beta_1$ and Dopamine-receptor Agonist with NA Release

Dopamine (DA) is a catecholamine and the immediate metabolic precursor of noradrenaline (NA). It acts on dopaminergic $D_1$ receptors as well as $\beta_1$- and $\alpha_1$-adrenergic receptors. DA, like adrenaline and noradrenaline, is not effective orally. Dopamine is rapidly inactivated by COMT and MAO, and is administered by i.v. infusion.

Pharmacological actions
- **At low doses** (<2 mcg/kg/min), it selectively dilates renal, mesenteric and coronary blood vessels by acting on $D_1$ receptors resulting in an increase in glomerular filtration rate (GFR) and urine output.
- **At moderate doses** (2–5 mcg/kg/min), dopamine stimulates $\beta_1$-receptors of heart, increases myocardial contractility and cardiac output, but tachycardia is less prominent. It also stimulates dopaminergic receptors resulting in increase in GFR.
- **At high doses** (>10 mcg/kg/min), it stimulates vascular $\alpha_1$-adrenergic receptors and causes generalized vasoconstriction. This increases afterload and reduces blood flow to renal, mesenteric and other vital organs. So, the beneficial effect seen with low-to-moderate dose of DA is lost at higher doses.

Precautions and adverse effects
During dopamine infusion, the dose, BP, heart rate, ECG and urine output should be carefully monitored. The adverse effects seen are mainly due to sympathetic stimulation. They are nausea, vomiting, headache, hypertension, tachycardia, cardiac arrhythmias and angina.

Therapeutic uses
1. **Cardiogenic and septic shock**: Dopamine can be used because it increases BP as well as selectively dilates renal, mesenteric, coronary blood vessels and improves blood flow to vital organs.
2. **Severe heart failure with renal impairment**: Dopamine improves both cardiac and renal function.

Anorectics (Anorexiants)

Amphetamine-like drugs promote weight loss by acting on hypothalamic feeding centre.

- Mazindol
- Phentermine

\[
\begin{align*}
\text{Inhibit reuptake of NA} & \quad \rightarrow \\
\text{Enhance noradrenergic transmission in the brain} & \quad \rightarrow \\
\text{Inhibits hypothalamic feeding centre} & \quad \rightarrow \\
\text{Suppress appetite} & \quad \\
\end{align*}
\]

- Sibutramine

\[
\begin{align*}
\text{Inhibits NA and 5-HT reuptake} & \quad \rightarrow \\
\text{Suppresses appetite and enhances satiety} & \quad \\
\end{align*}
\]

The main adverse effects of these agents are addiction liability, rise in BP, palpitation, sleep disturbances, depression and dry mouth.

**Key Points for Dentists**

- Check the strength and expiry date of adrenaline before administration.
- Adrenaline should be avoided in patients with hypertension, angina, cardiac arrhythmias, CCF, etc.; also in patients on $\beta$-blockers.
- Care should be taken to avoid extravasation of noradrenaline during infusion, as it will lead to necrosis of surrounding tissues.
- Monitor pulse, BP and urine output in patients receiving dopamine infusion.