Drugs Affecting Alpha Adrenoceptors

The term adrenoceptor is widely used to describe receptors that respond to catecholamines such as norepinephrine and epinephrine. There are two main subtypes of alpha adrenoceptors, α₁ and α₂, with different mechanisms of actions (Figure 1 and Figure 2) and different pharmacological effects due to their stimulation (Table 1).

Table 1: alpha adrenoceptors, their locations, and actions

<table>
<thead>
<tr>
<th>Adrenoceptors</th>
<th>Tissue</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha1</td>
<td>Most vascular smooth muscle</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Papillary dilator muscle</td>
<td>Contraction (dilates pupil)</td>
</tr>
<tr>
<td></td>
<td>Pilomotor smooth muscle</td>
<td>Erects hair</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>Increases force of contraction</td>
</tr>
<tr>
<td>Alpha2</td>
<td>Postsynaptic CNS adrenoceptors</td>
<td>Probably multiple</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Aggregation</td>
</tr>
<tr>
<td></td>
<td>Adrenergic and cholinergic nerve</td>
<td>Inhibition of transmitter</td>
</tr>
<tr>
<td></td>
<td>terminals</td>
<td>release</td>
</tr>
<tr>
<td></td>
<td>Some vascular smooth muscle</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Pancreas</td>
<td>Inhibition of insulin secretion</td>
</tr>
<tr>
<td></td>
<td>Fat cells</td>
<td>Inhibition of lipolysis</td>
</tr>
</tbody>
</table>

Figure 1: Stimulation of α₁ receptors by catecholamines leads to the activation of a G₉ coupling protein. The alpha subunit of this G protein activates the effector, phospholipase C, which leads to release of IP₃ (inositol triphosphate) and DAG (diacylglycerol) from phosphatidylinositol diphosphate. IP₃ stimulates the release of calcium, leading to an increased concentration of cytoplasmic Ca²⁺. It then activates Ca²⁺-dependent protein kinases, which in turn, activate their substrate. DAG activates protein kinase C.
stimulation of α2 receptors inhibits adenylyl cyclase activity and cause intracellular cAMP level to decrease. This is mediated by the inhibitory regulatory protein, G\textsubscript{i}.

\textit{(a) Alpha Adrenoceptors Agonists}

Alpha adrenoceptors can be stimulated either directly or indirectly by increasing endogenous catcholamines release (\textit{Table 2}).

\textit{Table 2:} Examples of alpha adrenoceptors agonists

- Endogenous catecholamines
  - Epinephrine
  - Norepinephrine
  - Dopamine
- Indirectly acting sympathomimetics
  - Ephedrine
  - Amphetamine
- α\textsubscript{1} agonists
  - Phenylephrine
  - Midodrine
- α\textsubscript{2} agonists
  - Clonidine
  - Methyldopa
  - Dexmeditomidine
- **Endogenous Catecholamines:**

  **Epinephrine** (adrenaline) is a very potent vasoconstrictor and cardiac stimulant. The rise in systolic blood pressure that occurs after its release or administration is caused by its positive inotropic and chronotropic actions on the heart (predominantly \( \beta_1 \) receptors) and the vasoconstriction induced in many vascular beds (\( \alpha_1 \) receptors). It also activates \( \beta_2 \) receptors in skeletal muscle blood vessels, leading to their dilation. It is available for parenteral injection, ophthalmic and nasal drops, nasal spray and aerosol for bronchospasm.

  **Norepinephrine** (noradrenaline) and epinephrine have similar effects on \( \beta_1 \) receptors in the heart and similar potency at \( \alpha \) receptors. Norepinephrine has relatively little effect on \( \beta_2 \) receptors. Consequently, it increases peripheral resistance and both diastolic and systolic blood pressure. Compensatory vagal reflexes tend to overcome the direct positive chronotropic effects of norepinephrine; however, the positive inotropic effects on the heart are maintained. It is available for parenteral injection only.

  **Dopamine**, the immediate metabolic precursor of norepinephrine, activates \( D_1 \) receptors in several vascular beds, which leads to vasodilation. The effect on renal blood flow may be of clinical value. The activation of presynaptic \( D_2 \) receptors, which suppress norepinephrine release, contributes to these effects. In addition, dopamine activates \( \beta_1 \) receptors in the heart. At low doses, peripheral resistance may decrease. At higher rates of infusion, dopamine activates vascular \( \alpha \) receptors, leading to vasoconstriction, including the renal vascular bed. Thus, high concentrations may mimic the actions of epinephrine. It is available for parenteral injection only.

- **Other sympathomimetics**

  These agents are of interest because of pharmacokinetic features (oral activity, distribution to the central nervous system) or because of relative selectivity for specific receptor subclasses.

  **Ephedrine** was the first orally active sympathomimetic drug. Because it is not a catechol derivative, it has high bioavailability and a long duration of action. A significant fraction of the drug is excreted unchanged in the urine. Since it is a weak base, its excretion can be accelerated by acidification of the urine. Ephedrine acts primarily through the release of stored catecholamines; in addition, it has some direct actions on adrenoceptors. It is nonselective and mimics epinephrine in its spectrum of effects. Because it gains access to the central nervous system, it is a mild stimulant. Clinically, ephedrine is utilized when a prolonged duration of effect is desired, particularly after oral
administration. The main applications are as a nasal decongestant and as a pressor agent. Pseudo-ephedrine, one of the four ephedrine enantiomers, is available over-the-counter as a component of many decongestant mixtures. It has also been recommended for use in stress incontinence in women.

**Xylometazoline (Otrivin®) and oxymetazoline** are direct-acting α agonists. These drugs have been used as topical decongestants because of their ability to promote constriction of the nasal mucosa. When taken in large doses, oxymetazoline may cause hypotension, presumably because of a central clonidine-like effect.

**Amphetamine** and amphetamine like drugs are important chiefly because of their use and misuse as central nervous system stimulants. Pharmacokinetics of amphetamine are similar to those of ephedrine, but it enters the central nervous system even more readily and has a much more marked stimulant effect on mood and alertness and a depressant effect on appetite. Its peripheral actions are mediated primarily through the release of catecholamines. Amphetamine-like drugs appear to have efficacy in some children with attention deficit hyperactivity disorder.

**Phenylpropanolamine** is a sympathomimetic drug with weak effects on mood that is available over-the-counter in numerous weight reduction medications. Though apparently safe in recommended dosage, it has been associated with significant rises in blood pressure and target organ damage in case reports of persons ingesting large doses.

- **Receptor-Selective Sympathomimetic Drugs**

  **Phenylephrine** is relatively pure α₁ agonist. Because it is not a catechol derivative, it is not inactivated by COMT (catechol–O–methyle transferase) and has a much longer duration of action than the catecholamines. It is an effective mydriatic and decongestant and can be used to raise the blood pressure. It is available for parenteral injection, oral tablets, and nasal drops, spray and jelly.

  **Methoxamine** acts pharmacologically like phenylephrine, a direct-acting α₁-receptor agonist. It may cause a prolonged increase in blood pressure due to vasoconstriction; it also causes a vagally mediated bradycardia. Clinical applications are rare and limited to hypotensive states. It is available for parenteral injection only.

  **Midodrine** is a prodrug that is enzymatically hydrolyzed to desglymidodrine, an α₁ receptor-selective agonist. The peak concentration of desglymidodrine is achieved about 1 hour after midodrine is administered. The primary indication for midodrine is the treatment of postural hypotension, typically due to impaired autonomic
nervous system function. While the drug has efficacy in diminishing the fall of blood pressure when the patient is standing, it may cause hypertension when the subject is supine. It is available as oral tablets.

\textbf{α}_2\text{-selective agonists} have an important ability to decrease blood pressure through actions in the central nervous system even though local application may cause vasoconstriction. Such drugs (eg, clonidine, methyldopa, guanfacine, guanabenz, dexmedetomidine) are useful in the treatment of hypertension.

\textit{Other Actions of α}_2 \& I_1 \text{ Agonist Drugs}

It was found that clonidine and several congeners have significant affinity for a nonadrenergic class of binding sites in addition to α_2 adrenoceptors. These nonadrenergic receptors are known as imidazoline receptor group after the distinctive ring structure found in clonidine but not in catecholamines. Subgroups of imidazoline receptors have been identified and named I_1 and I_2. The I_1 subgroup seems to be the primary binding site for imidazoline drugs that have useful antihypertensive effects. These drugs include moxonidine and rilmenidine.

Clonidine has analgesic effects and it has been found to have efficacy in the treatment of diarrhea in diabetics with autonomic neuropathy, perhaps due to its ability to enhance salt and water absorption from the intestines. In addition, clonidine has efficacy in diminishing craving for narcotics and alcohol during withdrawal and may facilitate cessation of cigarette smoking. Clonidine has also been used to diminish menopausal hot flushes and is being used to reduce hemodynamic instability during general anesthesia and may also decrease intraocular pressure. The latter effect is recognized by the availability of apraclonidine and brimonidine for glaucoma.

The ability of α_2 agonists to alter neuronal activity in the spinal cord has resulted in the development of tizanidine for the treatment of spasticity, withdrawal syndromes, and chronic pain syndromes. \textbf{Dexmedetomidine} is another imidazoline congener of clonidine and has been shown to have hypnotic effects and ocular hypotensive effects when given systemically and significant analgesic effects when given by the intrathecal route. These effects are probably mediated primarily by α_2 agonist action. Dexmedetomidine retains some sympathoplegic and hypotensive effect.
Clinical Applications of α - Adrenoceptors Agonists

• Cardiovascular Applications

A. Increasing Blood Flow or blood Pressure:

Hypotension may occur in a variety of settings. The use of sympathomimetic drugs merely to elevate a blood pressure that is not an immediate threat to the patient may increase morbidity. Sympathomimetic drugs may be used in a hypotensive emergency to preserve cerebral and coronary blood flow. Such situations might arise in severe hemorrhage, spinal cord injury, or overdoses of antihypertensive or central nervous system depressant medications. The treatment is usually of short duration while the appropriate treatment of the cause is being administered. Direct acting α agonists such as norepinephrine, phenylephrine, or methoxamine can be utilized in this setting if vasoconstriction is desired. For the treatment of chronic orthostatic hypotension, oral ephedrine has been the traditional therapy. Midodrine may be considered as a replacement for oral ephedrine in this situation.

Shock, if untreated, usually progresses to a refractory deteriorating state and death. Volume replacement and treatment of the underlying disease are the mainstays of the treatment of shock. While Sympathomimetic drugs have been used in the treatment of virtually all forms of shock, their efficacy is unclear. In most forms of shock, vasoconstriction mediated by the sympathetic nervous system is already intense. Efforts aimed at reducing rather than increasing peripheral resistance may be more fruitful if cerebral, coronary, and renal perfusion are improved. A decision to use vasoconstrictors or vasodilators is best made on the basis of information about the underlying cause, which may require invasive monitoring. Positive inotropic agents such as dopamine or dobutamine may have a role in Cardiogenic shock. In low to moderate doses, these drugs may increase cardiac output and, compared with norepinephrine, cause relatively little peripheral vasoconstriction.

Unfortunately, the patient with shock may not respond to any of the above therapeutic maneuvers; the temptation is then great to use vasoconstrictors to maintain adequate blood pressure. While coronary perfusion may be improved, this gain may be offset by increased myocardial oxygen demands as well as more severe vasoconstriction in blood vessels to the abdominal viscera. Therefore, the goal of therapy in shock should be to optimize tissue perfusion, not blood pressure.

B. Decreasing Blood Flow:

Reduction of regional blood flow is desirable for achieving hemostasis in surgery, for reducing diffusion of local anesthetics away from the site of administration, and for reducing mucous membrane congestion. In
each instance, α receptor activation is desired, and the choice of agent depends upon the maximal efficacy required, the desired duration of action, and the route of administration.

Effective pharmacologic hemostasis, often necessary for facial, oral, and nasopharyngeal surgery, requires drugs of high efficacy that can be administered in high concentration by local application. Epinephrine is usually applied topically in nasal packs (for epistaxis) or in a gingival string (for gingivectomy).

Combining α agonists with some local anesthetics greatly prolongs the duration of infiltration nerve block; the total dose of local anesthetic and the probability of toxicity can therefore be reduced. Epinephrine, 1:200,000, is the favored agent for this application, but norepinephrine, phenylephrine, and other α agonists have also been used. Systemic effects on the heart and peripheral vasculature may occur even with local drug administration.

Mucous membrane decongestants are α agonists that reduce the discomfort of hay fever and, to a lesser extent, the common cold by decreasing the volume of the nasal mucosa, probably mediated by α₁ receptors. Unfortunately, rebound hyperemia may follow the use of these agents, and repeated topical use of high concentrations may result in ischemic changes in the mucous membranes, as a result of vasoconstriction of nutrient arteries. Favoring short-acting topical agents include phenylephrine and phenylpropanolamine in nasal sprays and ophthalmic drops. Long-acting topical decongestants include xylometazoline and oxymetazoline.

- **Respiratory Applications**

  One of the most important uses of sympathomimetic drugs is in the therapy of bronchial asthma. Usually, selective β₂ agonists are used; but nonselective drugs (epinephrine) are sometimes indicated for their additional pulmonary decongestant effect mediated by stimulation of alpha receptors.

- **Anaphylaxis**

  Anaphylactic shock and related immediate (type I) IgE-mediated reactions affect both the respiratory and the cardiovascular systems. The syndrome usually responds rapidly to subcutaneous administration of epinephrine, 0.3-0.5 mg (0.3-0.5 ml of 1:1000 epinephrine solution). This drug is the agent of choice because of its great efficacy at α, β₁, and β₂ receptors; stimulation of all three is helpful in reversing the pathophysiologic process.
Ophthalmic Applications

**Phenylephrine** is an effective mydriatic agent frequently used to facilitate examination of the retina. It is also a useful decongestant for minor allergic hyperemia of the conjunctival membranes. Sympathomimetics administered as ophthalmic drops are also useful in localizing the lesion in Horner's syndrome. If the lesion of Horner's syndrome is postganglionic, indirectly acting sympathomimetics (eg, **coca ine**, hydroxyamphetamine) will not dilate the abnormally constricted pupil (because catecholamines have been lost from the nerve endings in the iris). In contrast, the pupil will dilate in response to phenylephrine, which acts directly on the α receptors on the smooth muscle of the iris. A patient with a preganglionic lesion, on the other hand, will show a normal response to both drugs, since the postganglionic fibers and their catecholamine stores remain intact in this situation.

**Apraclonidine** and **brimonidine** are α₂-selective agonists that also lower intraocular pressure and are approved for use in glaucoma.

Central Nervous System Applications

As noted above, the amphetamines have a mood-elevating (euphoriant) effect; this effect is the basis for the widespread abuse of this drug and some structurally related analogs. The amphetamines also have an alerting, sleep-deferring action. A therapeutic application of this effect is in the treatment of narcolepsy and attention-deficit hyperkinetic syndrome of children.

Toxicity of Sympathomimetic Drugs

The adverse effects of adrenoceptor agonists are primarily extensions of their receptor effects in the cardiovascular and central nervous systems. Adverse cardiovascular effects seen with pressor agents include marked elevations in blood pressure, which may cause cerebral hemorrhage or pulmonary edema. Increased cardiac work may precipitate severe angina or myocardial infarction. Special caution is indicated in elderly patients or those with hypertension or coronary artery disease. If an adverse sympathomimetic effect requires urgent reversal, a specific adrenoceptor antagonist should be used.

(b) **Alpha Adrenoceptors Antagonists**

**Mechanism of Action**

α-receptor antagonists may be reversible or irreversible in their interaction with these receptors. Reversible antagonists dissociate from receptors; irreversible drugs do not. **Phentolamine** and **tolazoline** are
examples of reversible antagonists. **Prazosin**, **labetalol** and several **ergot** derivatives are also reversible **α**-adrenoceptor blockers. **Phenoxybenzamine** covalently binds to **α** receptors, resulting in irreversible blockade.

The duration of action of a reversible antagonist is largely dependent on the half-life of the drug in the body and the rate at which it dissociates from its receptor. However, the effects of an irreversible antagonist may persist long after the drug has been cleared from the plasma. In the case of **phenoxybenzamine**, the restoration of tissue responsiveness after extensive **α**-receptor blockade is dependent on synthesis of new receptors, which may take several days.

**Pharmacologic Effects**

- **Cardiovascular Effects**
  
  **α**-receptor antagonist drugs cause a lowering of peripheral vascular resistance and blood pressure. They can prevent the pressor effects of usual doses of **α** agonists. In the case of agonists with both **α** and **β**₂ effects (eg, epinephrine), they convert a pressor to a depressor response (epinephrine reversal). **α**-receptor antagonists may cause postural hypotension and reflex tachycardia. Postural hypotension is due to antagonism of sympathetic nervous system stimulation of **α**₁ receptors in venous smooth muscle. Tachycardia may be more marked with agents that block **α**₂ presynaptic receptors in the heart, since the augmented release of norepinephrine will further stimulate **β** receptors in the heart. Chronic use of **α** antagonists may result in a compensatory increase in blood volume.

- **Other Effects**
  
  Minor effects that signal the blockade of **α** receptors in other tissues include miosis and nasal stuffiness. **α**-receptor blockade of the base of the bladder and the prostate is associated with decreased resistance to the flow of urine.

**Specific Agents**

**Phentolamine** (*Regitine⁰*), is a potent competitive antagonist at both **α**₁ and **α**₂ receptors. It causes a reduction in peripheral resistance through blockade of **α**₁ receptors and possibly **α**₂ receptors on vascular smooth muscles. Since phentolamine potently blocks both alpha receptors, antagonism of presynaptic **α**₂ receptors may lead to enhanced release of norepinephrine from sympathetic nerves which may contribute to marked cardiac stimulation via unblocked **β** adrenoceptors. In addition to being an **α**₁ and **α**₂-receptor antagonist, phentolamine also inhibits responses to serotonin. Phentolamine is an
agonist at muscarinic and H$_1$ and H$_2$ histamine receptors. Phentolamine has limited absorption after oral administration. Its gastrointestinal stimulation may cause diarrhea and increased gastric acid production. Phentolamine has been used in the treatment of pheochromocytoma and male erectile dysfunction.

**Tolazoline** is similar to phentolamine. It is less potent but is better absorbed from the gastrointestinal tract. It is rapidly excreted in the urine. Tolazoline has very limited clinical application in the treatment of pulmonary hypertension in newborn infants with respiratory distress syndrome. Its efficacy in this condition is doubtful, and the drug is rarely used.

**Ergot derivatives** (e.g., ergotamine, dihydroergotamine) cause reversible α-receptor blockade. However, most of the clinically significant effects of these drugs are the result of other actions (ergotamine probably acts at serotonin receptors in the treatment of migraine).

**Phenoxybenzamine** causes irreversible blockade of long duration (14-48 hours or longer). It is somewhat selective for α$_1$ receptors but less than prazosin. The drug also inhibits reuptake of released norepinephrine by presynaptic adrenergic nerve terminals. Phenoxybenzamine blocks histamine (H$_1$), acetylcholine, and serotonin receptors as well as α receptors. Phenoxybenzamine is absorbed after oral administration, though bioavailability is low. The drug is usually given orally, starting with low doses of 10-20 mg/d and progressively increasing the dose until the desired effect is achieved. Less than 100 mg/d is usually sufficient to achieve adequate α-receptor blockade. The major use of phenoxybenzamine is in the treatment of pheochromocytoma. The most important adverse effects of phenoxybenzamine are postural hypotension and tachycardia. Nasal stuffiness and inhibition of ejaculation also occur. Since phenoxybenzamine enters the central nervous system, it may cause less specific effects, including fatigue, sedation, and nausea.

**Prazosin** (Minipress®) is effective in the management of hypertension. It is highly selective for α$_1$ receptors, having relatively low affinity for α$_2$ receptors. This may partially explain the relative absence of tachycardia seen with prazosin as compared to what is reported with phentolamine and phenoxybenzamine. Prazosin leads to relaxation of both arterial and venous smooth muscle. Prazosin is extensively metabolized and degraded by the liver; therefore, only about 50% of the drug is available after oral administration. The half-life is normally about 3 hours.
**Terazosin** is another reversible \( \alpha_1 \)-selective antagonist that is effective in hypertension; it has also been approved for use in men with urinary symptoms due to benign prostatic hyperplasia (BPH). Terazosin has high bioavailability yet is extensively metabolized in the liver, with only a small fraction of parent drug excreted in the urine. The half-life of terazosin is about 9-12 hours.

**Doxazosin** (Cardura\textsuperscript{®}) is also approved for use in hypertension. It differs from prazosin and terazosin in having a longer half-life of about 22 hours. It has moderate bioavailability and is extensively metabolized, with very little parent drug excreted in urine or feces. Doxazosin has active metabolites, though their contribution to the drug's effects is probably small. Doxazosin is also effective in the symptomatic treatment of BPH.

**Tamsulosin** is a competitive \( \alpha_1 \) antagonist with a structure quite different from that of most other \( \alpha_1 \) receptor blockers. It has very high bioavailability and a long half-life (in the range of 9-15 hours). It is metabolized extensively in the liver. Tamsulosin has greater selectivity for \( \alpha_{1A} \) receptors than for the \( \alpha_{1B} \) subtype. The drug's efficacy in BPH suggests that the \( \alpha_{1A} \) subtype may be the most important alpha subtype mediating prostate smooth muscle contraction. There is evidence that tamsulosin has less potency in inhibiting \( \alpha_1 \)-receptor-mediated smooth muscle contraction in vascular smooth muscle compared with other \( \alpha_1 \)-receptor antagonists. This finding suggests that \( \alpha_{1A} \) receptors are less important in mediating contraction in human arteries and veins and is supported by clinical trials showing little change in blood pressure in humans taking this drug.

**Indoramin** is another \( \alpha_1 \)-selective antagonist that also has efficacy as an antihypertensive. **Urapidil** is an \( \alpha_1 \) antagonist that also has weak \( \alpha_2 \)-agonist and 5-HT\textsubscript{1A}-agonist actions and weak antagonist action at \( \beta_1 \) receptors. It is used as an antihypertensive agent and for BPH. **Labetalol** has both \( \alpha_1 \)-selective and \( \beta \)-blocking effects. Neuroleptic drugs such as chlorpromazine and haloperidol are potent \( \alpha \)-receptor and dopamine-receptor antagonists. Although these drugs are not used clinically to block \( \alpha \) receptors, this action may contribute to their adverse effects (e.g. hypotension). Similarly, the antidepressant **trazodone** has the capacity to block \( \alpha_1 \) receptors.

**Yohimbine** is an \( \alpha_2 \)-selective antagonist. It has no established clinical role. Theoretically, it could be useful in autonomic insufficiency by promoting neurotransmitter release through blockade of presynaptic \( \alpha_2 \) receptors. Yohimbine may improve symptoms in some patients with painful diabetic neuropathies. It has been suggested that yohimbine improves male sexual function. Yohimbine can
abruptly reverse the antihypertensive effects of an $\alpha_2$-adrenoceptor agonist such as clonidine; a potentially serious adverse drug interaction.

**Clinical Applications of $\alpha$ - Adrenoceptors Blocking Drugs**

- **Pheochromocytoma**
  
  The major clinical use of both phenoxybenzamine and phentolamine is in the management of pheochromocytoma. Unavoidable release of stored catecholamines sometimes occurs during operative manipulation of pheochromocytoma; the resulting hypertension may be controlled with phentolamine or nitroprusside. Nitroprusside has many advantages, particularly since its effects can be more readily titrated and it has a shorter duration of action.

  $\alpha$-receptor antagonists are most useful in the preoperative management. Administration of phenoxybenzamine in the preoperative period will prevent precipitation of acute hypertensive episodes during studies undertaken to localize the tumor and will tend to reverse chronic changes resulting from excessive catecholamine secretion such as plasma volume contraction. Oral doses of 10-20 mg/d may be increased at intervals of several days until hypertension is controlled. Some surgeons prefer to operate on patients in the absence of treatment with phenoxybenzamine, counting on modern anesthetic techniques to control blood pressure and heart rate during surgery. Phenoxybenzamine may be very useful in the chronic treatment of inoperable or metastatic pheochromocytoma. Hypertension in patients with pheochromocytoma may also respond to reversible $\alpha_1$-selective antagonists or to conventional calcium channel antagonists. Beta antagonists should not be employed prior to establishing effective $\alpha$-receptor blockade, since unopposed $\beta_1$-receptor blockade could theoretically cause blood pressure elevation from increased vasoconstriction.

- **Hypertensive Emergencies**
  
  The $\alpha$-adrenoceptor-blocking drugs have limited application in the management of hypertensive emergencies, though labetalol has been used in this setting. In pheochromocytoma, overdosage of sympathomimetic drugs, or clonidine withdrawal, phentolamine can be used to control high blood pressure; however other drugs are generally preferable.

- **Chronic Hypertension**
  
  Members of the prazosin family of $\alpha_1$-selective antagonists are efficacious drugs in the treatment of mild to moderate systemic hypertension. They are generally well tolerated by most patients. Their
major adverse effect is postural hypotension, which may be severe after the first dose. Nonselective $\alpha$ antagonists are not used in primary systemic hypertension.

- **Peripheral Vascular Disease**
  Occasionally, individuals with Raynaud's phenomenon and other conditions involving excessive reversible vasospasm in the peripheral circulation do benefit from phentolamine, prazosin, or phenoxybenzamine, though calcium channel blockers may be preferable for many patients.

- **Local Vasoconstrictor Excess**
  Phentolamine is also useful to reverse the intense local vasoconstriction caused by inadvertent infiltration of $\alpha$ agonists into subcutaneous tissue during intravenous administration. The $\alpha$ antagonist is administered by local infiltration into the ischemic tissue.

- **Urinary Obstruction**
  $\alpha_1$-receptor antagonists: prazosin, doxazocin, and terazosin have been used successfully in patients with BPH. These drugs are particularly useful in patients who also have hypertension.

- **Male Sexual Dysfunction**
  A combination of phentolamine with the nonspecific vasodilator papaverine, when injected directly into the penis, may cause erections in men with sexual dysfunction. The long-term risk of this form of therapy is not known; there is a risk of fibrotic reactions with long-term administration. Systemic absorption may lead to orthostatic hypotension; priapism may require direct treatment with an $\alpha$-adrenoceptor agonist such as phenylephrine. Orally administered phentolamine is being investigated in patients with erectile dysfunction. Alternative therapies include prostaglandins, sildenafil, and apomorphine.

- **Applications of $\alpha_2$ Antagonists**
  $\alpha_2$ antagonists have so little clinical usefulness. There has been experimental interest in the development of highly selective antagonists for use in Raynaud's phenomenon to inhibit smooth muscle contraction and for use in type II diabetes and psychiatric depression.
Further readings

Evaluation
1) Dopamine is useful in all the following conditions except:
   (a) Neurogenic shock
   (b) Cardiogenic shock
   (c) Hemorrhagic shock
   (d) Anaphylactic shock

2) Alpha adrenoceptor agonists in the form of nasal drops could have all of the following effects except:
   (a) Atrophic rhinitis
   (b) Nasal decongestion
   (c) Decreased peripheral vascular resistance
   (d) Bradycardia

3) All the following are side effects of clonidine except:
   (a) severe rise in blood pressure on sudden withdrawal
   (b) bradycardia
   (c) salt and water retention
   (d) anxiety and irritability

4) The life saving measure for treatment of anaphylactic shock is:
   (a) calcium gluconate
   (b) corticosteroids
   (c) epinephrine
   (d) chlorpheniramine
5) Epinephrine increases the concentration of all the following except
   (a) blood glucose
   (b) plasma free fatty acids
   (c) serum K⁺
   (d) renin secretion

6) The following are true regarding phenylephrine except:
   (a) useful in treatment of nasal congestion
   (b) raises blood pressure
   (c) causes severe tachycardia
   (d) produces mydriasis

7) Which of the following antagonists has higher affinity to α₁ than α₂:
   (a) prazocin
   (b) phenoxybenzamine
   (c) phentolamine
   (d) yohimbine

Answers key
1)d  2)d  3)d  4)c  5)c  6)c  7)a