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**ANS 1:-** NEUROTRANSMISSION:-

**Neurotransmission** (Latin: *transmissio* "passage, crossing" from *transmitter* "send, let through") is the process by which signaling molecules called [neurotransmitters](https://en.m.wikipedia.org/wiki/Neurotransmitter) are released by the [axon terminal](https://en.m.wikipedia.org/wiki/Axon_terminal) of a [neuron](https://en.m.wikipedia.org/wiki/Neuron) (the presynaptic neuron), and bind to and react with the [receptors](https://en.m.wikipedia.org/wiki/Receptor_%28biochemistry%29) on the [dendrites](https://en.m.wikipedia.org/wiki/Dendrite) of another neuron (the postsynaptic neuron) a short distance away.

NEUROTRANSMISSION PROCEES:- A similar process occurs in [retrograde neurotransmission](https://en.m.wikipedia.org/wiki/Retrograde_neurotransmission), where the dendrites of the postsynaptic neuron release retrograde neurotransmitters (e.g., [end cannabinoids](https://en.m.wikipedia.org/wiki/Endocannabinoids); synthesized in response to a rise in [intracellular](https://en.m.wikipedia.org/wiki/Intracellular) [calcium](https://en.m.wikipedia.org/wiki/Calcium_in_biology) levels) that signal through receptors that are located on the axon terminal of the presynaptic neuron, mainly at [GABA ergic](https://en.m.wikipedia.org/wiki/GABAergic) and [glutamatergic](https://en.m.wikipedia.org/wiki/Glutamatergic_neurotransmission) [synapses](https://en.m.wikipedia.org/wiki/Synapse).

Neurotransmission is regulated by several different factors: the availability and rate-of-synthesis of the neurotransmitter, the release of that neurotransmitter, the baseline activity of the postsynaptic cell, the number of available postsynaptic receptors for the neurotransmitter to bind to, and the subsequent removal or deactivation of the neurotransmitter by enzymes or presynaptic reuptake.

In response to a threshold [action potential](https://en.m.wikipedia.org/wiki/Action_potential) or [graded electrical potential](https://en.m.wikipedia.org/wiki/Membrane_potential#Graded_potentials), a neurotransmitter is released at the [presynaptic](https://en.m.wikipedia.org/wiki/Chemical_synapse) [terminal](https://en.m.wikipedia.org/wiki/Axon_terminal). The released neurotransmitter may then move across the synapse to be detected by and bind with receptors in the postsynaptic neuron. Binding of neurotransmitters may influence the postsynaptic neuron in either an [inhibitory](https://en.m.wikipedia.org/wiki/Inhibitory_synapse) or [excitatory](https://en.m.wikipedia.org/wiki/Excitatory_synapse) way.

The binding of neurotransmitters to receptors in the postsynaptic neuron can trigger either short term changes, such as changes in the [membrane potential](https://en.m.wikipedia.org/wiki/Membrane_potential) called [postsynaptic potentials](https://en.m.wikipedia.org/wiki/Postsynaptic_potential), or longer term changes by the activation of [signaling cascades](https://en.m.wikipedia.org/wiki/Signal_transduction).

Neurons form complex biological neural networks through which nerve impulses (action potentials) travel. Neurons do not touch each other (except in the case of an [electrical synapse](https://en.m.wikipedia.org/wiki/Electrical_synapse) through a [gap junction](https://en.m.wikipedia.org/wiki/Gap_junction)); instead, neurons interact at close contact points called synapses.

 A neuron transports its information by way of an action potential. When the nerve impulse arrives at the synapse, it may cause the release of neurotransmitters, which influence another (postsynaptic) neuron.

 The postsynaptic neuron may receive inputs from many additional neurons, both excitatory and inhibitory. The excitatory and inhibitory influences are summed, and if the net effect is inhibitory, the neuron will be less likely to "fire" (i.e., generate an action potential), and if the net effect is excitatory, the neuron will be more likely to fire.

 How likely a neuron is to fire depends on how far its [membrane potential](https://en.m.wikipedia.org/wiki/Membrane_potential) is from the [threshold potential](https://en.m.wikipedia.org/wiki/Threshold_potential), the voltage at which an action potential is triggered because enough voltage-dependent [sodium channels](https://en.m.wikipedia.org/wiki/Sodium_channel) are activated so that the net inward sodium current exceeds all outward currents.

 Excitatory inputs bring a neuron closer to threshold, while inhibitory inputs bring the neuron farther from threshold. An action potential is an "all-or-none" event; neurons whose membranes have not reached threshold will not fire, while those that do must fire.

 Once the action potential is initiated (traditionally at the [axon hillock](https://en.m.wikipedia.org/wiki/Axon_hillock)), it will propagate along the axon, leading to release of neurotransmitters at the [synaptic bouton](https://en.m.wikipedia.org/wiki/Synaptic_bouton) to pass along information to yet another adjacent neuron.

**ANS 2:-DIRECT CHOLINGIC AGENT:-**

cholinergic agents are compound which mimic the action of acetylcholine and /or butyrylcholine.

In general, the word “choline” describes the various quaternary ammonium salts containing the N, N, N-trimethylethanol ammonium action found in most animal tissues, choline is a primary component of the neurotransmitter acetylcholine and function with inositol as a basic constituent of lecithin.

Choline also prevents fat deposits in the liver and facilitates the movement of fats into cells.

The direct-acting cholinergic agonists work by directly binding to and activating the muscarinic receptors.

**EXAMPLES OF DIRECT CHOLINERGIC AGENTS:**

1. ACTETHYLCHOLINE
2. METHACHOLINE
3. CARBACHOL
4. BETHANECHOL
5. TACRINE

**INDERECT CHOLINERGIC AGENTS:-**

Indirect-acting cholinergic agents increase the availability of acetylcholine at the cholinergic receptors.

These include reversible agents (physostigmine, neostigmine, pyridostigmine, endophonium, rivatigmine, donepezil, galantamine) and irreversible agents (echothiophate, parathion, Malathion, diazinon and tabun)

**MECHANISM OF ACTION OF INDIRECT ACTING CHOLINERGIC AGENTS:-**drugs that inhibit the hydrolysis of Ach by the enzyme acetyl cholinesterase produce their cholinomimetic effects indirectly.

They are therefore called indirectly acting cholinergic drugs. These anticholinesterases prolong the effective life of Ach released from cholinergic nerves.

**THERAPUETIC APPLICATION OF CHOLINERGIC AGENTS:**

**1 MYASTHENIA GRAVIS:**

* Myasthenia gravis is an autoimmune disorder that attacks the nicotinic ACH receptors at the neuromuscular junction
* Leads to profound muscle weakness
* Acetyl cholinesterase inhibitor increase the amount of acetylcholine in the neuromuscular junction.
* Neostigmine is frequently used for the disorder
* If muscarinic side- effects are prominent, anticholinergic can be administered (e.g. atropine)
* Tolerance usually occurs to the muscarinic side-effects

**2 Reversal of NeuroMuscular Blockade:-**

* By increasing levels of acetylcholine in the NMJ, the compound are able to facilitate recovery from competitive neuromuscular blockade.
* Restore neuromuscular transmission.

 **3. Glaucoma:-**

* Constriction of the ciliary body promotes aqueous humor outflow-🡪 decreased intraocular pressure.
* Direct and indirect cholinomimetics can be used to treat glaucoma
* Pilocarpine is the most commonly used agent
* Typically formulated as eye drops

 **4. Atonic GI/GU:-**

* The smooth muscle of the GI and GU system can show depressed activity in certain states
* Post-operative ileus
* Congenital megracolon
* Bethanechol and neostigmine are the most widely used agents
* Increased secretion and motility in the G.I tract
* Can be given orally or by injection
* These agents cannot be used if there is a mechanical obstruction of the GI or urinary tract.

**QNO 3.(a). EXPLAIN THE EFFECTS AND ADVERSE EFFECTS OF ORGANIC NITRATES IN ANGINA PECTORIS.**

**ANS:- EFFECT OF ORGANIC NITRATES IN ANGINA PECTORIS:-**

The effect of organic nitrates in the optimal medical management of angina are following.

* Organic nitrates are potent vasodilators and are the most widely used antinational agents during acute events.
* They selectively dilate epicardial coronaries and also enhance collateral flow; they also inhibit platelet aggregation.
* Essentially, nitrates dilate – that is, widen or relax the arteries and the veins not only in the heart but also elsewhere in the body.
* By dilating the blood vessels of the heart, nitrates can reduce the stress on the angina by improving blood flow to the angina muscle. This will relieve angina symptoms.

**ADVERSE EFFECTS OF ORGANIC NITRATES IN ANGINA PECTORIS:-**

* Headache is more common with GTN, both sublingual and transdermal preparations.
* Dizziness
* Lightheadedness
* Nausea
* Flushing
* Burning and tingling under the tongue.
* Low blood pressure

**ANS.E.(b). WRITE DOWEN THE TREATMENT ALGORITHM FOR IMPROVING SYMOTOMS OF STABLE ANGINA?**

**TREATMENT OF STABLE ANGINA:-**

A person can treat an episode of stable angina by resting or taking medication if necessary.

However long-term treatment will focus on making changes to reduce the chance of further incidents.

Treatment may include:

**MEDICATION:**

Nitroglycerin is a standard medicine for relieving the pain from stable angina. It relaxes coronary arteries, which reduces the workload of the heart.

Doctors will recommend a specific dosage, depending on a person’s symptoms and overall health.

A doctors may also prescribed medication to treat underlying conditions, such as high blood pressure or high cholesterol, to reduce the risk of an episode.

If doctors believe blood clots are an underlying risk, they may recommend blood thinner to help prevent blockages in the arteries.

**SURGERY:**

An angioplasty is a common surgical procedure used to treat stable angina. It involves locating the problem area in the artery, then adding a permanent stent to widen it and hold it open.

**QNO.4.(a). DIFFERENTIATE BETWEEN PRIMARY AND SECONDARY HYPERTENSION?**

**ANS:-PRIMARY HYPERTENSION:-**

* Primary (essential) hypertension is diagnosed in the absence of an identifiable secondary cause. Approximately 90-95% of adults with **hypertension** have **primary hypertension**.
* Primary hypertension has no single known cause but several mechanisms are linked to altered pathways in BP control. These are genetic factors, diet especially increased salt (sodium chloride) intake, obesity, insulin resistance, endothelial dysfunction, chronic excess alcohol, ageing, stress and sedentary lifestyle.
* The pressure against the blood vessel walls is affected by cardiac output and peripheral resistance. Altered pathways in BP control leads to sustained constriction of the arterioles (microscopic blood vessels in the circulation) resulting in increased peripheral resistance in the blood vessels. As the heart continues to pump normally, the pressure in the whole arterial system rises. This normally has no outward symptoms for the individual, unless very high.
* Constricted, stiff arteriole vessel walls lead to increased pressure from blood flow within the arterioles
* The increased pressure of blood flow against the artery wall leads to damage, resulting in atherosclerotic plaque formation. Signs of prolonged or severe hypertension can be found in target organ damage in the eyes, left ventricle, and kidneys. Presence of target organ damage increases the risk of vascular morbidity and mortality, and the need for treatment to lower blood pressure.

**Secondary Hypertension:-**

* **Secondary hypertension** (**secondary high blood pressure**) is **high blood pressure** that's caused by another medical condition. **Secondary hypertension** can be caused by conditions that affect your kidneys, arteries, heart or endocrine system.
* In secondary hypertension BP is raised due to a known underlying cause:
	+ Renal disorders (e.g. chronic pyelonephritis, diabetic nephropathy).
	+ Vascular disorders (e.g. coarctation of the aorta).
	+ Endocrine disorders (e.g. primary hyperaldosteronism).
	+ Drugs (e.g. alcohol, cocaine)
	+ Miscellaneous causes (e.g. scleroderma, obstructive sleep apnoea).
* A search for secondary hypertension is only suggested by history, physical examination or routine tests indicate abnormalities.
* Investigations for secondary hypertension are not cost effective.

**ANS 4.(b). EXPLAIN THE EFFECT OF RENIN ON HYPERTENSION:-**

* Plasma AGT levels are close enough to the Michaelis constant for **renin** that small increases in either **renin** or AGT may increase Ang II production and alter blood pressure14). Notably, elevated renal-specific expression of AGT causes systemic **hypertension** without a change in circulating Ang II.
* Renin's primary function is therefore to eventually cause an increase in blood pressure, leading to restoration of perfusion pressure in the kidneys. Renin is secreted from juxtaglomerular **kidney** cells, which sense changes in renal perfusion pressure, via stretch receptors in the vascular walls.

ANS 4.(C).IMPORTANCE OF PHARMACOLOGICAL TREATMENT OF HYPERTENSION**:- Hypertension**, or **high blood pressure**, is dangerous because it can lead to strokes, heart attacks, heart failure, or kidney disease. The goal of **hypertension treatment** is to lower **high blood pressure** and protect **important** organs, like the brain, heart, and kidneys from damage.

**Drugs to Treat High Blood Pressure:-**

 There are several types of drugs used to treat high [blood](https://www.webmd.com/a-to-z-guides/rm-quiz-blood-basics) pressure, including:

* Angiotensin-converting enzyme (ACE) inhibitors
* Angiotensin II receptor blockers (ARBs)
* Diuretics
* Beta-blockers
* Calcium channel blockers
* Alpha-blockers
* Alpha-agonists
* Renin inhibitors
* Combination medications

**QNO 5.(a). DIFFERENTIATE BETWEEN RIGHT HEART FAIUR ANF LEFT HEART FAILURE:**

Heart failure is a general term used to describe the failure of the heart’s ability to pump blood effectively around the body. Heart failure can broadly be split into two types – Left and Right ventricular failure

**Left ventricular failure (LVF):**

LVF is an acute life threatening condition. It occurs when the muscle of the left ventricle is strained and it may be the result of a heart attack. The strain on the muscle reduces the efficiency of the left ventricle so that there is backpressure into the left atrium and from there into the lungs. This leads to swelling in the lung tissues (pulmonary oedema) and resulting breathlessness

**Signs and Symptoms of LVF**

* Severe breathlessness (sudden onset)
* Anxiety
* Cough producing frothy sputum (sometimes blood stained)
* Excess sweating.

**Right ventricular failure (RVF)**

Unlike LVF this is a chronic condition, which usually develops slowly. It occurs when the right ventricle is strained and this leads to back pressure in the same kind of way but into the right atrium and the venous system. Oedema (swelling) is usually seen around the ankles but may be on the back if the casualty is in bed for long periods of time.

**Signs and symptoms:-**

* Oedema (swelling) especially in the ankles, shins or lower back
* Nausea & vomiting
* Abdominal pain and distension
* Lethargy and tiredness.

**ANS 5.(b). Summarize the pharmacotherapy of the heart failure.**

Heart failure (HF) affects more than 6.5 million people in the United States and has a 50% mortality rate within five years of diagnosis. The lifetime risk of HF at 45 years of the lifetime risk of HF at 45 years of can result from any structural or functional changes of the heart, leading to the impairment of ventricular filling or ejection of blood. As a consequence, the heart cannot pump blood fast enough to meet the demands of the body.

Typical symptoms of HF include dyspnea and fatigue. The symptoms that present are usually nonspecific to HF but can lead to the review of more specific signs, such as elevated jugular venous pressure or displacement of the apical impulse, and can guide a practitioner to review radiological data consistent with HF.

 Imaging plays an important role in the diagnosis of HF, with echocardiography being the gold standard. Transthoracic echocardiography is the method of choice for assessment of myocardial systolic and diastolic function of both the left and right ventricles.

4 Once the diagnosis is confirmed, the goals of treatment are to improve clinical status, functional capacity, and quality of life; to prevent hospital admission; and to reduce mortality.

In addition to HF type, patients can be assigned a class and/or stage of HF. The New York Heart Association (NYHA) defines four classes of HF

Class I: No physical limitation; ordinary physical activity does not cause HF symptoms

Class II: No symptoms at rest, but ordinary physical activities cause HF symptoms

Class III: No symptoms at rest, but less-than-ordinary physical activities cause HF symptoms

Class IV: Symptoms of HF at rest.

**ACE INHIBITORS:-**

 The ability of ACE inhibitors, such as enalapril and lisinopril, to reduce mortality when taken concurrently with other HFrEF medications has made this class of medications the mainstay for treatment of HFrEF in patients free from any contraindications to their use. ACE inhibitors decrease peripheral resistance and reduce the load on the failing myocardium by inhibiting the conversion of angiotensin I to angiotensin II, thus preventing vasoconstriction and causing relaxation of the vasculature. The efficacy of ACE inhibitors has been proven over several decades. Major trials analyzing ACE inhibitors in HFrEF have utilized them in addition to standards of care such as digoxin, vasodilators, loop diuretics, potassium-sparing diuretics, and beta blockers The CONSENSUS trial, which compared enalapril with placebo in addition to standard of care, showed that enalapril reduced overall mortality risk by 27% and significantly decreased the number of patients with HFrEF progression.

**ANGIOTENSIN RECEPTOR BLOCKERS:-**

 Angiotensin receptor blockers (ARBs) inhibit the renin–angiotensin–aldosterone system (RAAS) by blocking the binding of angiotensin II to its receptor, which in turn leads to vasoconstriction and prevents the release of aldosterone. Although their mechanism of action is similar to that of ACE inhibitors, ARBs do not cause an inhibition of kinase, which reduces the incidence of cough in comparison with ACE inhibitors. The 2016 ACCF/AHA/HFSA guidelines recommend that ARBs be used to reduce morbidity and mortality in patients who are intolerant of ACE inhibitors because of cough or angioedema or in patients who are tolerating ARBs for another indication. In addition, the 2016 guidelines recommend that ARBs be used with caution in patients with a history of angioedema with ACE inhibitors because of the risk of cross-reaction. For patients with HFrEF NYHA class II or III, the guidelines recommend replacing ARB therapy with an ARNI, which will be discussed later in this article.

**BETA BLOCKERS:-**

 The beneficial effect of beta blockade in HFrEF has been documented for more than 40 years.22 since 1975, data have shown that the use of bisoprolol, carvedilol, or sustained-release metoprolol succinate reduces morbidity and mortality in patients with HFrEF. These are the only beta blockers tested in large clinical trials to show a mortality benefit, which led to their inclusion in the HF guidelines as first-line agents in all patients with HFrEF to reduce morbidity and mortality unless contraindicated.3,23–25 These three agents share a common pathway: They all block the β1-adrenergic receptor located on the heart. HFrEF stimulates the RAAS and sympathetic system in order to compensate for the reduced EF. However, this activation may accelerate ventricular remodeling. By blocking β1 receptors, these beta blockers prevent ventricular remodeling promoted by the stimulated RAAS and sympathetic system. While metoprolol and bisoprolol are selective for the β1 receptor, carvedilol also blocks the β2 and α1 receptors, leading to vasodilation. Beta blockers should be initiated at low doses and titrated slowly to target doses if tolerable (Table 1). Adverse events include fluid retention and worsening HFrEF, fatigue, bradycardia or heart block, and hypotension.

ALDOSTERONE ANTAGONISTS Aldosterone receptor antagonists (also called mineralocorticoid receptor antagonists [MRAs]) are recommended for NYHA class II–IV HF patients with an EF of 35% or less, glomerular filtration rate of at least 30 mL/min/1.73 m2, and a potassium level of 5.0 mEq/dL or lower.3 Studies have demonstrated that aldosterone receptor antagonists (when given in conjunction with ACE inhibitors and beta blockers) reduce the risk of morbidity and mortality in patients with NYHA class III–IV HFrEF with an EF of 35% or less.27,28 Further studies found similar benefits in NYHA class II HFrEF patients with an EF of 35% or less.29. Two aldosterone receptor antagonists are available in the United States—spironolactone and eplerenone. Spironolactone is a nonselective aldosterone antagonist, while eplerenone is selective to the aldosterone receptor.30, 31 Aldosterone is an endogenous steroid hormone that increases sodium retention and facilitates magnesium/potassium loss. Aldosterone may ultimately cause myocardial fibrosis, vascular injury, direct vascular damage, and baroreceptor dysfunction leading to the development and progression of HFrEF.

**DIURETICS:-**

 Although no data have shown that they reduce mortality or hospital readmission, diuretics are the only agents that can adequately control the fluid retention associated with HFrEF. Unless contraindicated, diuretics are recommended in all HFrEF patients with fluid retention to improve symptoms. Diuretic use is generally combined with moderate dietary sodium restriction.3 Loop diuretics, such as furosemide, are the preferred diuretic agents for most HFrEF patients.3 Loop diuretics work at the thick ascending limb of the loop of Henle to inhibit sodium and chloride reabsorption.38 In comparison, thiazide diuretics are less potent and thus have a less significant effect on fluid retention/edema. Adverse effects of diuretics include fluid depletion, hypotension, azotemia, and depletion of sodium, potassium, magnesium, chloride, and calcium. Typical monitoring parameters for these agents include daily weight and blood pressure measurements, and periodic monitoring of renal function.

**VASODILATORS:-**

 Vasodilators have been shown to reduce mortality in patients self-described as African-Americans with NYHA class III–IV HFrEF. They are also recommended to reduce morbidity and mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.6 both hydralazine and isosorbide nitrate have vasodilatory effects. Isosorbide dinitrate causes a release of nitric oxide that relaxes vascular smooth muscle, affecting both arteries and veins. In comparison, hydralazine works to selectively relax arterial smooth muscle and may minimize nitrate tolerance. A 1986 trial demonstrated that the one-year mortality rate for the hydralazine and isosorbide dinitrate treatment group was 38% lower than the placebo control group.9 Furthermore, a study that analyzed hydralazine and isosorbide dintirate treatment specifically in black patients found a 43% reduction in relative mortality risk and a 33% reduction in first HFrEF hospitalization compared with placebo.

**DIGOXIN:-**

 Digoxin has been shown to decrease the rate of HFrEF-related hospitalizations when used in addition to standard of care. Digoxin is a cardiac glycoside that has been used for more than 200 years. It inhibits the sodium–potassium ATPase pump, causing positive inotropy (increasing force and velocity of myocardial contraction) and deactivating neurohormonal effects (decreasing sympathetic and RAAS responses). Despite extensive use of digoxin, its role and utility in chronic HF have been controversial. However, various studies have elucidated the effects of digoxin on morbidity and mortality in HFrEF patients. HFrEF patients on digoxin who were switched to placebo showed a significant worsening of HF compared with those who continued to receive digoxin therapy (relative risk, 5.9; P < 0.001).

**IVABRADINE:-**

 Ivabradine is a heart-rate–reducing agent approved in the U.S. in 2015 for use in patients with HFrEF. It is indicated in patients with stable, symptomatic, chronic HF with an EF of 35% or less and a resting heart rate greater than 70 beats per minute (bpm).52, 53 it is an inhibitor of the “funny current” or (f) channel. The (f) channel controls heart rate through modulation of autonomic neurotransmitters, such as epinephrine. Specific blockade of these channels removes the contribution (f) has on pacemaker depolarization and thus slows the heart rate. 54 . Ivabradine was evaluated in a randomized, placebo-controlled trial to determine whether lowering a patient’s resting heart rate leads to a reduction in cardiovascular death or hospital admission for worsening HF. At baseline, 89% of the patients randomized to the ivabradine group were taking a beta blocker, 79% were taking an ACE inhibitor, 14% were using an ARB, and 22% were taking cardiac glycosides, such as digoxin. The study enrolled patients who had an EF of less than 35% and were in sinus rhythm with a heart rate of 70 bpm or higher. Twenty-four percent of patients in the ivabradine group versus 29% of patients in the placebo group had a primary endpoint event (HR, 0.82; 95% CI, 0.75–0.90; P < 0.0001).55 A subgroup analysis showed that the effects of ivabradine are related to the patient’s heart rate.

 **SACUBITRIL/VALSARTAN :-**

 ARNIs are a new class of medications that may have a growing role in HF treatment. Sacubitril/valsartan is a novel therapy approved in July 2015 to reduce the risk of cardiovascular death and hospitalization for patients with HFrEF (NYHA class II–III). Sacubitril/valsartan consists of the neprilysin inhibitor sacubitril and the ARB valsartan. Neprilysin is a neutral end peptidase that metabolizes endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and substance P into their inactive metabolites. Inhibition of neprilysin increases the levels of these substances and decreases vasoconstriction, sodium retention, abnormal growth, and remodeling.5 However, angiotensin II is also a substrate of neprilysin. Thus, the addition of an ARB to the neprilysin inhibitor is necessary to prevent activation of the RAAS.

**THE END**