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A review on Parkinson's disease

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ABSTRACT:
Parkinson's disease is a progressive neurodegenerative movement disorder. In the Parkinson's disease a motor and non motor symptoms are affect movement, balance, and mental health and memory problems. Thesedisease divided infivestages. In 1967Hoehn andYahr are defined five stages of Parkinson's disease the level of clinical disability. Thepathologically the movement of disorder occurs due to the loss of dopaminergic neurons in the substantia nigra parscompacta. It is a loss of nigrostriatal dopamine. The certain drugs are helps to boost dopamine level such as a levodopa acetylcholine. One surgical option is deep brain stimulation. Dopamine receptors are large g-protein couple receptor. This receptor has five subtypes are including D1, D2, D3, D4, D5. These subtypes are extra divided intosubclasses D1like family receptor and D2like family receptor for the different pathways and function of dopaminergic hormone and the four major dopaminergic pathways is anigrostriatal, mesolimbic, and mesocortical and tuberoinfundibular pathways. The current drug treatment for Parkinson's disease is a dopamine agonists and levodopa.

KEYWORDS: Parkinson's disease, pathophysiology, motor-nonmotor symptoms, deep brain stimulation therapy, dopamine, dopamine receptor, dopaminergicpathways, dopamine agonists, levodopa.

I. INTRODUCTION:

Parkinson's disease (PD), or simply Parkinson's disease, is a chronic degenerative disease of the central nervous system that affects both the motor and non-motor systems. The motor symptoms of the disease caused death of nerve cell in the substanita nigra, a region of midbrain that supplies dopamine to the basal ganglia. The result of this cell death is poorly understood but the proteinalpha-synuclein into lewy body into the neurons. The motor symptoms parkinsonian syndrome or Parkinsonism. The non motor symptoms are mostly common symptoms are like anxiety, sleep disorder, dysfunction.Non-motor symptoms are common in Parkinson's disease (PD) and are often unrecognized by clinicians, but have a significant impact on disability and health-related quality of life, especially in advanced disease . Autopsy studies in Parkinson's disease have provided us with important insights into the possible pathological basis of these non-motor features. According to the Hoehn and Yahr scale was described in1967 five stages of Parkinson's disease on the basis of clinical disability. The first and second stage is identify early stage. Second and third stage is mid stage and four and five are advanced stage of Parkinson's disease. Dopamine is a brain hormone that acts as a neurotransmitter. It is Produced in an area of the brain called the substantia nigra. There is also Produced in other parts of the brain, such as the ventral tegmental area And the hypothalamus. C8H11NO2 is the chemical formula of dopamine. Differential Diseases of the nervous system are caused by abnormal functioning Of dopamine. Dopamine is increased in the brain by drugs Function inAnd in response to happiness. The brain controls body movementsunder the influence of dopamine . Understand like dopamine Regulates brain activity in controlling body movement, It Can identify some important treatments for brain-related diseases such as Such as Parkinson's disease (PD) and some psychiatric disorders. Social The importance of dopamine as a neurotransmitter in the brain plays an important role in need- and habit-related abuse. Positron in living patients Emission tomography (PET) is used to demonstrateavailability. Dopaminergic ligands and dopamine loss in PD patients. There are five subtypes of dopamine receptors, including D1, D2, D3, D4 and D5, which are a superfamily of receptors associated with large G-protein couple receptor. There are four major pathways in

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theDopaminergic system, the nigrostriatal, mesocortical, tuberoinfundibular, and mesolimbic pathways .the currently drug treatment for Parkinson's disease is a levodopa and dopamine agonists. These drugs areincreased dopamine activities in brain. Dopamine agonists and levodopa is the different types of drugs. The dopamine agonists imitate effects of dopamine without converting. The levodopa is converted in brain into dopamine.

PATHOPHYSIOLOGY: Parkinson's disease is increasingly seen complicated neurodegenerative disease. This disease is arising insufficient of dopamine in substanita nigra, a region concerned with regulation of movement. Physiologically, the symptoms associated with Parkinson's disease are caused by the loss of several neurotransmitters, especially dopamine. Symptoms worsen over time as more and more cells affected by the disease are lost. The course of the disease is highly variable, with some patients having very few symptoms as they age, while others have rapidly progressive symptoms. Parkinson's disease is increasingly recognized as a complex progressive neurodegenerative disease. There is strong evidence that it first affects the dorsal motor nucleus and olfactory bulb and nucleus, then the locus coeruleus, and finally the substantia nigra.

The main pathological features of Parkinson'sdisease are cell death in the brain and basal ganglia (affecting up to 70% of dopamine-secreting neurons in the substantia nigra pars compacta at the end of life).In Parkinson's disease, alpha-synuclein disarrange and sticks together with other alpha-synuclein. Cells are unable to remove these fragments, and alpha-synuclein becomes cytotoxic and damages cells. These lumps can be seen in neurons under a microscope these are called Lewy bodies. Neuronal loss is accompanied by the death of astrocytes (star-shaped glial cells) and an increase in the number of microglia (another type of glial cell) in the substantia nigra. The severity of progression of the parts of the brain affected by Parkinson's disease can be measured using braak stage. According to this phase, Parkinsondisease begins in the nucleus accumbens and olfactory bulb before moving into the substantia nigra pars compacta and the rest of the midbrain or forebrain. Movement symptoms begin when the disease begins to affect the substantia nigra pars compacta

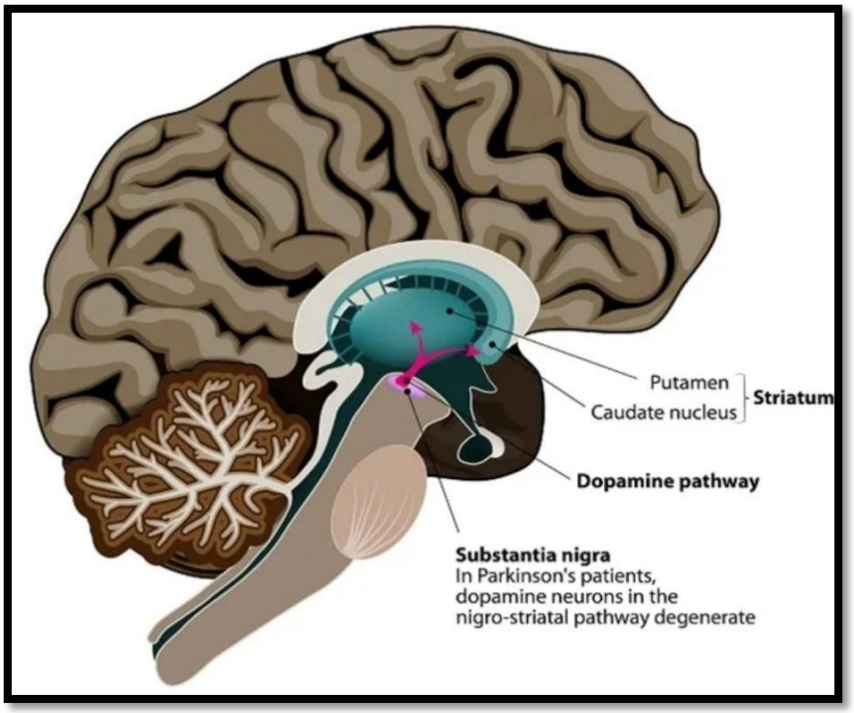

Figure:-pathophysiology of Parkinson's disease

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STAGES OF PARKINSON'S DISEASE:

In 1967, are published Hoehn and Yahrscale for five stages of Parkinson's disease on the basis of clinical disability?

1] The first stage –

In this initial stage, the person has mild symptoms that usually do not interfere with daily activities. Tremors and other movement symptoms occur only on one side of the body. There are changes in body position, gait and facial expressions.

2] Thesecond stage –

In this stage symptoms begin to worsen. Tremors, stiffness and other motor symptoms affect both sides of the body or the midline (example - neck and trunk). Problems with walking and poor posture may occur. A person can live alone, but daily tasks are more difficult and longer.

3] The third stage –

In the mid-stage view, there is a characteristic loss of balance (example -instability when turning the person or standing). Falls are more common. Motor symptoms continue to worsen. The person is somewhat functionally limited in their daily activities, but is still physically able to live an independent life. At this stage, the disability is mild or moderate.

4] The fourth stage –

At this stage, the symptoms are fully developed and cause severe disability. The person is still able to walk and stand without assistance, but may need to use a cane or walker for safety. A person needssignificant help in everyday life and cannot live alone.

5]The fifth stage –

This is the most advanced and exhausting stage. The stiffness of the leg can make it impossible to stand or walk. The person is in bed or in a wheelchair unless help is available. All activities require 24/7 care

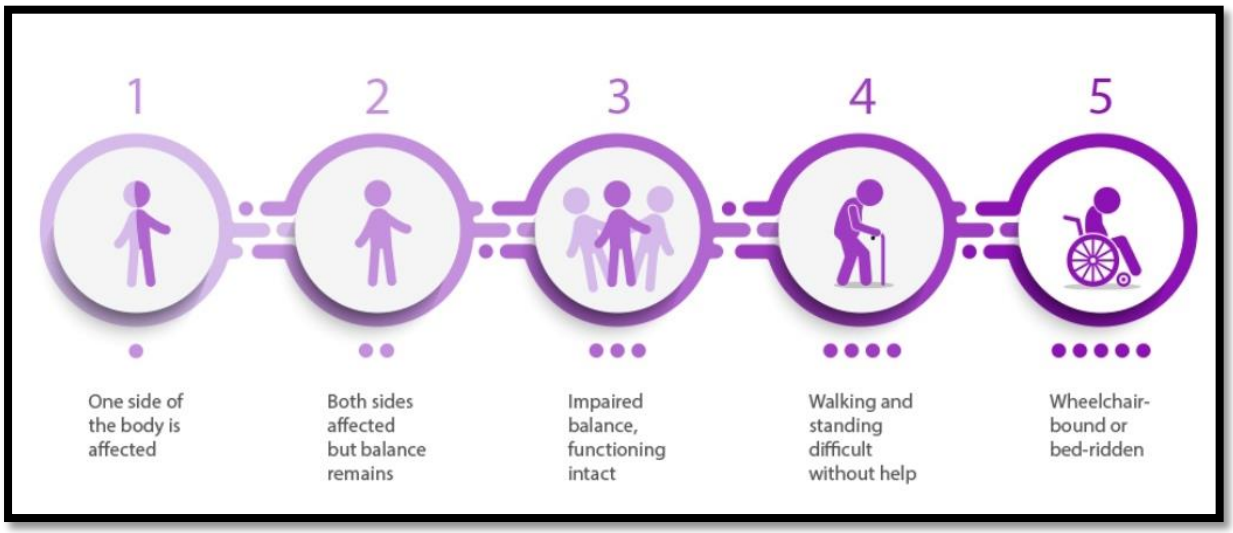

Figure : five stages of Parkinson's disease

SYMPTOMS :

The Parkinson's disease is a brain disorder causes uncontrolled movement. Or difficulties in balance and coordination. These are two types of symptom one is motor symptoms and non motor symptoms

1] Motor symptoms –Motor symptoms affect movement and balance. It is important to remember that the progression of symptoms varies from person to person and most people experience only a few of them.

1]Tremor
2]Rigidity (stiffness)
3]Slowness of movement
3]postural instability
4]Bradykinesia
5]Dystonia and muscle cramps,
6]vocal symptoms

2]Nonmotor symptoms –Non-motor symptoms of Parkinson's disease do not affect movement. These include other problems such as mental health, memory problems and pain.

1]Pain , fatigue, sweating
2]Low blood pressure
3]Restless legs, eye problems,
4]Bladder and bowel problems
5]Sleep ,eating, swallowing and saliva control

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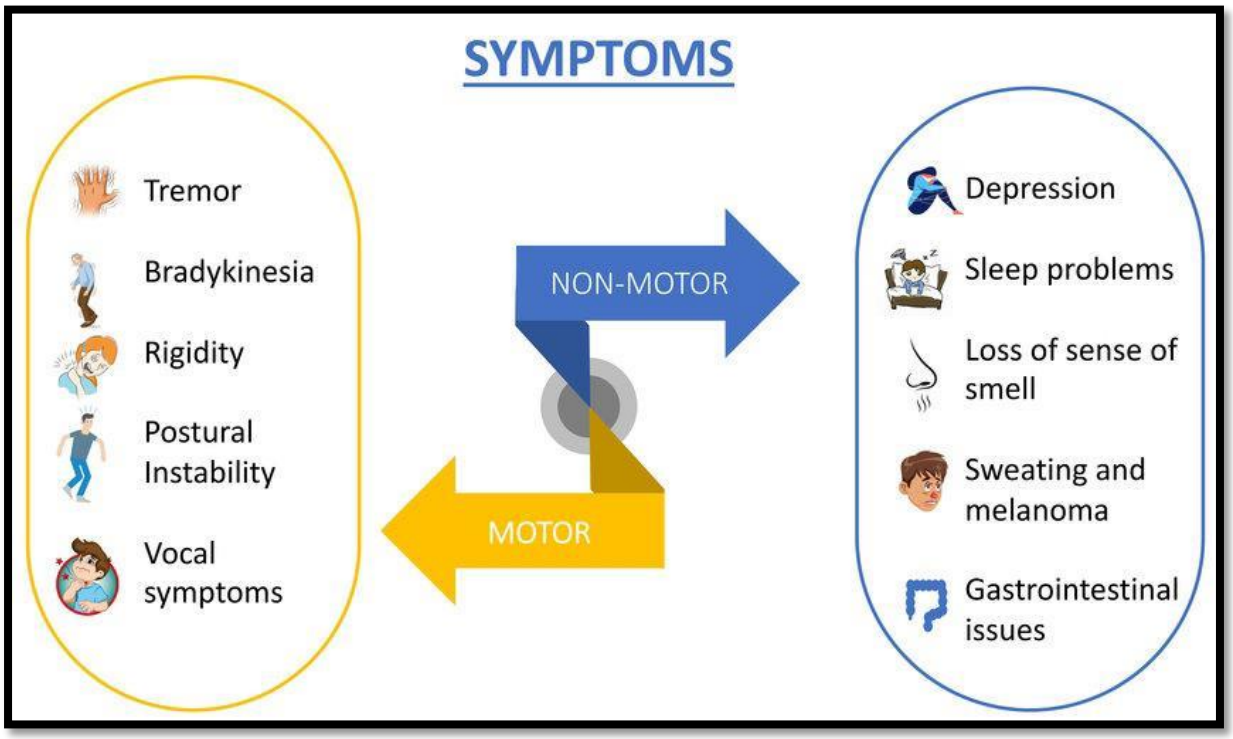

Figure : motor and non motor symptoms of Parkinson's disease

PHARMACOLOGICAL TREATMENT AND THERPIES OF PARKINSON'S DISEASE:

1]Deep brain stimulation

the deep brain stimulation is the powerful surgical therapy. This therapy is mostly impact on the movement of symptoms in Parkinson's disease and the certain side effects are caused by the medication. This therapy is also beneficial in the non motor symptoms of Parkinson's disease. In this therapy the electrodes are insert into a targeted region of brain using the magnetic resonance imaging(MRI) and at a time during the procedurethe brain cell activities was recorded. The second stage of the procedure is performed to insert impulse generator battery called IPG is same as heart pacemaker. IPG is place in the collarbone or in unusual and delivers electrical stimulation to targeted regionin the brain control movement. Those who have undergo this therapy are giving controller to turn the device shut and down. The brain surgery like deep brain stimulation have result a small risk of infection andbleeding or seizure. The deep brain stimulation therapy is a damage healthy brain tissue anddestroy nerve cells. A critical element in determining successful surgical issues for casesWith PD is having the support of a multidisciplinary platoon that specializes in theCare of cases with DBS bias. This platoon generally includes a neurologist .Is a specialist in movement diseases, a neuropsychologist who has excellentKnowledge of PD and itsnon-motor features, and a neurosurgeon who has aSpecialty training in stereotactic and functional neurosurgery. Since DBS for PDWas approved by the food and drug administration , there has been a growing trend for DBS surgery to bePerformed at lower hospitals with lower volumes of movement complaint surgery.Large, database studies examining the National Inpatient Sample(NIS) have dem-Onstrated that patient issues after DBS surgery for PD are more .when theseOperations are performed at hospitals with moderate or high volumes for these procedure.

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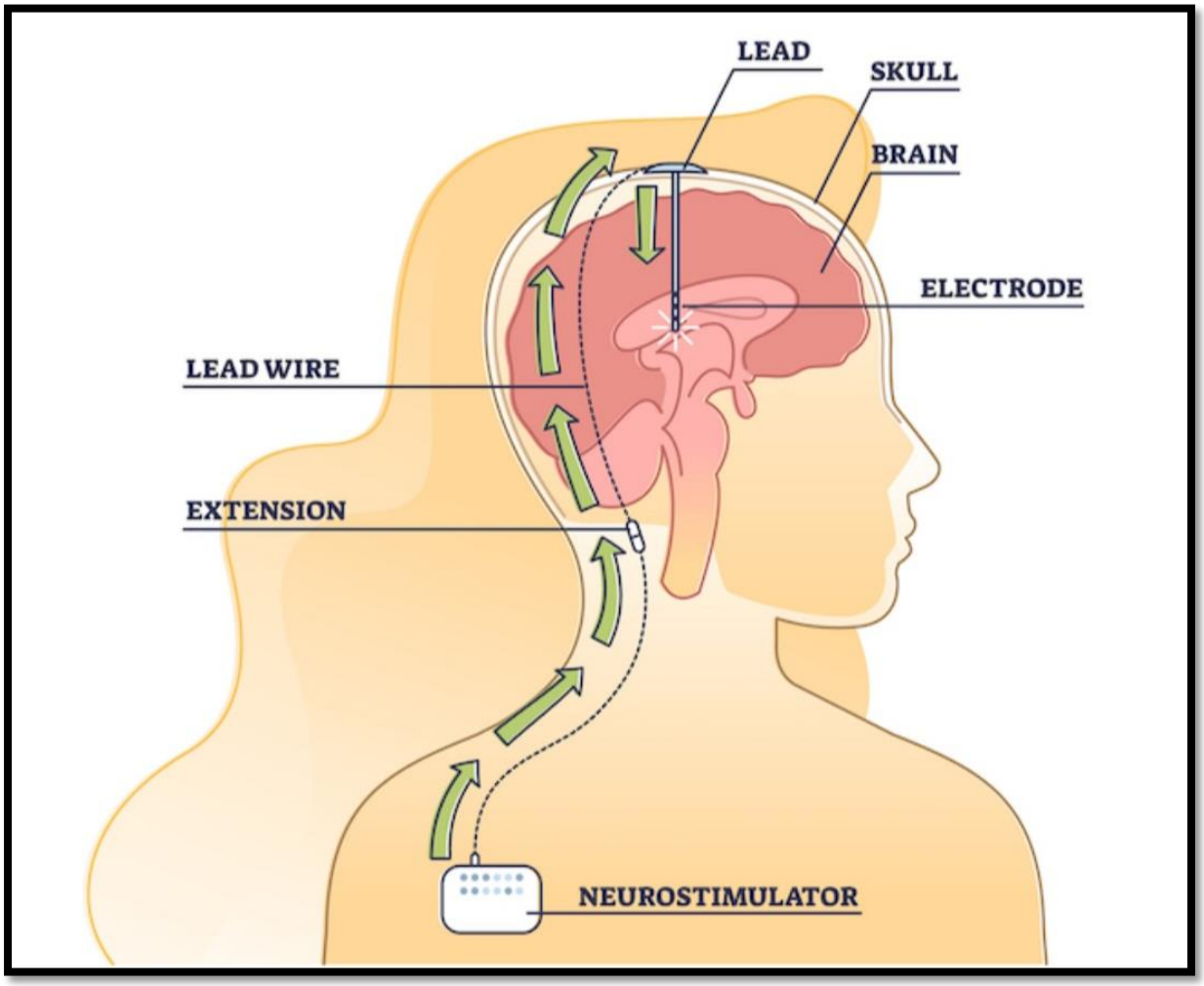

Figure : deep brain stimulation therapy

DRUG TRETMENT :DOPAMINE

Dopamine is a brain hormone that acts as a neurotransmitter. It is Produced in an area of the brain called the substantia nigra. There is alsoProduced in other parts of the brain, such as the ventral tegmental area And the hypothalamus. C8H11NO2 is the chemical formula of dopamine. Differential Diseases of the nervous system are caused by abnormal functioning Of dopamine. Dopamine is increased in the brain by drugs And in response to happiness. The brain controls body movements Under the influence of dopamine . Understand like dopamine Regulates brain activity in controlling body movement, It Can identify some important treatments for brain-related diseases such as Such as Parkinson's disease and some psychiatric disorders. The importance of dopamine as a neurotransmitter in the brain plays an important role in need- and habit-related abuse. Positron in living patients Emission tomography (PET) is used to demonstrate availability.

DOPAMINE RECEPTOR :

Dopaminergic ligands and dopamine receptor loss in Parkinson'sdisease patients. There are five subtypes of dopamine receptors, including D1, D2, D3,D4 and D5, which are a superfamily of receptors associated with large protein (G protein). These subtypes are further divided into two subtypes Classes, D1-like family receptors (types 1 and 5) and D2-like family Receptors (type 2, 3 and 4).

D1like family receptor – type 1and 5
D2like family receptor- type 2,3and 4

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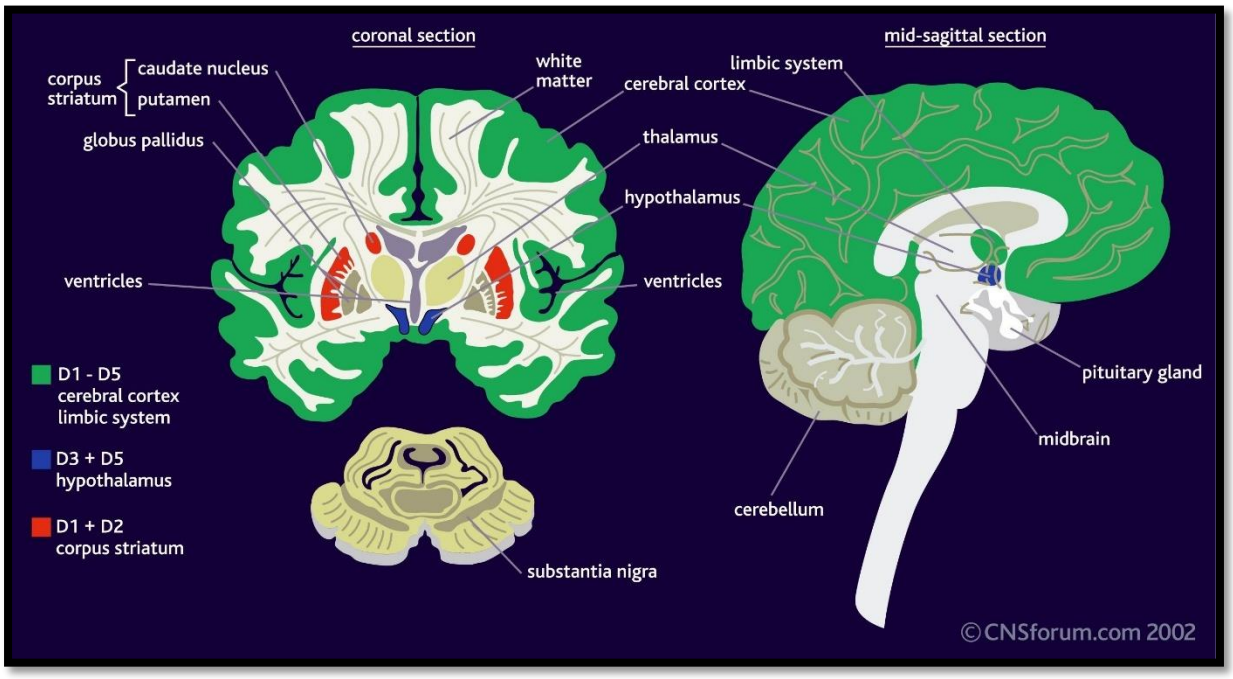

Figure : cellular function of dopamine receptor

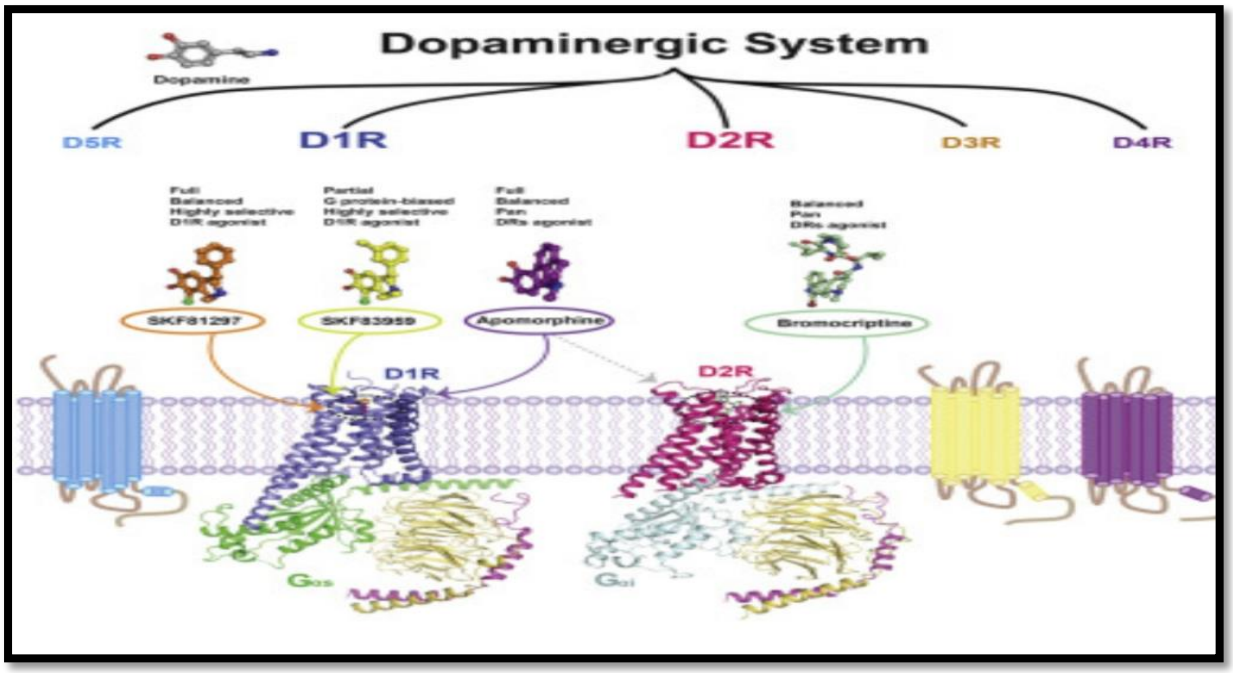

Figure : Dopaminergic receptor system

1]D1like family receptor- D1like receptor consistingD1R and D5R. It is a subfamily of dopamine. That are binding to the endogenous neurotransmitters dopamine. TheD1like subfamily receptor consists g-protein couple receptor And the two G-protein couple receptor are couple to Gs and mediateexcitatory neurotramission include in D1and D5.This receptor are stimulate effecton adenylate cyclase.

2]D2like family receptor - D2like family receptor consisting D2R, D3R, D4R are the subfamily of dopamine. It is ag protein couple receptor. Couple

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to Gi/o and mediate inhibitory neurotransmitter includes D2, D3,D4 . This receptor is inhibiting the adenylatecyclase activity.

DOPAMINERGICPATHAWAYS :

The human being brain are involved in behaviour and physiological process includingmovement, motivation, control of movement.Dopamine is a neuromodulatorhormone or molecule. Dopamine has four major pathway. Each pathways are included in dopamine formation. The four main dopaminergic pathways are the mesolimbic pathway, the mesocortical pathway, the nigrostriatal pathway, and the tuberoinfundibular pathway. The mesolimbic pathway and the mesocortical pathway make up the mesocortical system. Two other dopaminergic pathways to consider are the hypothalamospinal pathway and the incertohypothalamic pathway. The dopamine neurons of the dopaminergic pathways synthesize and release the neurotransmitter dopamine. Enzymes tyrosine hydroxylase and dopamine decarboxylase are required for dopamine synthesis. These enzymes are both produced in the cell bodies of dopamine neurons. Dopamine is stored in the cytoplasm and vesicles in axon terminals. Dopamine release from vesicles is triggered by action potential propagation-induced membrane depolarization.The axons of dopamine neurons extend the entire length of their designated pathway.

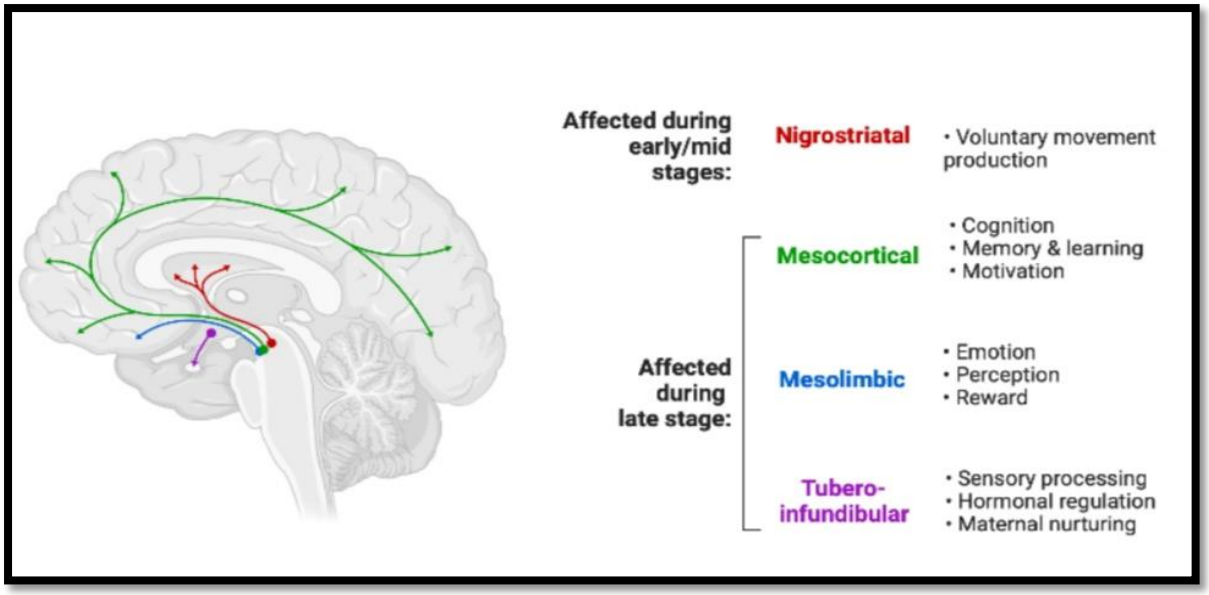

Figure : Dopamine pathways affected by Parkinson's disease

1]Nigrostriatal pathway–nigrostriatal pathway are affected in early and mid stage of Parkinson's disease. The nigrostriatal pathway is a bilateral dopaminergic pathway in the brain that connects themidbrain substantia nigra pars compacta with the dorsal striatum (ie, the caudate and putamen) of the forebrain. It is one of the four main dopamine pathways in the brain and is critical for generating movement in a system called the basal ganglia motor circuit. Dopaminergic neurons in this pathway release dopamine from axon terminals that synapse on GABAergic medium spiny neurons (MSNs), also known as spiny projection neurons (SPNs), located in the striatum. Degeneration of dopaminergic neurons in the Substantia nigra pars compacta is one of the main pathological features of Parkinson's disease, leading to a marked decrease in dopamine function and the motor deficits characteristic of Parkinson's disease, includehyperkinesia, tremor, rigidity and postural imbalance. Nigrostriatalpathwayare influence brain works.

2]Mesocorticolimbic pathway–The Mesocorticolimbic pathway consists of two dopaminergic pathways: the mesolimbic and the mesocortical pathway. The mesolimbic pathway is characterized by dopaminergic projections from the ventral tegmental area. To the nucleus accumbens and olfactory tubercle and is involved in reward processing. Preclinical studies emphasize its involvement in reward and reinforcement, and atypical development of this pathway has been

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implicated in attention deficithyperactivity disorder(ADHD) and addiction in humans. Preclinical maternal high fat diet studies have detailed decreased neuronal innervation associated with important neurotransmitter systems. Both serotonin and dopamine innervation are reduced in anterior regions involved in inhibitory control in maternal high fat diet offspringThis reduction is associated with impaired inhibition, which supports results from animal models showing that subjects consume greater amounts of palatable foods and addictive substances.

1)Mesocortical pathway - mesocortical pathway are affected in the last stage. That are affected on the memories, learning and motivation. The mesocortical pathway is characterized by dopaminergic projections from the ventral tegmental area to the prefrontal cortex.

2) Mesolimbic pathway –mesolimbic pathway are originated in ventraltegmental area. Of the brain. This pathway consist dopaminergic neurons. This is last stage of dopaminergic pathway. That affected the emotion.

4]Tuberoinfundibular pathway –the tuberoinfundibularpathway is the major dopaminergic pathway in the brain. This pathway is affected in the last stage of Parkinson's disease. In this pathway are secretion of prolactin by the pituitary gland.

CURRENT TREATMENTS –There are presently no complaint- modifying medicines for Parkinson's disease but the treatments that areUsed can offer significant characteristic relief of the motor symptoms. They offerLittle clinical benefit in terms of then non-motor instantiations of Parkinson's disease. It's usualPractice to delay the inauguration of treatment until the case's symptoms comedisquieting, to reduce the impact of adverse effects.

LEVODOPA –

The dependence of current PD treatment are levodopa- grounded medications, designed .To replace the dopamine in the depleted striatum. As is described over, dopamine itself is unfit to cross the blood brain barrier and can not be used to treat PD.In contrast, the dopamine precursor levodopa is suitable to cross the blood brain barrier and can beAdministered as a remedy. After immersion and conveyance across the blood brain memory, it's converted into the neurotransmitter dopamine by DOPA decarboxylase. It's usual practice for cases to be commenced on a low cure of levodopa, withThe cure being titrated up grounded on the case's response to treatment, balancedAgainst the adverse goods endured. Utmost cases bear a cure in the rangeOf 150 – 1000 mg daily, divided into multiple boluses. Adding boluses affect inElevated threat of developing problematic adverse goods, as bandied below. Generally, the clinical effect of levodopa is noticed snappily, and may last for severalHours, particularly in the early stages of complaint .Still, as complaint becomesMore advanced, the effect of the medicine generally wears off after shorter durations, And an increased frequency of dosing is frequently needed. Levodopa, though effective, comes with significant side goods that constituteAn important part of the illness endured by the case, particularly inAdvanced complaint. Some of its associated side goods affect from the conversion ofLevodopa to dopamine outside the CNS(supplemental conversion) by DOPA decarboxylase. These goods are minimized by administering levodopa in combination with supplemental impediments of DOPA decarboxylase, as is bandied below. Dragged use can affect in significant motor complications, including dyskinesia's, and severe on – off motor oscillations.

DOPAMINE AGONIST – Dopamine receptor agonists came into the request for the treatment of PD in1978. The generally used agonists contain an ethanolamine half, and theyMay be distributed into ergot and non-ergot deduced, grounded on receptor specificities. These medicines stimulate the exertion of the dopamine system by the binding to the dopaminergic receptors and, unlike levodopa, don't need to beConverted into dopamine. Dopamine agonists are frequently specified as anOriginal remedy for Parkinson's disease, particularly in youngish cases. This approachAllows for a detention in the use of levodopa, which may reduce the impact of theProblematic motor complications, bandied over. Some of the medicines are no longer used in clinical practice, as significant idiosyncraticAdverse goods were observed. For illustration, pergolide(act as dopamine receptor agonist) was withdrawn as a treatment in 2007, after studies set up that it was associated with a threat of pericardial, Retroperitoneal, and pleural fibrosis .Some of these medicines are available in controlled or dragged release formulations in the form of tablets, patches, and injections.

The treatment with dopamine agonists has been shown to affect in a reduced incidence and inflexibility of dystonia, motor oscillations, and dyskinesia in comparisonto livodopa.Still, they may beget other severe adverse goods ,Common

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side goods include nausea and vomiting(which occurs due to stimulation of the area postrema, positioned in the medulla at a point in which the BBB isDisintegrated), dry mouth, wakefulness, supplemental edema, constipation, fainting, hallucinations, and somnolence .Maybe, the most important adverse effect of dopamine agonists is the development of obsessive and impulsive behavioural problems(impulse control disorder(ICD)). Symptoms may include hyper sexuality, gambling, binge eating, Obsessive buying/ shopping, , and hobbyist(obsessive Internet use, Cultural trials, and jotting. It's important that clinicians are watchfulFor similar problems after inauguration of dopamine agonists. Another important consideration is the threat of dopamine agonist pull out Pattern dopamine agonists withdrawal syndrome (DAWS), which may do when a person with obsessive or impulsive geste either stops taking or reduces the lozenge of dopamine agonists .Symptoms of pullout pattern may include anxiety, fear attacks, wakefulness,Perversity, dysphoria, agitation, fatigue, orthostatic hypotension, diaphoresis, andMedicine cravings.

II. CONCLUSION :

Parkinson's disease is one of the most common neurodegenerative diseases in the aging population and is associated with increased morbidity and mortality. Awareness of disease manifestations, treatment methods, and long-term disease progression is essential for optimal case management. Great progress has been made in understanding the neuropathology of PD and its progression throughout the nervous system. Because dopamine is a neurotransmitter, it has low concentrationsBlack matter prevents the transmission of nerve impulses and The brain cannot transmit signals in the right way. Therefore there is a loss Relationship between the brain and other parts of the body. Loss of dopamine leads to loss of control of body movements. Dopamine is a chemical in the brain whose concentration is directly linked to PD. There are five subtypes of dopamine receptors, D1, D2, D3, D4 and D5. These subtypes are further divided into two subclasses of the D1 type family Receptors (type 1 and 5) and D2-like receptors (type 2, 3 and 4). Suppression of prolactin production, movement, behaviour, motives Giving, punishment, learning, reward, cognition, attention, dream, Different functions are related to working memory, mood and sleep. Formed by dopamine. Dopamine is formed by four main pathways . The loss of dopamine are causes Parkinson's disease. As the Parkinson's disease Progress to the advanced stage, care becoming increasingly difficult. Sleep disorders, gastric dysfunction, and a lost of other difficulties this challengesand research in feverish pace. Current treatments for PD are designed to restore dopaminergic activity in the dopamine depleted striatum of PD patients, resulting in improvement of motor symptoms. Unfortunately, there are few drug options for the treatment of non-motor symptoms of the Parkinson's disease. The current drug treatment is dopamine agonists and levodopa.

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