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Latest Progresses and Methods used to Treat Parkinson's Disease

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Abstract:- Millions of people throughout the world are affected by Parkinson disease (PD), which is a prevalent neurological ailment. The illness is now understood to be heterogeneous and to manifest both motor and non-motor symptoms. The latest study reveals that men are more likely than women to develop Parkinson's disease and that the number of people with the diagnosis rises with age regardless of sex. There have been significant improvements in PD pathophysiology, etiology, and treatment. Depending on the progression and stage of the disease, many surgical techniques are available that can improve the condition of PD patients This article offers a summary of our current knowledge on Parkinson's disease (PD), including its pathology, genesis, recent developments, clinical research review, and case studies of patients to assess how treatments and drugs affect them. Latest translation studies are aimed into understanding the disease pathogenesis and pathophysiology and in many areas translational research on this has catalysed a better understanding of basic biological phenomena including intrinsically disordered proteins autophagy mitochondrial function homeostatic plasticity and basal ganglia physiology. This review focuses on compiling all the fundamental data and therapies available in medical research for the relief of symptoms and suggested therapies proven successful in PD. We also provided an overview of Parkinson's clinical trials and the effects of Parkinson medication in animal models. The most recent developments and trends in PD were also covered, including information on biomarkers, sexual differences, cell therapy, genetic relationships, and improvements in PD study models.

Keywords:- *Parkinson's disease, Cognitive behavioural therapy, deep brain stimulation, chemotherapy, patient counselling.*

I. INTRODUCTION

A. Parkinson:

Parkinson's disease is a progressive neurodegenerative condition that weakens and/or kills the nerve cells (or neurons) in the part of the brain that regulates movement.

Weakened neurons produce lower quantities of dopamine than healthy neurons do, despite the fact that the brain requires a specific quantity of dopamine to control movement.

Norepinephrine, a substance that sends information across nerve endings and regulates numerous activities, including blood pressure and heart rate, is depleted in some Parkinson's disease patients.

Parkinson's disease presently affects more than 10 million people globally, and this year, there will be close to 1 million cases in the US. Annually, 60,000 Americans receive a PD diagnosis, and more than 10 million people worldwide suffer from PD. Parkinson's disease is more common as people get older, although just 4% of cases are discovered before age 50, according to estimates [1].

B. Objective of the article:

The latest study reveals that men are more likely than women to develop Parkinson's disease and that the number of people with the diagnosis rises with age regardless of sex. The last significant study on the prevalence of PD was finished in 1978.

According to the latest study, there are regional differences in the prevalence of PD diagnoses.

Researchers on the study will now spend more time figuring out how.

To raise awareness among the public, it is important to talk as much as possible about the rising incidence of mental illnesses.

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People with Parkinson's who seek professional care have better outcomes, fewer complication risks, and can live longer, more fulfilling lives. Parkinson's disease patients can recover and avoid incapacitating symptoms, but any danger or delay might result in the patient suddenly losing the ability to move, walk, or speak.

The goal of this review is to inform readers on all available PD treatments, raise public awareness of the importance of mental health, and draw the pharmaceutical industry's attention to the pressing need to address Parkinson's disease [2].

C. How to identify if it happens?

Tremor, rigidity, postural instability, unstable eye movements, dementia, and autonomic dysfunctions are symptoms. Depression, cognitive impairment, sleep issues, hypertension, type 2 diabetes, blood volume reductions, and many other clinical symptoms also appear in later stages [2, 3].

D. How does it take place?

Numerous factors contribute to the growth in Parkinson's. The number of causes and contributing factors for PD is growing as the disease does. Environmental, genetic, chemical, or other unidentified causes could be to blame. In light of recent studies:

- Elderly population
- By industrial byproducts including toxic metals, solvents, and pesticides.
- substances like trichloroethylene that are neurotoxic (semiconductor industry)
- Parkinson's disease has also been linked to smoking.
- Parkinson's disease (PD) is known to be greatly influenced by genetic variables and genes such as α-synuclein (SNCA), parkin, leucine-rich repeat kinase 2 (LRRK2), PTEN-induced putative kinase 1 (PINK1), and DJ-1.
- biological factors: basal ganglia neural network faults, sophisticated neurosurgery techniques, aberrant synchronus oscillating neuronal activity in the basal ganglia, and cortical loops [4].

E. Concise etiology of the disease:

Genetical susceptibility + environmental toxins + other factors → pathogenesis → mitochondrial dysfunction (inflammation) + oxidative stress (excitotoxicity) + protein aggregation →ultimately leads to apoptosis (cell death).

F. Chemotherapy for the disease:

Parkinson disease treatment will depend on a wide range of variables; while the diseases and symptoms are generally the same, they vary to varying degrees from patient to patient. Age, general health, family history, pedigree, and the severity of the patient's disease are among the factors.

The patient's tolerance for a particular medicine, the severity of cognitive impairment, expectations for the condition's course, and the stage of the disease are additional significant factors that need to be taken into consideration.

II. RECOMMENDED MEDICATIONS

- **Levodopa (Dopamine precursor)-** The first effective medication for Parkinson's disease was the amino acid l-3,4-dihydroxyphenylalanine (levodopa, or l-dopa). Levodopa is a precursor of dopamine, whose concentration is markedly decreased in parkinsonism. Levodopa can enter the brain when taken orally in high doses daily and avoid being metabolised there by surviving dopamine neurons. There, the substance is decarboxylated to create dopamine (the removal of a carboxyl group, COOH). Carbidopa, a levodopa analogue, is added to levodopa medications to increase the quantity of levodopa that enters the brain. Levodopa's conversion to dopamine is stopped by carbidopa before it enters the blood-brain barrier (dopamine itself cannot penetrate the blood-brain barrier).

  The main negative effect of levodopa is an increased chance of schizophrenia-like episodes, which is probably caused by excessive dopamine production [16, 36].

- **Carbidopa-levodopa-** The most effective treatment for Parkinson's disease is levodopa, a natural substance that enters your brain and is changed into dopamine. Most effective for symptom management and frequently linked to motor problems Dyskinesias are a side effect of long-term treatment. COMT inhibitors are prescribed for better results [16, 36].
- **Inhaled carbidopa-levodopa-** For improved patient compliance, use the above mixture in an inhaled form [16, 36].
- **Dopamine agonists**- The neurons that typically produce and use dopamine are known as dopaminergic neurons, and dopamine-receptor agonists work by binding to dopamine receptors on these neurons. The brain's dopaminergic activity is boosted by activating the receptors, which lessens the severity of parkinsonism symptoms. The group that mimics dopamine's effects in the brain comprises pramipexole, ropinirole, and rotigotine (in patch form), as well as apormorphine. It is less effective than levodopa but has a longer half-life. There are few side effects such as hallucinations, sleepiness and compulsive behaviours [16, 36].
- **MAO B inhibitors-** Dopamine in the brain is slowly degraded by MAO-B inhibitors. It consists of safinamide, selegiline, and rasagiline. They function by halting the decomposition of the enzyme monoamine oxidase B, which inhibits dopamine. This class of drugs have ill effects like headaches, nausea, insomania and hallucinations and personality disorders [16, 36].
- **Catechol o-methyltransferase (COMT) inhibitor-** Dopamine is broken down enzymatically by the enzyme catechol-O-methyltransferase, and COMT inhibitors like tolcapone and entacapone stop this from happening. These drugs are frequently used with levodopa and carbidopa because they stop the breakdown of levodopa by COMT in peripheral tissues. This increases the amount of medicine that may cross the blood-brain barrier and prolongs the drug's half-life in the blood. The main negative effects are dyskinesia, nausea, vomiting and hallucination [16, 36].

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- **Antichollinergics-** The aberrant neurotransmitter activation of acetylcholine contributes to several parkinsonism symptoms. Acetylcholine mediates this action by attaching to muscarinic acetylcholine receptors in the brain (the receptors are named for their sensitivity to the chemical muscarine and their selectivity for acetylcholine). As a result, although their effects are minimal, drugs like trihexyphenidyl and benztropine mesylate are used to treat symptoms. Furthermore, it's believed that these drugs increase dopamine levels in the brain. However, due to its sedative effects and vision-related side effects, their use in older patients is restricted. Negative consequences include trouble with memory, confusion, and difficulty in micturition reflex and constipation [16, 36].
- **Amantadine-** Amantadine, an antiviral drug used to treat influenza A infections, can assist patients with Parkinson disease have fewer tremor and bradykinesia (slow movement) symptoms. It has been found to trigger the release of dopamine from brain cells, albeit its precise mode of action in this capacity is unknown. Additionally, it prevents excitatory transmission and movement-related neuronal overactivity. When used in conjunction with carbidopa-levodopa therapy during the latter stages of Parkinson's disease to reduce involuntary movements (dyskinesia) brought on by carbidopa-levodopa, amantadine is used to temporarily relieve the symptoms of mild, early-stage Parkinson's disease. Hallucinations or ankle swelling, confusion, wooziness, nausea, and vomiting are some of the side effects [16, 36].

III. SURGICAL THERAPY

Depending on the progression and stage of the disease, many surgical techniques are available that can improve the condition of PD patients when medications don't seem to have much of an impact or don't help with the disease's movements [29].

- Deep brain stimulation (DBS)
- Focused ultrasound
- Lesion surgery (burning of tissue) Pallidotomy, Thalamotomy and subthalamotomy [6]
- Neural grafting or tissue transplant [7]
- **Deep brain stimulation -** DBS is a non-invasive surgical procedure used to treat Parkinson's disease. It includes implanting a device that sends electrical impulses to specific parts of the brain using a battery-operated neurostimulator. This is the most popular surgical treatment for PD's motor symptoms.

Additionally, it lessens the frequency of "off" episodes, which frequently happen throughout the day in more advanced stages of PD that are being treated medically.

The subthalamic nucleus (STN) and the globus pallidus pars interna are the two brain regions that receive DBS the most frequently (GPi). Similar motor advantages have been seen between these two targets in large, randomised, controlled studies. It is thought that the electrical signals produced by DBS block the aberrant signalling patterns in the brain that are the source of the motor control difficulties. Parkinson's disease symptoms can only be relieved; a cure is not available [5,7].

- **Leison surgery-** Methods like pallidotomy, thalamotomy, and sub-thalamotomy are used to burn tissue. Both sides of the brain can be affected during a pallidotomy, which involves the destruction of a small area in the globus pallidus interna, however only one side of the brain can be affected during a thalamotomy, which involves lesioning or destroying the thalamus [5,7].
- **Focused ultrasound -** Focused ultrasound is a new treatment that provides a minimally invasive substitute for conventional surgical methods. Multiple ultrasound beams are focused on targets deep inside the body, and an MRI is used to track and direct the process in real time. Ineffective brain circuits can be disrupted or undesirable tissue can be destroyed using focused sonic energy at the target point [5,7].
- **Neural grafting -** While nigral transplants clearly work well in some PD cases, the technique needs to be improved before it can be successfully used in a large series of patients because of the side effects it causes in patients. Clinical studies performed in the 1990s where dopaminergic neurons derived from the human embryonic brain were transplanted into the striatum of patients with PD provided proof-of-principle that long-lasting therapeutic benefits can be achieved [5,7].

IV. NUTRITIONAL THERAPY

Food supplements are frequently used to correct nutritional deficiencies or to support specific physiological functions, combined with common drug therapy, to manage many chronic diseases. The use of food supplements or functional foods has significantly increased over the past few decades, especially to compensate for both the modern lifestyle and better health [8].

A. What should you add to your meal?

- Phytochemicals containing food→ broccoli, berries, soynuts, pears, celery, carrots, beetroot and many more.
- Omega 3 DHA containing food →fish, seafood, plants oil
- Caffeine →works as a neuroprotector.
- Soy (genistein) →good for menopausal women suffering from PD
- Magnesium rich foods→ spinach, pumpkin seeds, almonds, seeds etc.
- biological compounds like → coenzyme Q10, lipoic acid, N-acetyl cysteine, carvacrol, turmeric, creatine , melatonin niacin and lycopene.
- Vitamins like → vit D_3, C.
- Plants like→Gingko biloba extract and 6-shogaol.
- Antioxidants containing food→ berries and beans.
- Zinc and iron containing food.

B. What should you avoid eating?

- Avoid or drastically cut back on high-sugar foods.
- Processed foods
- Excessive oil, fat and carbohydrates
- Dairy products

- Excess meat
- Hard to chew and swallow food items.

C. Key ideas for controlling your food intake:

- Throughout the day, eat a variety of minimally cooked meals.
- Consume foods that regulate your blood pressure, heart rate, and blood sugar.
- Checks on the body's nutritional status.
- Get adequate vitamin D from sunshine exposure.
- Improve digestion
- Take a test for food allergies and intolerances.
- Eat regularly spaced meals.
- Don't miss meals.

V. HERBAL THERAPY

- **Withania somnifera(Family: Solanaceae)**- WS, also known as winter cherry or poison gooseberry, contains a variety of bioactive molecules that have been isolated from the plant. These molecules include triterpene lactones, alkaloids, tropine, steroidal lactones, and withanolides, all of which are used to treat a variety of neurological deficits, such as poor memory, depression, epilepsy, and neurodegeneration. It was also discovered that the ethanol extract of WS roots considerably increases the locomotor activity of PD mice and dopamine production in the substantia nigra. Additionally, their research showed that the ethanol extract of WS roots dramatically reduced the levels of GFAP protein, a pro-inflammatory marker of astrocyte activation, and iNOS concentration (oxidative stress) in the brain tissues of PD mice. Neuronal apoptosis may be triggered by the substantial oxidative and inflammatory stress in the brain, which may then gradually result in PD phenotypes [33, 34].
- **Gastrodiaelata blume (Family: Orchidaceae)-** The ethanolic extract of Gastrodiaelata Blume at different concentrations (10, 100, 200 g/mL) reduced the MPP+-induced elevation of the Bax/Bcl-2 ratio in SH-SY5Y cells, attenuated capase-3 activation and PARP cleavage in a dose-dependent manner, shows anti-oxidant effect with significant radical scavenging activity for DPPH, and alkyl radicals, suppressed [33, 34].
- **Centella asiatica (Family: Umbelliferae) –**The treatment of MPTP-induced parkinsonism with Centella asiatica's aqueous extract at a dose of 300 mg/kg for 14 days is beneficial. It works by displaying its antioxidant activity in the brain's corpus striatum and hippocampus. Extract boosts Super oxide dimutase, Glutathione peroxidase, Catalase, Total Antioxidants, and Xanthine Oxidase while decreasing lipid peroxidation and protein carbonyl concentration [33, 34].
- **Pueraria thomsonii (Family:Fabaceae)**- The bioactive components of Pueraria thomsonii, daidzein and genistein, have neurocytoprotective properties when 6-OHDA induces aptosis in differentiated PC12 cells. Daidzein and genistein reduced caspase-8 and partially inhibited caspase-3 activation at doses of 50 µM and 100 µM, respectively, offering a defence mechanism against 6-OHDA induced cytotoxicity in PC12 cells with NGF differentiation [33-35].
- **Plumbago scandens (Family: Plumbaginaceae**)- Reduce locomotor activity, catalepsy, and palpebral ptosis, which counteracts parkinsonism [34].
- **Chrysanthemum-** In the SH-SY5Y cell model, BV-2 Parkinson's disease microglial cells, and 1-methyl-4-phenylpridinium ion, the indicum Chrysanthemum L extract is protective against lipopolysaccharide-induced cytotoxicity. Reduces ROS aggregation, elevates the ratio of Bax to Bcl-2 in SH-SY5Y cells, inhibits the mitochondrial apoptotic pathway, and reduces SH-SY5Y cell death [34,35].
- **Clausenalansium-** The fruit tree is a native of southern China. Treatment is ongoing with Bu-7, a flavonoid derived from Clausenalansium leaves that reduced rotenone-induced apoptosis and increased protein phosphorylation [34,35].
- **Ocimum sanctum (Family:Lamiaceae)**. Ocimum sanctum leaf extract has a neuroprotective effect on albino mouse catalepsy brought on by haloperidol. O. sanctum extract had a neuroprotective impact on rotenone-induced parkinsonism, haloperidol-induced catalepsy, and muscular rigidity in mice [34,35].
- **Cassia-** The ripe, dried seed of Cassia obtusifolia L. Tora's Cassiae Semenis Clarissa L. (Tora C.). Alaternin, a component of C. tora, is powerful in scavenging peroxynitrite and is thought to cause Parkinson's disease (PD). It also protects mice from temporary cervical hypoperfusion-induced neuronal cell death. In PD models of 6-OHDA-induced neurotoxicity in PC12 cells and MPTP-induced neuronal degeneration in the PD form of the animal, as well as seed extract in hippocampal cultures of the mouse, Cassiae Semen extract exhibits therapeutic characteristics [35].

VI. PHYSICAL THERAPY

There is no specific therapy that is recommended to treat Parkinson's disease, however there are sufficient studies and evidence to show that exercise is beneficial in enhancing movement.

The advantages of exercise in preventing and slowing the progression of Parkinson disease have been supported by experimental research in recent years. Exercise increases quality of life, sleep, mood, and independent mobility, Gait training on a treadmill, Nordic walking, brisk walking, balance training, virtual reality interventions, dancing, aerobics, and resistance training are only a few of the short-term effects of this treatment, but they all help to relieve symptoms and enhance neurophysiological function [9-11].

- **Massage therapy-** Relaxation and reduced muscle tension are two benefits of massage therapy. Most of the time, massage therapy appears to promote relaxation, which is followed by biological processes involving urinary stress hormones. It has been demonstrated that several therapeutic massage modalities enhance quality of life. Anma and Yin tui Na are more advantageous [12].
- **Tai-chi -** Tai chi is a traditional Chinese workout that uses slow, flowing motions to increase muscle strength, flexibility, and balance. Tai chi may also reduce the risk of

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falling. Any age or physical condition can benefit from one of the many tai chi styles. According to a study, tai chi may enhance balance better than stretching and weight exercise in persons with mild to moderate Parkinson's disease [15].

- **Alexander technique-** This method, which emphasises muscle posture, balance, and thinking about how you utilise muscles, could lessen discomfort and stiffness in the muscles.
- **Yoga-** Yoga positions and mild stretching exercises can help you become more flexible and balanced [12, 14].
- **Meditation -** During meditation, you reflect in silence and fix your attention on a concept or picture. Your sense of wellbeing may increase and pain and stress levels may decrease with meditation.
- **Practice fall prevent methods-** Older folks who live in the community can avoid falling by exercising alone. Exercise regimens that demand good balance and are more intense have greater results. [13]
- **Dance-** Participants with Parkinson disease gain from the motor, cognitive, and quality of life benefits of rhythmic stimulation and dance. Thus, dance and sound stimuli have positive impacts on gait and enhance cognitive skills including spatial memory and motor control.

VII. PSYCHOLOGICAL THERAPY IN PARKINSON

Living with PD can be a little challenging because it is frustrating to adjust to the body's movements, and it is challenging since performing everyday activities like walking, talking, and eating take a lot of time. Therefore, the majority of Parkinson's patients experience psychosocial issues including-

- Depression and Anxiety
- Mental Breakdowns and Frustrations
- Insecurities and low self esteem
- Lack of emotional expression& motivation
- Social interactions and high social anxiety

VIII. MANAGEMENT TECHNIQUES

- **Pharmacological approach** → Serotonin reuptake inhibitors, tricyclic antidepressants, dopamine agonists, and trazodone are examples of antidepressants that have been shown to be effective in treating or reducing depression in Parkinson's disease.
- **Non-pharmacological approach** → Today, a variety of treatments are thought to be beneficial for PD. These are used to manage it to some level in order to avoid further psychological difficulties, not to treat or cure it.
- **Cognitive behavioural therapy (CBT)**→ PD-tested to be extremely effective helpful in lowering tension and improving patient calm and flexibility.
- **Mindfulness behavioural therapy (MBT)**→ displays similar benefits and has been shown to be beneficial, especially when CBT and MBT are used to improve outcomes, lower anxiety, and lessen depressive features.
- **Acceptance and commitment therapy (ACT)**→ PD technique that was useful but less popular than other ways.
- **Family supports** → The mindset of PD patients can be improved, and they may feel less frustrated and anxious about social situations if they feel understood by those around them.
- **Social acceptance**→ Social acceptance is essential for those with Parkinson's disease or really any illness because it lowers the possibility of many negative psychological side effects, calms patients, and makes them more optimistic about their treatment and likely to take their prescriptions carefully [32].

IX. SPEECH THERAPY IN PARKINSON

A voice problem that includes reduced vocal intensity, reduced vocal pitch, monopitch and monoloudness as well as incorrect articulation affects about 80% of PD patients. Prior to the 1970s, research had not shown that speech therapy led to meaningful changes. Recent studies have however demonstrated that speech therapy is the most effective therapeutic approach for enhancing voice and speech function (when people with PD are receiving appropriate medication).

A. Is it beneficial?

Regular practise makes speech better, and studies comparing patients receiving physical therapy and speech therapy have revealed some patients have improved more than others.

Approaches to therapy: Several techniques are

- **Articulation therapy-** centred on creating sounds and articulating various speaking sounds.
- **Language intervention therapy-** aimed towards improving public speaking skills.
- **Oral motor therapy-** focuses on improving speaking muscles with exercise.
- **Vital stem therapy-** aimed at improving muscular function through electrical stimulation.
- **LSVT-** comprehensive approach used to help patients speak more clearly and manage their voices by strengthening their laryngeal muscles [32].

B. Patient counselling:

The benefits, choices, and treatment options that are available must be discussed with the PD patient. It can be challenging to accept the challenges associated with this sickness, but with good counselling, appropriate procedures, and frequent treatments, it can be simply handled. They also need to be guided about the fundamental knowledge on how to deal with this disease to smooth out the symptoms [32].

C. Principles of the Counselling Method:

- Clinical pharmacy
- Proper medication adherence
- Regular and timely appointments
- Timely checking of nutritional imbalance
- Proper diet and avoid intake of harmful products like, toxins, smoke etc
- Daily activity with improved movement methods
- Enough sleep and enough exercise.

D. Review of clinical trial for Parkinson therapies:

- New formulations of L-Dopa, dopamine agonists, amantadine, and new MAO-B and COMT inhibitors are currently being explored in clinical studies for a more effective therapy of motor problems, with some of them already showing promising results in phase 3 trials. Adenosine A2A antagonists (istradefyline, preladenant, and tozadenant) and modulators of the metabolic glutamate receptor 5 (mGluR5 - mavoglurant) and serotonin (eltoprazine) receptors have also been investigated in the early clinical phase for the treatment of motor fluctuations and dyskinesia [30].

- Coenzyme Q10, the dopamine agonist pramipexole, creatine monohydrate, pioglitazone, and AAV-mediated gene therapy to increase neurturin expression were all unsuccessful in recent clinical trials. Clinical trials are currently being conducted to examine the effects of treatment with nicotine, caffeine, inosine (a precursor to urate), and isradipine (a dihydropyridine calcium channel blocker), as well as active and passive immunisation against -synuclein and inhibitors or modulators of -synuclein-aggregation [31].

- The visual evaluation of ioflupane (^{123}I) pictures in this pooled research revealed high levels of sensitivity and specificity in determining the presence or absence of an SDDD. Ioflupane (^{123}I) imaging may increase diagnostic precision in patients exhibiting signs and symptoms of a dementia or mobility impairment.

- For each intervention, four clinical criteria were taken into account: stopping the progression of the disease, treating Parkinsonism as a standalone condition or when necessary as an addition to levodopa, preventing motor complications, and treating motor problems. 27 new research met the criteria for an efficacy review, and other studies addressed brand-new safety concerns. The efficacy ratings for apmorphine, piribedil, unilateral pallidotomy, and subthalamic nucleus stimulation increased. Rasagiline was recently assessed as an effective monotherapy for the management of Parkinson's disease. Human fatal nigral transplants, as they have been carried out to date, were downgraded from Insufficient Data to Non-effective for the treatment of Parkinsonism, motor fluctuations, and dyskinesias based on new Level I data. The classification of selegiline as ineffective for the prevention of dyskinesias was revised. Others remained unchanged. It is critical to often update therapy-based reviews in a sector with as many clinical trials as PD.

- Two eating patterns—prudent and Western—were discovered using the designation principle component analysis. The Western diet was not inversely linked with PD risk, but the sensible diet, which emphasises high intakes of fruit, vegetables, and seafood ect.

- Although 10 of the eleven trials with 280 participants reported that physiotherapy had a beneficial effect, few of the outcomes examined were statistically significant. Four trials were conducted to test walking speed, and two of the trials saw a substantial increase. The only other outcome that was assessed in more than one experiment was stride length, which showed a substantial improvement in two of them. Eight additional outcomes did not significantly improve, whereas five other outcomes did so in their respective investigations.

E. Effects of anti-parkinson medicines on animal models:

- In animal models of Parkinson's disease, N-methyl-D-aspartate (NMDA) receptor antagonists show antiakinetic and antidyskinetic effects (PD). An activity-dependent antagonist of NR2B-containing NMDA receptors, which are mostly expressed in the striatum, is Ro 25-6981. Without stimulating locomotion in healthy rats, Ro 25-6981 caused contraversive rotations in 6-hydroxydopamine (6-OHDA) lesioned rats, and it alleviated parkinsonian symptoms in common marmosets that had been given MPTP treatment. The Page test revealed a significant trend toward differences, but due to the small number of marmosets [3] there were no significant differences between Ro 25-6981 and vehicle. In addition, Ro 25-6981 enhanced the effects of levodopa in both species and reduced the maximal levodopa response in rats with chronic 6-OHDA lesioning while maintaining the same level of responsiveness. In 6-OHDA-lesioned rats, Ro 25-6981 additionally enhanced the effects of the dopamine receptor agonists apomorphine, A68930, and quinpirole. The current findings point to the potential therapeutic value of NR2B-selective NMDA receptor antagonists in the treatment of PD [17, 18].

- The first extensively utilised animal models for Parkinson's disease were the significant dopamine depletion of the basal ganglia in Parkinson's disease patients and the behavioural abnormalities brought on by cholinergic medications, reserpine and similar substances, and unselective neuronal injuries. The discovery that animals circled after receiving a unilateral intranigral injection of 6-hydroxydopamine was fundamental [4].

- The newest and best animal model for Parkinson's disease is the parkinsonism that the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes in mice and monkeys. The biochemical, behavioural, and neuropathological alterations caused by MPTP, especially when given to monkeys, closely resemble those of Parkinson's disease in people. The monkey's MPTP-induced parkinsonism can be exploited to research the neurobiology of Parkinson's disease and develop new pharmacological therapies. The MPTP monkey model is costly and time-consuming, hence it is not the best option for testing novel medications. The development of medications that can stop or slow the progression of the disease is a

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recent innovation in the treatment of Parkinson's disease. Selegiline has shown promising benefits in preventing behavioural alterations in old rodents, which is utilised as an animal model [30].

F. New developments and trends in the disease:

Current research on Parkinson has identified a number of novel elements that both contribute to its pathology and can assist treat it [27].

- **Biomarkers for diagnosis of PD-** Due to the lack of early diagnostic methods, the disease's cure is on hold and typically only becomes apparent in the later stages, when neurons have entirely deteriorated. Therefore, biomarkers are necessary to identify the disease in its early stages, when treatment can be started. Imaging, cerebrospinal fluid, oxidative stress, neuroprotection, and inflammatory biomarkers are among the many that help with early illness identification. Additionally, biomarkers are used, singly or in combination, in the diagnosis and progression of PD. the advancements made in disease-modifying medicines and biomarkers for Parkinson's disease (PD), with an emphasis on the most prevalent and sophisticated genetically linked targets alpha-synuclein (SNCA), leucine-rich repeat kinase-2 (LRRK2), and glucocerebrosidase (GBA1) [19].

- **Cell therapy-** With the transplantation of foetal rat dopamine-containing neurons, cell therapy for Parkinson's disease (PD) got off to a strong start a year ago, improving motor impairments in the rat model of the disease with good graft survival and axonal outgrowth. The development of cell therapy as a viable treatment option for PD patients is anticipated as a result of the advancement in biotechnology represented by pluripotent stem cells. True neuro-restoration might be possible with cell treatment [20].

- **Genetic link-** The creation of knowledge resources and the development of highly parallel genotyping techniques gave rise to the tools and guidelines needed to comprehend how common genetic diversity affects human features, including disease. Our estimates of common variant heritability in PD have been provided and refined through the use of heritability estimation methods like Genome-wide Complex Trait Analysis (GCTA) and Linkage Disequilibrium Score Regression (LDSC), which suggests that 16–36% of the liability of disease is driven by common genetic variability. Mendelian randomization in practise (MR). Using genetic variability for the trait as an instrumental variable, this approach intends to investigate the association between a modifiable trait and disease (in our example, PD). This approach can be used to determine whether a trait is causally linked to PD [20,26].
- **Gender difference-** Several sex-based population-based incidence studies of Parkinson's disease have been carried out recently in a range of populations all over the world. Men have a considerably higher incidence of Parkinson's disease than women do, and their relative risk is 1.5 times higher. Toxicant exposure, head trauma, neuroprotection by oestrogen, mitochondrial dysfunction, or X linkage of genetic risk factors are potential causes of this increased risk of Parkinson's disease in men [26].

- **Study models-** In vitro and in vivo models, animal models for PD, stem cell models for PD, newer 3D models, and it is also discovered that FDG-PET studies are a great tool to find patterns of brain metabolism are all examples of significant advances in modelling [28].

X. EXTRACT OF FEW CASE STUDIES CARRIED SO FAR ON PARKINSON PATIENTS

Parkinson's disease has a negative impact on patients, so numerous studies and research have been conducted to examine their behaviour, perspective, issues, and how the medications and therapies have impacted them personally [21].

- **Effect of chemotherapy**- In a trial, a significant dose of ropinirole was administered to a group of participants for a full year. The majority of patients have improved, but only a small portion of the group needs further levodopa. After 12 months of treatment, a standard dosage was determined based on the patient's side effects [25].

- **Effect of speech therapy-**Parkinson's disease patients receiving speech-language therapy participated in interviews. Thematic network analysis was used to examine participant replies. Between 65-84% of people with PD have speech-language disorders. Reduced volume (hypophonia), reduced pitch variation, and difficulty articulating syllables (dysarthria) are the most prevalent speech defects reported in studies. Other issues include difficulty initiating speech, tremor, a weak breathy voice, and increased pauses and hesitations, which can lead to psychological issues like depression and social anxiety. Numerous approaches, including NHS and LVPT therapy, were employed to reach the conclusion that long-term therapy assisted patients in controlling their speech ability to some level. LVPT has shown to be more effective and efficient [24].

- **EFFECT OF DBS-** studies carried out to record patient experiences and the effects of DBS. Deep brain stimulation has the potential to make a significant difference by significantly lowering symptoms, making it a wonderful alternative for patients who are not responding well to drugs. About their experiences using DBS, people were questioned. Regarding the procedure, a number of people reported feeling incredibly hopeful, excited, nervous, overwhelmed, and mixed emotions. More than 90% of patients who responded to a structured questionnaire used to poll patients on the perioperative management of the awake stage of the procedure felt well-informed. One-half of the patients reported experiencing discomfort throughout the surgery, which was frequently severe. Burr-hole drilling and stereotactic frame placement was the main times this happened. The body was significantly affected by the procedure. During the first year of Deep Brain Stimulation therapy, participants

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underwent significant physical changes and underwent a three-phase adjustment process. Following Deep Brain Stimulation, patients go through a significant transformation process. Their entire environment is affected by a shifting body. Some people adapt to changes without much difficulty, while others experience loss of control, uncertainty, and the loss of their familiar way of life. It is crucial that medical practitioners are aware of these substantial life changes in their patients and provide support during the period of adjustment following Deep Brain Stimulation [22, 23].

XI. CONCLUSION

More than 6 million people worldwide have Parkinson disease, the most prevalent form of parkinsonism, a set of neurological illnesses with movement issues like those of Parkinson disease, such as rigidity, slowness, and smaller dot Parkinson's disease is diagnosed based on a patient's medical history and physical examination. Pharmacological and non-pharmacological treatments, including deep brain stimulation and labour dopa carbidopa internal suspension, can help people who have tremors that get worse when their medication wears off and dyskinesis. It indicates that there are various types of Parkinson's disease. New neuroimaging techniques, like SPECT scans, may now help with disease diagnosis while intriguing research into the aetiology and pathogenesis of the disease continues. For simpler administration and increased clinical efficacy, new formulations of medicines for Parkinson's disease are now available. Parkinson's disease is treated using a variety of techniques, including deep brain stimulation neural grafting, targeted ultrasound, and lesion surgery in addition to chemotherapy, which covers all Parkinson's meds and pharmaceuticals. Various other techniques are being employed, such as nutritional therapy, which includes diet and supplements, to treat Parkinson's disease. To reduce the rigidity and stiffness in the body, physical therapy and psychiatric therapies are also used today. Recent translational studies have improved our understanding of several fundamental biological concepts, including intrinsically disordered proteins, autophagy, and mitochondrial function. These studies are targeted at understanding the pathogenesis and pathophysiology of Parkinson's disease, basal ganglia and homeostatic plasticity Physiology. Research continues to concentrate on alpha-synuclein-targeted medicines as well as neuroprotective and disease-modifying methods. Future studies into the causes, pathology, and maybe a treatment for Parkinson's disease (PD) seem encouraging.

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