Research Results

Overview of Parkinson its Treatment and Secondary Effects

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ABSTRACT

In this review article, we explained and thoroughly evaluated various PD-based articles on how Parkinson's disease manifests in an individual. Due to degeneration of neurons in the brain, a decrease in substantia nigra and dopamine levels in the brain causes a disease similar to Parkinson's disease. We also included the effects of Parkinson's disease on the body organs, i.e. Primary and secondary effects. Its historical background, causes, MOA and main drugs used in the treatment of PD like levodopa etc. for the treatment of PD. The main signs and symptoms of PD are tremors, muscle stiffness, incoordination, rhythmic muscle contractions, slow body movement, vocal cord spasms and many others. so after looking through several articles we realized that PD is not a curable disorder, if we take medication we can reduce the symptoms and also taking some other kind of therapy the sign and symptoms of PD can be treated.

KEYWORDS

PD, alpha synuclie, neurodegenerative, tremor, dopamine, levo dopa

1. INTRODUCTION

Parkinson's Disease (PD) is a complicated neurological condition that causes a variety of motor and non-Motor symptoms due to the gradual death of dopaminergic neurons in the brain's substantia nigra pars Compact. The understanding of parkinson's disease (pd) has changed dramatically over the past 200 years, Since the disease was first dubbed "shaking palsy" by james parkinson in 1817. Parkinson's Disease (PD) is still a difficult condition to manage, with major effects on the quality of life for both patients and their caretakers, despite advancements in research and therapy.

In this review, we are going to focus on the etiology, mechanism of action \ pathophysiology and the effects of the Parkinson's on other organs along with the possible treatments and the future scope for treating Parkinson's.

2. HISTORICAL BACKGROUND

a. Parkinson's disease (PD) is the second most common neurodegenerative disease after

b. First described as a neurological disorder by James Parkinson in 1817.(1)

c. Jean-Martin Charcot (1800s), considered Parkinson's as the shaking palsy in a monograph entitled "An Essay on the Shaking Palsy.(1)

d. Leonardo da Vinci (1500s) presented PD as a combination of difficulty with voluntary movement and tremor (2)

e. Ferenc Papai Pariz (1690), described the clinical symptoms of PD (3)

f. Édouard Brissaud (1899) first suggested PD originated pathologically from the damaged substantia nigra (3)

g. Frederick Lewy and Konstantin Tretiakoff (1912-1919) describes inclusive location of PD in substantia nigra.

h. André Barbeau (1961) levo-dopa , was first noted to be effective in improving PD symptoms *via* the oral route (4)

i. George Cotzias and Donald Brian Calne (1970s) preposed that dopamine receptor agonists i.e. bromocriptine and apomorphine potent for PD therapy (4,5)

j. The first double- double controlled trial of a cell-based therapy in PD (2001)

k. Heiko Braak proposed a pathological staging of PD (2003)

l. New hypothesis of cell to cell transmission of alpha-synuclein in PD (2014)

Aim: This review article aim is to address important questions and controversies in the field of Parkinson's disease, provide guidance for improving clinical care for those with this debilitating and complex neurological disorder, and consolidate and critically evaluate the body of knowledge currently available.

Objective:

1. Create An Extensive Database
2. Examine Methodological Quality
3. Synthesize Current Knowledge

4. Examine Therapeutic Interventions
5. Examine New Developing Biomarkers
6. Examine Neuroprotective Techniques
7. Determine Non-Motor Symptoms
8. Analyze Unfavorable Impacts
9. Determine Any Limitations And Gaps
10. Describe The Clinical Implications

The aforementioned objectives encompass a wide range of research topics related to parkinson's disease, including etiology, pathophysiology, diagnosis, treatment, and clinical management. This comprehensive overview aims to present the current level of knowledge in the field.

3. MATERIAL AND METHOD

This review articles gives the complete information about the developments that took place in understanding the parkinson's disease and its treatment.

The materials that are used to makeup this review article are

1. PUBMED
2. SCI-HUB
3. KD TRIPATHI
4. PARAPHRASING (https://quillbot.com/)
5. GRAMMARLY (https://www.grammarly.com/)
6. PLAGARISM CHECKER FREE (https://plagiarismdetector.net/)

Etiology-

Our understanding of the etiology of Parkinson's disease has greatly advanced during the past century. The loss of pigmentation in the midbrain's substantia nigra was initially identified through brain examinations in 1919. The dopaminergic pigmented neurons that are lost in the substantia nigra were further identified in the 1950s.[6]One of the main components of Lewy bodies, abnormally high levels of aggregated alpha-synuclein are discovered. Alphasynuclein's altered function is thought to have a part in the etiology of Parkinson's disease (PD). [6,7] Different causes of Parkinsons disease are as follows-

A. Cigarette Smoking

With regards to Parkinsons disease (PD), cigarette smoking has been well examined, with generally reliable findings. [7] Parkinson's disease belongs to that small group of conditions that occur less often among cigarette smokers than in non-smokers.[8] Larger cohort studies also support the lower risk of Parkinson's disease (PD) found in the majority of epidemiological data, which are case-control studies. Smoking and Parkinson's disease (PD) were found to be inversely correlated in a major meta-analysis included 44 case-control studies and 8 cohort studies from 20 different countries. Further meta-analyses also found an inverse relationship between smoking and Parkinson's disease (PD)—indicating a preventive mechanism against the disease. They also discovered an inverse relationship between the risk of Parkinson's disease (PD) and the number of pack cigarette/ year and years of smoking. [9]

- **Caffeine**

Research has examined the impact of caffeine on Parkinson's disease development and found that coffee consumers have a lower chance of developing Parkinson's disease. An adenosine A2A receptor antagonist, caffeine is thought to be protective against Parkinson's disease (PD) and has demonstrated neuroprotective effects. Coffee consumers have been shown to have a 25% lower chance of acquiring Parkinson's disease (PD). Numerous retrospective studies and two sizable prospective epidemiological studies have also demonstrated a lower risk of Parkinson's disease (PD) among coffee consumers compared to non-drinkers, with a relative risk ranging from 0.45 to 0.80.[10]

- **Pesticide, herbicide and metal exposure-**

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was originally linked to nigrostriatal degeneration in 1983 when a number of individuals who had injected themselves with a medication tainted with MPTP began to exhibit typical Parkinson's disease symptoms. MPTP is converted into MPP+ (1-methyl-4-phenylpyridinium), a neurotoxin that preferentially destroys dopaminergic cells in the substantia nigra and is a mitochondrial complex-I inhibitor. The notion that PD might be brought on by an environmental toxin originated with the discovery that MPTP is a cause of nigral degeneration. Since then, a number of studies have demonstrated a link between pesticides and Parkinson's disease (PD). One case-control research found a higher correlation between males' professional pesticide exposure and late-onset PD. Rotenone and paraquat are some of the herbicides.[16]

Other epidemiological studies have looked into the connection between exposure to these chemicals and the chance of acquiring Parkinson's disease. It has also prompted research on surrogate markers, such as the link between rural living, farming, and well water consumption and Parkinson's disease risk. Investigations on the connections between welding and exposure to heavy metals (such as iron, copper, lead, aluminium, and zinc) and Parkinson's disease (PD) have yielded conflicting results.

- **Genetics**

Genes are crucial because if one member of the family has Parkinson's disease (PD), siblings are more likely to develop the ailment. Additionally, these occurrences typically happen considerably earlier in life. Even though PD is typically an idiopathic condition, family history is reported in 10-15% of cases, and Mendelian inheritance accounts for roughly 5% of cases. Moreover, a person's risk of Parkinson's disease (PD) is partly determined by poorly characterized polygenic risk factors. In the order that they were discovered, the genes that have been linked to Parkinson's disease (PD) are given "PARK" names. PD has been associated with 23 PARK genes thus far. Mutations in the PARK genes that show either autosomal recessive inheritance (e.g., PRKN, PINK1, and DJ-1) or autosomal dominant inheritance (e.g., SCNA, LRRK2, and VPS32).

Mutations in GBA1, a gene producing β-glucocerebrosidase, a lysosomal enzyme responsible for the hydrolysis of glucocerebrosides, are the numerically most significant genetic risk factors predisposing to Parkinson's disease. The most prevalent lysosomal storage illness, Gaucher disease, is known to be caused by GBA1 mutations. The major histocompatibility complex, class II (HLA-DQB1) and the gene encoding the tau protein, MAPT, are two additional genetic risk factors.

- **Autosomal dominant PD**

In 1997, a point mutation in the α-synuclein gene (SNCA) was found to be the cause of the first kind of familial Parkinson's disease. Autosomal dominant Parkinson's disease has now been associated with duplication or triplication of genes, in addition to four other point mutations. These mutations are rather uncommon, though. The most common autosomal dominant monogenic Parkinson's disease is brought on by mutations in the leucine-rich repeat kinase 2 (LRRK2) gene. Other autosomal dominant PD-causing genes, such as VPS35, have also been shown to have additional mutations as a result of more recent genetic research.

- **Autosomal recessive PD**

Compared to classical PD, autosomal recessive types of the disease usually manifest earlier in life. The PARKdesignated genes PRKN, PINK1, and DJ-1, which cause autosomal recessive Parkinson's disease, have been connected to mitochondrial homeostasis. In particular, the proteins PINK1 and parkin (which are both expressed by the PRKN gene) participate in the same mechanism of mitochondrial quality control, whereby PINK1 attracts parkin to defective mitochondria and thereby starts the process of mitophagy. Up to 50% of cases with early start are caused by mutations in PRKN, making it the most common cause of autosomal recessive familial Parkinson's disease.

4. MECHANISM OF ACTION

1. Parkinson's disease (PD) is a neurodegenerative disorder that is clinically distinguished by four primary symptoms: resting tremor, bradykinesia (slowness of movement), rigidity, and postural instability.
2. Regarded as the most frequent movement disorder of neurodegenerative origin. PD is typified by a widespread and progressive degeneration of dopaminergic neurons in a part of the brain called the substantia nigra pars compacta. The presence of Lewy bodies - intracellular accumulations of clustered α-synuclein proteins - feature prominently as a pathological signature of this disease.[17]
3. The deterioration of neurons has been associated with a plethora of cellular and molecular alterations, encompassing the accumulation of α-synuclein, irregular protein management, excitotoxicity, oxidative tension, apoptosis, and malfunction of mitochondria. Anomalous clustering of α-synuclein is a key theory elucidating the demise of nigrostriatal neurons in Parkinson's Disease. [18]
4. Parkinson's disease is initially identified through its distinctive clinical manifestations and is conclusively confirmed through postmortem examination, which reveals the presence of Lewy bodies and the depletion of dopaminergic neurons in the substantia nigra pars compacta. Consequently, the neuronal loss results in a reduction of striatal dopamine, which leads to the observed clinical phenotype. [18]
5. When α-synuclein comes into contact with negatively charged lipids, like the phospholipids constituting cell membranes, it changes into α-helical structures via its N-terminal. However, in Parkinson's Disease, αsynuclein assumes a β-sheet-rich amyloid-like formation, which is susceptible to clumping. [18]

Motor effects	Non-motor effects
1. Resting Tremor- The predominant motor indications witnessed in Parkinson's disease encompass involuntary quivering of hands, arms, legs, jaw, cranium, tongue, lips, and chin. This tremor commonly manifests either in the hand or foot on one side of the body, or in rare instances, it may affect the jaw or face. The tremor usually exhibits a rhythmic, oscillatory motion at a frequency of 4-6 Hz.	**1. Depression** - A pervasive sense of sadness is a frequent issue and a preliminary sign of Parkinson's disease (PD), potentially presenting itself prior to the emergence of other symptoms. Individuals with PD frequently undergo periods of sorrow and despondency, leading to an undesirable disposition, inexplicably, which can diminish their overall life satisfaction. The intensity of this despondency can be so devastating for some PD sufferers that they might harbour thoughts and fantasies of ending their own lives
2. Rigidity – The rigidity or increase in stiffness or tonicity of a muscle is the second most common symptoms noted in PD patient. The person with PD often feels stiff or weak, pain and cramping in muscles and joints. Sometimes muscle rigidity can cause an increase in resistance to the extent that the person feels as if someone else is moving his or her joints.	**2. Dementia and or cognitive dysfunction-** Approximately 50% of individuals suffering from Parkinson's Disease (PD) experience cognitive impairments, including a slowed cognitive processing speed. Throughout their interactions, individuals with PD often encounter challenges in selecting the appropriate vocabulary and comprehending intricate statements. This phenomenon, known as the 'tip-of-the tongue' situation, frequently leads to numerous pauses in their speech, making it hard for their listeners to follow their train of thought. This type of dementia can influence memory, social discernment, language proficiency, logical thinking, among other cognitive aspects.

3. Slow movement (bradykinesia) - Bradykinesia, a common symptom in Parkinson's Disease (PD), often leads to involuntary movements, reduced motion range, and a gradual decline in spontaneous and autopilot movements. This condition often manifests in various ways including, the shrinkage of handwriting size, commonly known as micrographia, a reduced level of facial expressiveness, a decrease in the frequency of eye blinking, and a noticeable reduction in speech volume. Occasionally, bradykinesia can interfere with day-to-day tasks, particularly those involving routine movements. Additional signs may encompass inadequate movements, struggles in commencing movements, and abrupt cessation of ongoing motions.	**3. Problems in sleep (insomnia) -** Sleep disturbances are a prevalent issue, with an estimated 80% of individuals suffering from Parkinson's Disease (PD) experiencing challenges in maintaining sleep throughout the night. They may be plagued by various sleep disruptions, including restless sleep, vivid nightmares, emotionally charged dreams, daytime sleepiness, or sudden bouts of sleep onset during daylight hours. Nighttime could be marked by muscle rigidity, tremors, stiffness, or frequent urges to use the bathroom. They may also have vivid dreams or hallucinations, including intense nightmares, contributing to their sleep disruption. The most frequently observed sleep related conditions in PD patients encompass insomnia, REM sleep behaviour disorder, sleep apnoea, sleep attacks, and restless legs syndrome.[13]

5. EFFECTS OF PARKINSON

(A) Primary Effects

These can be further classified as motor and non-motor effects –

Motor

1. Tremor - in hands, arms, legs, jaw, or head.
2. Muscle stiffness - where muscle remains contracted for a long time.
3. Bradykinesia - Slowness of movement.
4. Postural instability - Impaired balance and coordination, sometimes leading Non motor effects.[11]

Non motor-

1. Anxiety
2. Depression
3. Hallucinations
4. Delusion
5. Dementia
6. Memory and thinking problem.[12]

(**B) Secondary effects:**

Skin cancer-

The link between Parkinson's disease (PD) and melanoma, uncovered through various epidemiological research, is quite fascinating. Melanoma, a type of cancer, originates from melanocytes that are responsible for melanin production, the pigment adding color to our skin, eyes, and hair. This particular cancer is known for its aggressive nature and resistance to treatments, contributing to 75% of all fatalities associated with skin cancer. PD and cancer, despite being separate diseases, share some similarities. Cancer is characterized by unrestricted cell growth and multiplication, while PD is marked by the early demise of dopaminergic neurons. Numerous epidemiological research papers have documented a higher incidence of melanoma among individuals suffering from Parkinson's Disease (PD) than anticipated. It was also observed that people diagnosed with melanoma demonstrated an increased probability of developing PD. [14]

The protein involved in Parkinson' s disease, α-synuclein, is elevated in melanoma cells. In Parkinson' s disease, αsynuclein forms amyloid deposits that are thought to kill dopamine-producing neurons. Furthermore, higher levels of α- synuclein in melanocytes (the skin cells that give rise to melanoma) correlate with reduced melanin production.

Effect on dopaminergic neurons-

The elevated power requirements of the dopaminergic neurons projecting from the substantia nigra pars compacta seemingly make these neurons prone to decay. These needs arise from their anatomical configuration and their inherent continuous activity. The process of action potential transmission through the expansive and intricate unmyelinated network significantly escalates the neurons' energy needs. The energy expenditure isn't directly correlated to the surface area or the axonal arbor's length. Instead, it escalates linearly with the axon's branching levels and grows exponentially relative to its size and complexity, namely, its surface area and the number of branching points. Moreover, cellular transport along these elongated axons' microtubules puts an extra strain on the motor proteins and kinesin which are fueled by ATP.[15]

Urinary tract infection

A urinary tract infection (UTI) frequently triggers sudden neurological degradation in individuals suffering from Parkinson's disease (PD). It is a major instigator of delirium, diminished functionality, falls, and subsequent hospitalization. Several clinical characteristics of PD, such as autonomic irregularities and modified urodynamics, frailty, cognitive deficiencies, and the necessity for bladder catheterization, amplify the susceptibility to UTIs. One of the feared consequences of untreated UTI is sepsis which can lead to morbidity in the patients with PD.[16]

Constipation

Constipation is a significant issue that affects up to 66% of all patients with Parkinson's Disease (PD), a rate that is

notably higher than in the wider population. The causes of constipation in PD are diverse and complex. Besides physical debilitation, lifestyle factors such as inadequate fluid consumption can significantly contribute to its onset. A delayed colonic transit in PD originates from both central and peripheral parasympathetic system dysregulation. Further complications can arise from issues with the sacral parasympathetic nuclei and pelvic ganglia, which may lead to outlet obstruction. This obstruction refers to irregular contractions or the inability of the voluntary sphincter to relax during defecation, potentially making rectal evacuation challenging.[17]

Treatment

Treatment for Parkinson's disease is based on a combination of:

- lifestyle changes
- medications

Adequate rest, exercise and a balanced diet are important. Speech therapy, occupational therapy, and physical therapy can also help improve communication and self-care.

Almost all cases require medication to control the various physical and mental symptoms of the disease.

Following are the drugs use for the treatment of Parkinson's disease :-

Levodopa

Levodopa is the most common form of treatment for Parkinson's disease. It helps replenish dopamine.

Patients with Parkinson's disease experience degeneration of the substantia nigra. This condition causes disruption of the nigrostriatal pathway and thus reduces striatal dopamine levels. Unlike dopamine, levodopa can cross the blood-brain barrier (BBB). Levodopa is converted to dopamine both in the central nervous system and in the periphery(21)

Treatment must be started with small doses, and the recommended dose is 300-1200 mg (more if tolerated) divided into 3-12 doses per day. (22)|

To improve absorption, patients should take levodopa 1 hour before or 2 hours after a protein-rich meal.(23)

About 75 percent of cases respond to levodopa, but not all symptoms improve. Levodopa is usually administered together with carbidopa and benserazide

Carbidopa slows the breakdown of levodopa, which in turn increases the availability of levodopa across the blood-brain barrie.

Dopamine Agonists

Dopamine agonists can mimic the effects of dopamine in the brain. They are less effective than levodopa, but may be useful as a bridge drug when levodopa is less effective.

Drugs in this class include bromocripto, pramipexole, and ropinirole. Dopamine receptor agonists stimulate dopamine receptors. Dopamine agonists can be used as monotherapy for motor symptoms or as adjunctive therapy when symptoms are inadequately controlled by levodopa or when motor fluctuations occur (24)

In addition to two oral non-ergoline agents, pramipexole and ropinirole, rotigotine is available as a patch. . Apomorphine, an ergoline dopamine agonist, is water soluble and lipophilic (25)

Anticholinergics

Anticholinergics are used to block the parasympathetic nervous system. They can help with rigidity.

Benztropine (Cogentin) and trihexyphenidyl are anticholinergics used to treat Parkinson's.

Amantadine (Symmetrel)

Amantadine (Symmetrel) can be used along with carbidopa-levodopa. It's a glutamate-blocking drug (NMDA). It offers short-term relief for the involuntary movements (dyskinesia) that can be a side effect of levodopa.

COMT inhibitors

Catechol O-methyltransferase (COMT) inhibitors prolong the effect of levodopa. Entacapone (Comtan) and tolcapone (Tasmar) are examples of COMT inhibitors.

Tolcapone can cause liver damage. It's usually saved for people who do not respond to other therapies.

Ectacapone does not cause liver damage.

Stalevo is a drug that combines ectacapone and carbidopa-levodopa in one pill.(26)

MAO-B inhibitors

MAO-B inhibitors inhibit the enzyme monoamine oxidase B. This enzyme breaks down dopamine in the brain.

Selegiline (Eldepryl) and rasagiline (Azilect) are examples of MAO-B inhibitors.(27) They can interact with many drugs, including:

- antidepressants
- ciprofloxacin
- some narcotics

Over time, the effectiveness of Parkinson's medications can decrease. By late-stage Parkinson's, the side effects of some medications may outweigh the benefits. However, they may still provide adequate management of symptoms.

List of drugs containing API (Active pharmaceutical ingredient) other than Levodopa :-

Brand Name	Composition	Dosage Form	Drug-Release Mechanism	Development Stage
Requip® GlaxoSmithKline	Ropinirole, hypromellose, hydrogenated castor oil,	Prolonged-release tablet	The drug is released by diffusion and erosion where hypromellose	Approved/ Marketed

	carmellose sodium, povidone K29–32, maltodextrin, magnesium stearate, lactose monohydrate, anhydrous colloidal silica, mannitol, ferric oxide yellow (E172) and glycerol dibehenate		acts as rate-controlling matrix	
Mirapex ER® Boehringer Ingelheim, Pfizer	Pramipexole, hypromellose, corn starch, carbomer homopolymer, colloidal silicon dioxide, and magnesium stearate	ER tablet	Extended release was achieved by combining three polymers such as hypromellose, corn starch, and carbomer homopolymer, after encountering digestive fluid. Drug first dissolves from the surface followed by matrix swelling, slow diffusion of the drug, along with the erosion of the tablet	Approved/ Marketed
Dostinex® Pfizer	Cabergoline, leucine, and lactose	IR capsule		Approved/ Marketed
Zelapar® Valeant pharmaceutical	Selegiline, gelatin, mannitol, glycine, aspartame, citric acid, yellow iron oxide, and grapefruit flavor	Orally disintegrating tablet	When the tablet is kept on the tongue, it disintegrates into small particles, which then dissolve in the saliva and are absorbed through the mucous membranes of the mouth	Approved/ Marketed

6. CONCLUSION

As per various different articles which has been reviewed to make this article on Parkinson's overview ,it's primary and secondary effects on various body organs and treatment. we come to know that Parkinson is second most neurodegenerative disorder after Alzimer disorder, because of depletion of nerve cell in brain there's decrease in dopamine level in the brain and server sign and symptoms are seen such as tremors, sleep disturbance, body shaking, speech disturbance etc. shortly we can say that due to imbalance between Acetylcholine and Dopamine the Parkinson occurs in an individual ,to overcome this problems related to Parkinson medication treatment are to be taken the main line drug is levodopa which acts as dopamine precursor that balance the dopamine level in the body, many more drug combination are given with levodopa like carbidopa and changing the lifestyle like healthy diet, proper medication intake, regularly excercise, yoga etc. but Parkinson can not be totally eradicated from an individual person because it's an neuronal disorder once the nerve cell is degenerated it can be regenerated ,but to an extent one can reduce the sign and symptoms.if at early stage the problem is detected than it can be treated.

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