CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Review Article*

A REVIEW ARTICLE ON NOVEL DRUG'S TARGETING PARKINSONS DISEASE

[1]Honey.E, [2]Sai Aswini
Dr.K.V.Subbareddy Institute of Pharmacy, Dupadu, Kurnool dist,518218.
Affiliated to Jawaharlal Nehru Technological University, Ananthapuram,515001

Abstract:
Parkinson's Disease is a common neurodegenerative disease characterised by rigidity, rest tremor, postural instability. The main aim of this article is to provide knowledge about the novel drugs that are being used in the treatment of Parkinson disease which are currently investigated and study the possibility in therapeutic targets. The novel therapeutic approach is to ensure the symptological control in the Parkinson disease patient. The treatment options are limited with most of the current novel therapeutic approach based on restoration of the dopaminergic tone in the Striatum. As we understand the pathogenesis of PD Accomplished the novel therapeutic drugs are emerged to control the symptoms of PDwithout problematic side effects. This novel approach ensures the expedited route to the clinics by providing the safety data regarding the novel therapeutic approach in managing the PD patients. These novel therapeutic approaches targeting on PD treatment are likely toevolve considerably over the next coming years.

Keyword : *Novel Dopaminergic Drugs, Deep Brain Stimulation, Stem cell Therapy,Exabalate Neuro System, Novel Levodopa formulation.*

Corresponding author:
E.Honey ,
M.Pharm, Assistant Professor,
Dr.K.V.Subbareddy Institute of Pharmacy,Kurnool-518218,
Jawaharlal Nehru Technological University,Ananthapur,
Andhra Pradesh,515001,
Mobile: +91 6281873096
E-mail: honeyenagandla843@gmail.com

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Please cite this article in press E.Honey et al., ***A Review Article On Novel DrugsTargeting Parkinsons Disease****, Indo Am. J. P. Sci, 2024; 11 (01).*

INTRODUCTION and EPIDEMIOLOGY:

Parkinson's disease (PD) is an idiopathic disease of the nervous system characterized by both motor and non-motor system manifestations. It is a chronic progressive neurodegenerative disorder that occurs mostly in older persons but that can appear in much younger patients. It is the second most common neurodegenerative disease.[1]PD include Dementia with Lewy Bodies (DLB)Cortico-basal Degeneration (CBD), Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP). Parkinson Disease has been recognized since the early 1800's when the physician after whom the disease is named first described it. Sometimes called "paralysis agitans," PD is uncommon in young people, especially those under 40 [2]. As many as one million Americans are affected by PD and nearly 60,000 new cases are diagnosed each year. Worldwide, an estimated 7 to 10 million people are thought to be affected. Men are 1.5 times more prone to have PD than women.[3]

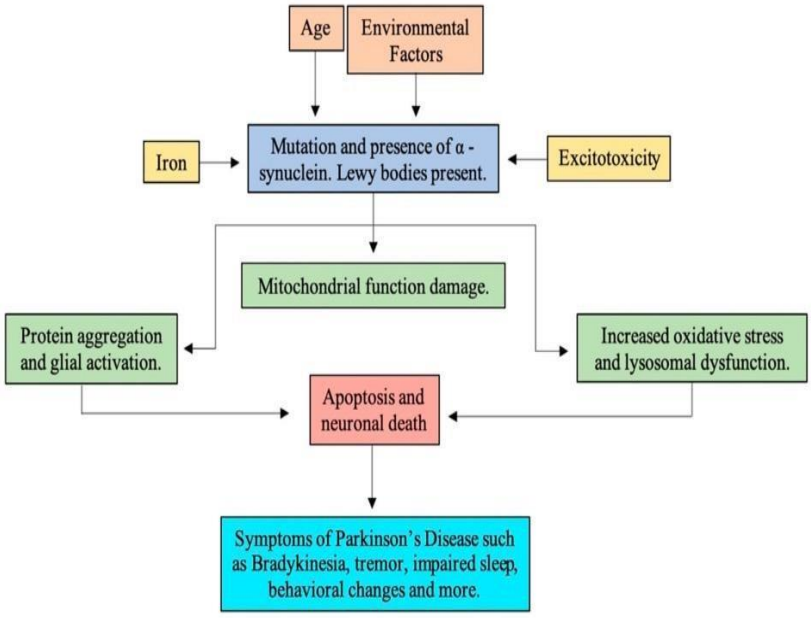
A population-based study of US Medicare beneficiaries found a mean prevalence of 1.6% for PD65Parkinson's disease: a review among persons 65 years and above. Less blacks and Asian Americans are affected than whites. Higher rates of PD are existent in the Midwest/Great Lakes region and the northeastern US seaboard.

Exposure to environmental toxins in these areas is suggested to be a possible etiologic factor[4][5].The prevalence of PD is expected to rise dramatically over the next 20 years as Americans age. Consequently, it will continue as an important health issue and strong economic drain due to its direct and indirect costs.[6]

PATHOPHYSIOLOGY

The pathological definition of PD is loss or degeneration of the dopaminergic (dopamine-producing) neurons in the substantia nigra and development of Lewy Bodies (a pathologic hallmark) in dopaminergic neurons [7]. Pathologic changes may precede obvious symptoms by two decades or more [8]. This preferential loss of dopamine producing neurons results in marked impairment of motor control. Lewy Bodies, or abnormal intracellular aggregates, contain various proteins including alpha-synuclein and ubiquitin that impair optimal neuron functioning. Specifically, exposure to environmental toxins (e.g., pesticides)[9], drugs of abuse, or the stress of the aging process promotes a chronic low-level inflammation in the brain. This inflammatory process over time generates cellular senescence in brain neurons[6][10].From a pathologic perspective, the brain's substantia nigra pars compacta and the pontine locus coeruleus are affected by typical abnormalities of PD patients including depigmentation, neuronal loss and gliosis. By the time PD symptoms occur, about 60-70 percent of the neurons in the substantia nigra pars compacta are gone[11][12].

Genetic Mutations that code proteins of the central nervous system play a role in neuronal death. Specifically, alpha-synuclein becomes abnormal and self- aggregates. This aggregated, insoluble alpha-synuclein is a major constituent of Lewy Bodies, cellular inclusions that are the hallmark of PD[11]. In addition, systems designed to break down abnormal proteins like the ubiquitin – proteasome system also become impaired. Other impaired processes that may play a role in PD are mitochondrial dysfunction or abnormal oxidative stress through reactive oxygen species causing neuronal degeneration[11].Some researchers use the theories of colleagues[13]to explain PD pathophysiological progression. Called the "dual-hit" hypothesis, the theory suggests that an unknown, possibly viral, pathogen enters the brain through the olfactory route.



PARKINSON'S DISEASE

NOVEL DRUGS TARGETING

DRUGS	MECHANISM OF ACTION	GROUP
Selegiline rasagiline	Selective irreversible inhibition of MAO-B. Inhibition of presynaptic dopamine receptors.	Monoamine oxidase-B inhibitors
Pramipexole	Stimulate D2,D3,D4 receptors	Dopamine agonist
safinamide	It is a potentreversible monoamine oxidaseB inhibitor.modulate glutamate transmission.	MAO inhibitor
amantadine	Increase synthesis and release of dopamine,blocks NMDA glutamatergic receptor	N-Methyl-D- aspartate receptor inhibition.
pimavanserin	It is an inverse agonist and antagonist (a partial inverse agonist)at 5-HT2 receptor	Atypical antipsychotic drug
Entacapone Tolcapone	Reversible inhibition of COMT	Catechol-O-Methyl transferase inhibitor
Carbidopa/Levodopa	A dopamine precursor;crosses the blood brainbarrier and it is converted to dopaminergic terminals by dopa decarboxase	Dopamine

NOVEL PHARMACOLOGIC MANAGEMENT

The major objective of PD research is to develop disease-modifying therapy that can slow or stop the neurodegenerative process. However, there is no existing definitive disease- modifying therapy to achieve this aim.

SURGICAL TREATMENT

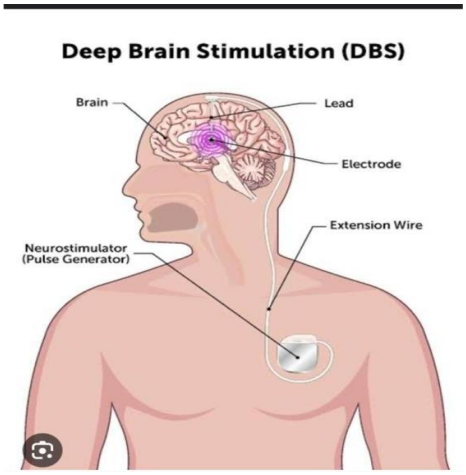
DEEP BRAIN STIMULATION(DBS)

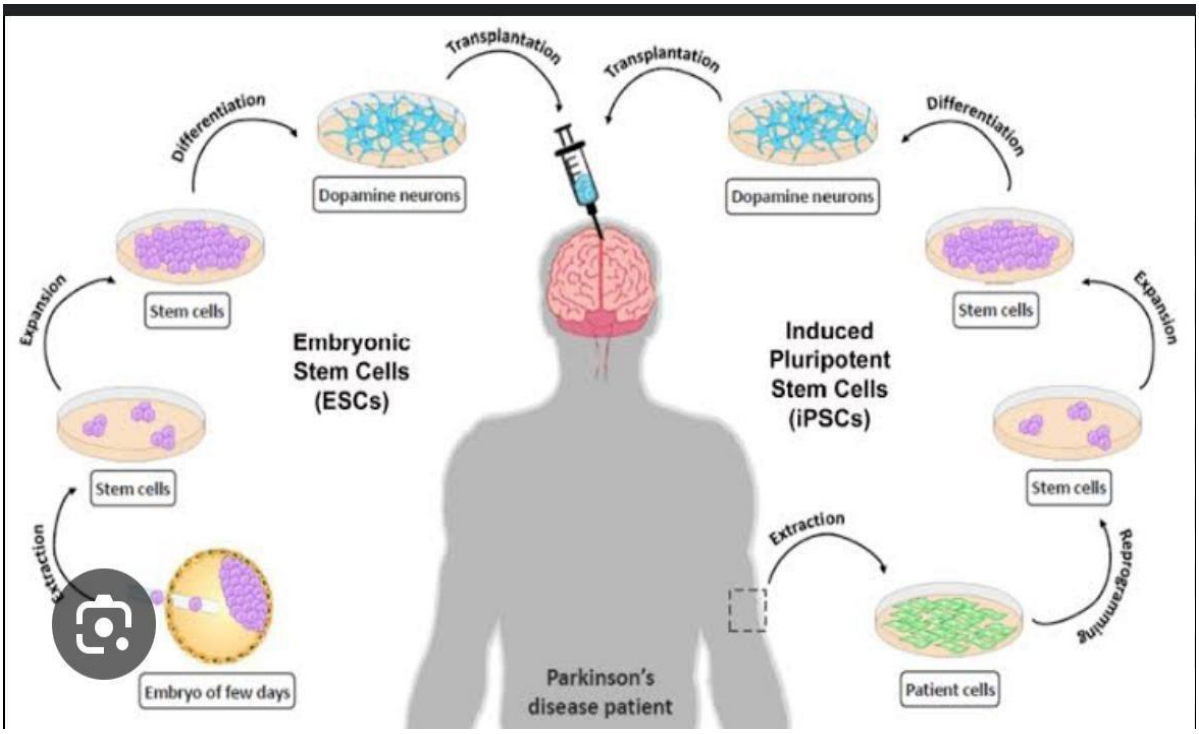
Deep brain stimulation (DBS) of either the subthalamic nucleus (STN) or globus pallidus interna

is a well-known treatment for patients with motor complications[14][15][16]. For treatment of tremors, thalamic DBS is a viable option. Surgical treatment is preferred when motor fluctuations and dyskinesias become disabling despite responsiveness of the motor symptoms to levodopa. The average time before DBS is performed is about 10–13 years after the diagnosis of Parkinson's disease has been established. Findings of the EARLYSTIM trial, a multicenter randomized control trial showed that DBS in the early course of disease (mean disease duration 7.5 years, with motor fluctuations for <3 years) could improve the patient's quality of life and several secondary outcome measures more than the best medical therapy[17]. DBS is reversible and can be adjusted for disease progression. The presence of dementia, acute psychosis and major depression are the exclusion criteria for DBS[18]. Bilateral DBS of the STN improves the UPDRS II (activities of daily living) and UPDRS III (motor) scores, on an average, by 50–60% compared with the preoperative medical OFF state. The total daily dopaminergic drug dosage is reduced by about 60% following the institution of DBS, and dyskinesias decrease by 60–70%[19][20]. Subthalamic nucleus (STN) DBS was associated with decreased requirement of levodopa doses[21].The mortality of DBS is <0.5% and the important adverse events include intracranial bleeding or device-related complications (such as infections and lead misplacements, among others[22]). non-pharmacological therapies available for PD include exercise, education, support groups, speech therapy and nutrition. Evidence from literature recommends their usage early on in the course of the disease.

Stem cell therapy in Parkinson's disease

The presence of α-synuclein is associated with cognitive impairment in Parkinson's disease dementia (PDD) (Kern et al., 2006). Although some studies have shown that transplantation of dopaminergic precursors caused improvement in motor symptoms of PD (Chen et al., 2004), studies evaluating the potential of stem cell transplantation in treating cognitive dysfunction in PDD are very few (Kern et al., 2006).α-synuclein aggregates are known to be toxic to cells, leading to neuronal deaths in many α-synucleinopathies (Hirschi et al., 2003). Neuronal cells release α-synuclein aggregates by the process of exocytosis (Hirschi et al., 2003), which are then taken up via endocytosis by neurons and glial cells (Van den Bos et al., 2022, Salem et al., 2014, Mo et al., 2012). Furthermore, it is suggested that the interaction between α-synuclein and N-methyl-D-aspartate (NMDA) receptors could facilitate clathrin-mediated endocytosis of NMDA receptors (Gomperts, 2016).Clathrin and early endosome antigen 1 (EEA1) expression was found to be increased in cells treated with α-synuclein. This expression, however, was significantly decreased when cells were cocultured with MSCs. The internalization of α-synuclein via clathrin-mediated endocytosis was also inhibited by transplanted mesenchymal stem cells. This was observed to occur by altering the interaction between α-synuclein and NMDA receptors, thus reducing α-synuclein transmission and cell death induced by it (Hirschi et al., 2003)[23].





EXABALATE NEURO 4000 DEVICE SYSTEM

The Exabalate Neuro 4000 system from InsighTec Plc is the leading system for brain Magnetic Resonance Focused Ultrasound (MRgFUS), an emerging technique that is at present predominantly used to treat movement disorders such as Essential Tremor (ET) and Parkinson's Disease (PD). Since the success of initial pilot studies using the ExAblate system to treat ET in 2013 in Virginia, USA[24], * further brain MRgFUS clinical trials have been undertaken interna-tionally which has built experience and confidence in the technique. The ExAblate Neuro 4000 System is now used internationally for the treatment of movement disorders. Furthermore, as the field expands with further technical and clinical research the utility of the ExAblate system and MRgFUS in the brain to treat neurological conditions grows beyond movement disorders. Certainly, there has been an acceleration of research activity in the field over the past two decades[25].

Device profile of the ExAblate Neuro 4000 system

The Exabalate Neuro 4000 system was given European regula-tory CE marking in 2015 and Premarket approval (PMA) from the United States Food and Drug administration (FDA) in 2016 for use in unilateral Thalamotomy treatment of idiopathic Essential Tremor patients with medication-refractory tremor. With increasing experience including the landmark interna-tional multi-center randomized control trial which involved several centers in United States of America (USA), Canada, Korea [26] and Japan; * further approvals have bestowed from other national and regional regulatory and commissioning bodies.

In the USA, FDA approval has been given for its use in the treatment of Essential Tremor and tremor dominant Parkinson's Disease. Worldwide there is a growing number of international centers using the ExAblate system to treat move-ment disorders and trialing its use in for other neurological conditions[27].

LEVODOPA AND NOVEL LEVODOPA FORMULATION

The mechanism for major motor symptoms in PD is the depletion of striatal dopamine due to loss of dopaminergic neuron in the SNpc. Administration of levodopa to substitute striatal dopamine was a major breakthrough in the treatment of PD, and since then, multiple additional targets for dopaminergic therapies have been identified. Levodopa is considered as gold standard therapy and almost all patient require this particular treatment during the course of their illness[28].

Long-term use of levodopa is complicated by motor fluctuations and dyskinesias. Mechanisms underlying these motor complications are still unclear. One accepted hypothesis for this manifestation is the involvement of both presynaptic and postsynaptic mechanisms that eventually lead to non-physiological pulsatile striatal dopamine receptor stimulation, causing various maladaptive neuronal responses[29][30].

Erratic drug delivery due to the short half-life of levodopa, as well as variability in its absorption and blood–brain barrier transportation also play an important role in the development of motor complications[31].

Levodopa bioavailability can be improved either by developing more effective oral formulations (e.g., sustained release formulations) or by devising innovative routes of administration (e.g., intestinal infusion, transcutaneous administration via mini pumps or by inhalation). RYTARY/IPX066 is a novel levodopa-carbidopa (LD/CD) oral formulation combining the immediate-release and extended-release LD/CD. This has been approved in the USA and the European Union. IPX066 is composed of LD/CD micro-beads designed to dissolve at various rates that allows for a quick absorption and sustained levodopa release over an extended period of time. Studies have shown that IPX066 administration improved the symptoms in patients with both early and advanced PD[32][33][34][35][36][37].. Significant improvement in the unified Parkinson's

disease rating scale (UPDRS) scores has been reported without the development of worsening troublesome dyskinesias, using this preparation when compared to other levodopa formulations[38][39][40][41][42][43].

Levodopa-carbidopa intestinal gel (LCIG) is an approved therapy for inpatients with advanced PD. LCIG is delivered continuously by a percutaneous endoscopic gastrojejunostomy tube (PEG-J), through a portable infusion pump. It reduces L-dopa-plasma level fluctuations and thereby decreases the motor complications[44][45][46]. Recently, researchers are evaluating the 'accordion pill' (AP09004), an extended release LD/CD formulation with Gastroretensive properties[47][48][49].

Other levodopa formulations currently active in studies include ND-0612, ODM-101, CVT-

301 and cyclops. ND-0612 is a proprietary liquid formulation of LD/CD that enables subcutaneous administration via a small patch-pump device; and, ODM-101is a new oral formulation of levodopa/carbidopa/entacapone that contains a higher amount of carbidopa (65 or 105 mg)[50][51][52] CVT-301 and cyclops are levodopa inhalation powders. As they possess a rapid onset of action, they are promising candidates for the treatment of PD[53][54].

Although, the highest levels of symptomatic relief is provided by levodopa, to delay the ensuing complications, MAO-B inhibitors/dopamine agonists can be considered asthe initial therapy. A randomized trial of newly diagnosed PD patients failed to show the long-term benefit of levodopa sparing therapy[55].

This study, however, had limitations characterized by a lack of generalizability, as patients

<60 years of age, who were at a high risk of developing dyskinesias, were not well represented[56].

SKIN RELATED COMPLICATIONS OF ANTI PARKINSONIANTHERAPHY

- skin biopsy plays an emerging role in diagnosis and stem cell therapy.

Non-iatrogenic: Melanoma, seborrhea, dyshidrosis. rosacea, and bullous pemphigoid.

Iatrogenic :
Livedo reticularis, nodules related
Subcutaneous levodopa infusions

Skin disorders in parkinsons disease have come at particular Complications for several reasons.

- Non- iatrogenic and Iatrogenic skin disorders are over-represented in parkinsons disease. Some skin disorders Such αs seborrheic dermatitis [SD] & sweating dysfunction may in part due to peripheral autonomic dysfunction & can predate onset of parkinson disease motor symptoms.
- Melanoma & Bullous pemphigoid[57][58] which seems to have a more complex relation to Parkinson disease, often develop years to established. As per these conditions can have severe implications on the patient's quality of life and prognosis.
- skin disorder conditions also be seen as a consequence of oral, parenteral, & Surgical therapies for parkinsons disease. such skin manifestation may be directly attribute to certain medications used in the treatment of Parkinsons disease.
- α-synuclein which plays a central role in parkinsons[59] disease pathogenesis that has been demonstrated Over the past few decades to be present in multiple peripheral tissues, including skin[60][61].
- This small protein involved in a variety of cellular mechanisms,undergoes misfolding & aggregates in the brain as well as in the skin[62] and may contribute to some non-motor symptoms[63].
- In the recent years,skin biopsy has been emerged as apotential hall mark and promising tool for diagnosis of α- synucleinopathies[64] skin may even have thepeutic implicationsa source of stem cells[65].

Non –iatrogenic complications of Parkinson's disease therapy

Skin disorder	complication	Treatment
melanoma	Skin lesions with variable color,irregular shape & flat (or)raised border,sometimes arising from pre-existing moles (or) denovo	Surgical therapies adjuvent radiationtherapy & targeting therapies.
Seborrheic dermatitis	Sharply demarcated erythematous lesions with itching & burning in sebaceous area	Topical therapies keratolytics &topical immune suppressants systemic therapy;antifungal &antimicrobial peptide
Sweating disorders	Hyperhidrosis &hypohidrosis	**Hyperhridosis**:it is associated with medication off state increases more continous dopaminergic therapy & DBSDyskinesias:reduces doperminergic therapy (amantadine) Focal symptoms:intradermal botulinumtoxin injection **Hypohidrosis:**avoidence of excessive heatexposure due to reduced evaporative cooling.
Perioral dermatitis	Perioral skin irritation associated with sialorrhea	Oral therapies (or) salivary glands injection with botulinum toxin

Iatrogenic complication of Parkinson's disease therapy

Therapy	Potential complication	Treatment
Levodopa carbidopa intestinal gel	Wound infection Granulation tissueStroma leakage	Systemic antibiotics possible PEG removal Topical silver nitrate Avoidance of topical creams keepstroma dry
Levodopa carbidopa subcutaneous infusion	Subcutaneous nodules	Prevention: rotation of infusionsites
Apomorphine subcutaneous infusion	Skin nodules infusion site erythema	Treatment: silicone dressing, ultrasound management
Sublingual apomorphine	Oesopharyngeal errythema	Resolution with drug discontinuation
DBS	skin erosin	Surgical revision wound debridement, hardware removal (or)re implantation

CONCLUSION:

Current novel drugs and treatments of PD deal well with the symptomatic clinical presentation. The available novel therapeutic strategies mainly elevate the reduced levels of dopamine by utilizing different pharmacological mechanisms as schematically presented in table. However, the available therapeutic options can slow down the progression of the disease. Novel drugs and treatments needs to create opportunities for developing and evaluating as neuroprotective agents. In theory, these drugs will modify the course of the disease by preventing or delaying the death of dopaminergic neurons and, moreover, other types of neuronal cells, thus being beneficial in the first stages of PD (Bonuccelli and Del Dotto 2006). MAO B inhibitors, such as selegiline and to a greater extent rasagiline, safinamide have been shown to have disease-modifying potential. The neuroprotective effect of selegiline is compromised by its many amphetamine neurotoxic metabolites, and introduction of rasagiline circumvents this problem. It is important to remember that the neuroprotective mechanism of rasagiline and other propargylamines derivatives in different neuronal models appear to be independent of MAO B inhibition. Therefore, it is essential to further elucidate the pharmacological mechanism of action of safinamide inorder to get a better insight into the neuroprotective path- ways and to apply them for new pharmacological targets for the development of novel anti-PD drugs. It is tempting to underst that in future the novel drugs to be developed for PD treatment will be multi functional by correcting both the lack of dopamine as well as providing neuroprotection to the degenerating neurons. To optimise fully their therapeutic efficacy it would be important to identify the proper mode of administration (pharmaceutical compounding) that takes into account to their pharmacokinetic properties.

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