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Parkinson's Disease: What is New?

ABSTRACT

Parkinson disease (PD) is one of the most common movement disorders in elderly population worldwide. It is a complex, progressive neurodegenerative disease with a constellation of heterogeneous motor and non-motor clinical features. Research developments in recent years have made remarkable progress in pathophysiology, diagnosis, and treatment of this disease. We wish to highlight these recent developments that have the potential to change the management of PD in routine clinical practice in near future. This manuscript will discuss the current developments in the diagnosis, pathophysiology and particularly, the treatment aspects of this commonly encountered disease.

Key words: Parkinsons disease, motor, non motor, recent treatments

INTRODUCTION

Parkinson disease (PD) is one of the common illnesses encountered in the general practice in India. Since its first description by James Parkinson in 1817,[1] we have come a long way in our understanding of the disease process. Over the past few years, there has been a great progress in research related to the pathophysiology and the diagnosis, and this has led to the evolution of strategies useful in the management of Parkinson disease. The incidence and prevalence of PD is increasing worldwide with aging population. Incidence increases 5–10-fold from sixth to ninth decade and prevalence is expected to double in next two decades.[2] The situation in India is already reflecting this trend as the average life expectancy has remarkably increased and India is going through its demographic transition. Hence, it is extremely important to remain up to date with newer developments for a better patient management. This manuscript will focus on recent developments and updates in Parkinson disease.

PATHOGENESIS: WHAT IS NEW?

The pathology of PD is defined by loss of dopaminergic neurons in substantia nigra pars compacta in the midbrain and presence of Lewy bodies, which are cytoplasmic inclusions of insoluble alpha-synuclein aggregates. Involvement of other regions of the brain and non-dopaminergic system is also well recognized. Developments in the past few years have focused more on the sequence of events leading to underlying defects, cellular level disturbances caused by various genetic and environmental factors, as well as new prion theory. Few of these important points are highlighted below.

1. The loss of dopaminergic terminals in striatum is important for onset of motor symptoms, as is the loss of dopaminergic neurons in substantia nigra[3,4]
2. Latest research has found possible prion-like role of alpha-synuclein assemblies, which may explain the propagation of Lewy pathology from one brain region to another[5]
3. Olfactory and gut theories of PD are being explored[6]
4. The contributions of environmental[7] and genetic[8] factors have been much explored recently.

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CLINICAL CHARACTERISTICS: WHAT IS NEW?

The well-known motor and non-motor clinical features are summarized in Table 1.

Literature now suggests three different stages in clinical evolution of a patient with PD as depicted in Table 2 and it is important to appreciate the first two stages.

A new subcategory of 'clinico-genetic PD' has been added recently.

DIAGNOSIS: WHAT IS NEW?

The UK brain bank criteria were used most commonly for diagnosis of PD in clinical practice since 1988, though they were primarily designed for diagnosis in pathological series.[8]

Table 1: Common clinical manifestation in Parkinson disease

Motor manifestation	Non-motor manifestation
Rest tremor	Hyposmia
Hypokinesia/bradykinesia	Constipation
Rigidity	Depression
Postural instability	Excessive daytime sleepiness
Shuffling gait	REM sleep behavior disorder
Freezing/festination	Pain
Micrographia	Fatigue
Hypomimia	Erectile dysfunction
Reduced arm swing	Dementia
Abnormal glabellar tap	Hallucination/anxiety/
Dysphagia/dysarthria	psychosis
Blepharospasm	
Camptocormia	

Table 2: Three different clinical stages in evolution of PD

Clinical stage	Predominant features
Preclinical stage	A state of initiation of pathologic neurodegeneration but without any signs or symptoms of the disease. Research is focusing on identifying biomarkers for this stage which may help in future for early recognition of the disease process
Premotor stage	Premotor or prodromal stage refers to a state in which patients usually present with some of the non-motor symptoms. This stage is important for early suspicion of PD
Motor stage	The third or final stage is the clinical stage with classical motor features that define parkinsonism (bradykinesia with either rest tremor or rigidity)

A number of changes have been incorporated in the latest 2015 MDS (movement disorder society) criteria[9] which are based on recent developments in knowledge about the disease. Important changes with its rationale are highlighted below.

1. The new criteria are more inclusive, having reduced the absolute exclusion criteria
2. A newer 'red flags' category is added, which allows a diagnosis of PD to be still compatible when the presence of equal number of supportive criteria exist
3. Olfactory loss and abnormal cardiac MIBG scintigraphy, the presence of either of the two, is now one of the supportive criteria. Similarly, normal functional neuroimaging of the presynaptic dopaminergic system is now included in the exclusion criteria
4. Dementia with Lewy body is no longer an exclusion criterion for PD
5. A new subset of "prodromal markers" have been added to predict the likelihood of developing established PD.

To summarize, new MDS criteria allow diagnosis of PD at an earlier stage, emphasizes more on importance of non-motor manifestations compared to older criteria, and eases some of the exclusion criteria for allowing a relatively broader clinical spectrum in the diagnosis of PD.

TREATMENT: WHAT IS NEW?

Most of the advances in recent years are related to the management part in patients with PD. Since non-motor manifestations are a major cause of poor quality of life in these patients, newer pharmacological treatment is emerging to address them. Further, as we know more about different aspects of pathophysiology in PD, research has also recently focused on the role of neuro-protective approach to halt or reverse the underlying degenerative process. We shall discuss the updates in the management of patients with PD below in the context of routine practical dilemmas.

WHEN TO START THERAPY IN EARLY DISEASE?

Initiation of pharmacological treatment in patients with PD depends on multiple factors like age at onset, premorbid level of activity of patient, and presence of severity of motor and nonmotor symptoms. Recent development recommends that treatment should be initiated as soon as patients have social or physical disability due to disease.[10] Treatment delay may lead to progressive impairment in quality of life.

SELECTION OF INITIAL AGENT FOR INITIATION OF TREATMENT?

Till date, there is no single disease-modifying therapy available that has established its role in clinical practice. Though several agents are being evaluated for its potential role in disease modification, current management remains symptom-driven. Primary goal of pharmacological treatment is to improve patient's overall quality of life without causing disabling side effects. Level A evidence exists for initiation of treatment with either of the threeclasslevodopa, dopamine agonist, or monoamine oxidase inhibitor (MAO-B inhibitor). Initial drug choice does not alter long-term outcome in PD.

Since approximately 40% of patients develop levodopa-induced dyskinesia by 4–6 years of treatment with levodopa,[11] one school of thought suggests the use of MAO-B inhibitor or dopamine agonists early, adding levodopa later, specifically in younger patients with predominant motor symptoms. However, the use of this concept should not deprive patients from potential benefits of levodopa whenever deemed necessary.

HOW TO MANAGE MOTOR FLUCTUATIONS AND DRUG-INDUCED DYSKINESIA AT VARIOUS STAGES OF THE DISEASE?

Wearing off effect (reduced motor activity and re-emergence of parkinsonian symptoms before the next due dose), delayed 'on' or no 'on' (delayed response to levodopa or failure of response to levodopa) and, peak dose dyskinesia (involuntary movement at the maximal on period of drug) are the major motor complications to be tackled at different times during the

disease progress. Two main strategies to manage these are- (1) optimization of medical therapy (2) use of device-assisted therapy in advanced stage.

Optimization of medical therapy

a. Intermittent non-physiological pulsatile manner of postsynaptic dopamine receptor stimulation delayed gastric emptying, and competing with amino acid when taken along with food are some of the major concerns postulated to be responsible for the motor complications. Following are the modifications that can be made to minimize fluctuations and dyskinesia
b. Levodopa should be taken at least half hour before or after food. Addition of a prokinetic agent such as domperidone may reduce gastric emptying time. Smaller doses with increased frequency of levodopa administration are also helpful
c. Adding MAO-B inhibitors (selegiline, rasagiline) or COMT inhibitor (entacapone) may reduce off period. Dopamine agonists may also be used in maximum tolerated doses. Transdermal rotigotine has shown improvement in early morning motor symptoms.[12] Amantadine is helpful to treat levodopa-induced dyskinesia, specifically when levodopa daily dosage cannot be reduced due to its potential benefits
d. Intermittent subcutaneous apomorphine injections can help as rescue therapy for off symptoms.
e. Safinamide and zonisamide (MAO-B inhibition and glutamate release modulation), both have shown benefit in prolonging on period in patients on levodopa.

Use of device-assisted therapy in advanced stage

As clinical course of PD is complex, heterogeneous, and slowly progressive, defining the advanced stage is a difficult task. A recent study has defined "advanced PD" when long-term disabling complications (both motor and non-motor), either due to natural disease course or due to side effects of medications, are not adequately controlled with optimum medical management.[13] Three main device-assisted therapies are available as shown in Table 3.

No single option is clearly superior to the others and hence individual patient selection is especially important while deciding advanced therapy option.

Table 3: Device assisted therapy for advanced PD

Device	How it works
Deep brain stimulation	Targeting either subthalamic nucleus or globus pallidus interna, this functional neurosurgical procedure improves dyskinesia, fluctuations, and tremor. However, non-dopaminergic symptoms such as autonomic, cognitive, or psychiatric symptoms are unlikely to improve
Continuous subcutaneous infusion of apomorphine	Apomorphine is D1 and D2 receptor agonist with rapid onset of action. Early stages, it is used as injection for rescue therapy of off period while in advanced stages, it is delivered continuously by means of a portable pump
Intra-intestinal infusion of levodopa carbidopa gel	Drug is delivered directly to proximal jejunum through gastrojejunostomy tube. It is beneficial in patients with erratic levodopa absorption

Table 4: Common non-motor manifestation in PD and its treatment options

Non-motor symptoms	Common medications in use
Sleep-related: Insomnia, excessive daytime sleepiness, REM sleep behavior disorder	Melatonin or Clonazepam Recent: Topical dopamine agonist rotigotine improves sleep[14]
Neuropsychiatric: Visual hallucinations, illusion, delusion	Pimavanserin (5HT2A inverse agonist), Quetiapine, Clozapine
Cognitive impairment: Dementia	Rivastigmine
Autonomic: Orthostatic hypotension Urinary dysfunction Erectile dysfunction Excessive salivation	Fludrocortisone, Droxidopa, Midodrine Oxybutinin, Solifenacin, Mirabegron, Tolterodine Sildenafil, Tadalafil Topical atropine, Botulinum toxin

HOW TO MANAGE NON-MOTOR SYMPTOMS?

Since non-motor symptoms are increasingly being identified as a major concern for quality of life, newer symptomatic treatment has emerged. The following table outlines few common medications for symptomatic relief of these features (Table 4).

NEWER TREATMENTS ON THE HORIZON

Several new treatment options are being evaluated which may transform the management of a patient with PD. In Table 5, we highlight some of the newer therapies that are currently undergoing or soon to be reaching clinical trials stage.

HOW HAS MY PRACTICE CHANGED?

1. Based on newer concepts and treatment options that have emerged in recent years, more personalized management on individual basis can be offered to our patients
2. Suspecting and confirming the diagnosis is possible relatively early nowadays, which is helpful to the patient for maintaining better quality of life from onset
3. Though primary treatment options remain the same, newer preparations and class of therapy coming up may allow better adjustment of the drug regime for side effect-free optimum benefit. Symptomatic management of non-motor symptoms would be much better with this new knowledge
4. Owing to the likely approval of newer therapies, a disease modifying treatment may be possible in upcoming years.

Table 5: Newer therapy options in trials or recently approved

Treatment strategy	Agent	Comment
Newer levodopa preparations	Inhaled levodopa	approved by FDA in 2018 for improved motor functions compared with placebo
	Extended-release formulation	Marketed in the U.S. (IPX066) to reduce off period
Immune therapy	Biogen and Prasinizumab	Humanized monoclonal antibody targeting N or C terminal of alpha-synuclein, respectively[15] Active and passive immunization techniques against alpha-synuclein as neuro-protective mechanism are being studied in trials[16]
Drug repurposing this concept uses already available drugs for different indications which are found to be useful in some way for Parkinson disease	Beta agonist	by modulation of SNCA transcription, may reduce alpha-synuclein levels and risk of PD[17]
	Exenatide (glucagon-like peptide 1 analogue)	anti-apoptotic and anti-inflammatory action, has been found useful in reducing UPDRS score for motor symptoms compared to placebo[18]
	Terazosin (an alpha antagonist)	due to its neuroprotective effects, has emerged as a putative treatment option for PD[19]
	Ambroxol	Used as an expectorant, has been recently shown to increase glucocerebrosidase activity in patients with GBA-1 mutation (found in 5% of sporadic PD)[20]
Neurotrophic factors	GDNF (glial cell line derived neurotrophic factors)	Neuroprotective therapies based on GDNF (glial cell line derived neurotrophic factors), such as intra- putaminal infusion; are currently being tried for their probable role in disease modification[21]
Gene therapy	Adeno associated virus therapy containing AADC	Adeno associated virus therapy containing the gene for AADC (aromatic L amino acid decarboxylase or Dopa decarboxylase) is targeted into putamen. Evidence showed that it increased enzymatic activity and reduction in levodopa dose[22]
Stem cell therapy	-	Grafting of pluripotent stem cells that provides a new source for dopaminergic progenitor cells is currently undergoing trials
Deep brain stimulation	-	Since gait disturbance and postural instability are dopamine unresponsive symptoms, these features usually do not improve by the DBS of subthalamic nucleus or globus pallidus interna. Pedunculopontine nucleus has been recently tried as a new target for gait issues.[23] Non-invasive DBS techniques are being used in trials that use external devices to deliver electric stimulation at the target area may reduce risks associated with neurosurgery[24]

(*Contd...*)

CONCLUSION

Newer understanding of the anatomical basis and underlying pathophysiology in Parkinson disease has led to opening of immense options for better management. In future years, management of PD may evolve from mainly symptomatic to disease-modifying or even disease-preventing approach.

REFERENCES

1. Parkinson J. An Essay on the Shaking Palsy. London: Sherwood, Neely, and Jones; 1817.
2. Dorsey ER, Sherer T, Okun MS, Bloem BR. The emerging evidence of the Parkinson pandemic. J Parkinsons Dis 2018;8:S3-8.
3. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: Substantia nigra regional selectivity. Brain 1991;114:2283-301.
4. Marras C, Beck JC, Bower JH, Roberts E, Ritz B, Ross GW, *et al.* Prevalence of Parkinson's disease across North America. NPJ Parkinsons Dis 2018;4:21.
5. Brundin P, Melki R. Prying into the prion hypothesis for Parkinson's disease. J Neurosci 2017;37:9808-18.
6. Johnson ME, Stecher B, Labrie V, Brundin L, Brundin P. Triggers, facilitators, and aggravators: Redefining Parkinson's disease pathogenesis. Trends Neurosci 2019;42:4-13.
7. Simon DK, Tanner CM, Brundin P. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. Clin Geriatr Med 2020;36:1-12.
8. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-4.
9. Postuma RB, Berg D. The new diagnostic criteria for Parkinson's disease. Int Rev Neurobiol 2017;132:55-78.
10. Grosset D, Taurah L, Burn DJ, MacMahon D, Forbes A, Turner K, *et al.* A multicentre longitudinal observational study of changes in self reported health status in people with Parkinson's disease left untreated at diagnosis. J Neurol Neurosurg Psychiatry 2007;78:465-9.
11. Ahlskog JE, Muenter MD. Frequency of levodopa related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001;16:448-58.

12. Trenkwalder C, Kies B, Rudzinska M, Fine J, Nikl J, Honczarenko K, *et al*. Rotigotine effects on early morning motor function and sleep in Parkinson's disease: A double-blind, randomized, placebo-controlled study (RECOVER). Mov Disord 2011;26:90-9.
13. Luquin MR, Kulisevsky J, Martinez-Martin P, Mir P, Tolosa ES. Consensus on the definition of advanced Parkinson's disease: A neurologists-based Delphi study (CEPA study). Parkinsons Dis 2017;2017:4047392.
14. Pierantozzi M, Placidi F, Liguori C, Albanese M, Imbriani P, Marciani MG, *et al*. Rotigotine may improve sleep architecture in Parkinson's disease: A double-blind, randomized, placebo-controlled polysomnographic study. Sleep Med 2016;21:140-4.
15. Schenk DB, Koller M, Ness DK, Griffith SG, Grundman M, Zago W, *et al*. First-in-human assessment of PRX002, an anti-α-synuclein monoclonal antibody, in healthy volunteers. Mov Disord 2017;32:211-8.
16. Fields CR, Bengoa-Vergniory N, Wade-Martins R. Targeting alpha-synuclein as a therapy for Parkinson's disease. Front Mol Neurosci 2019;12:299.
17. Mittal S, Bjørnevik K, Im DS, Flierl A, Dong X, Locascio JJ, *et al*. β2-Adrenoreceptor is a regulator of the α-synuclein gene driving risk of Parkinson's disease. Science 2017;357:891-8.
18. Athauda D, Maclagan K, Skene SS, Bajwa-Joseph M, Letchford D, Chowdhury K, *et al*. Exenatide once weekly versus placebo in Parkinson's disease: A randomised, double-blind, placebo-controlled trial. Lancet 2017;390:1664-75.
19. Chen X, Zhao C, Li X, Wang T, Li Y, Cao C, *et al*. Terazosin activates Pgk1 and Hsp90 to promote stress resistance. Nat Chem Biol 2015;11:19-25.
20. Migdalska-Richards A, Daly L, Bezard E, Schapira AH. Ambroxol effects in glucocerebrosidase and α-synuclein transgenic mice. Ann Neurol 2016;80:766-75.
21. Rosenblad C, Kirik D, Devaux B, Moffat B, Phillips HS, Björklund A. Protection and regeneration of nigral dopaminergic neurons by neurturin or GDNF in a partial lesion model of Parkinson's disease after administration into the striatum or the lateral ventricle. Eur J Neurosci 1999;11:1554-66.
22. Christine CW, Bankiewicz KS, van Laar AD, Richardson RM, Ravina B, Kells AP, *et al*. Magnetic resonance imaging-guided phase 1 trial of putaminal AADC gene therapy for Parkinson's disease. Ann Neurol 2019;85:704-14.
23. Stefani A, Lozano AM, Peppe A, Stanzione P, Galati S, Tropepi D, *et al*. Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. Brain 2007;130:1596-607.
24. Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk HJ, *et al*. Noninvasive deep brain stimulation via temporally interfering electric fields. Cell 2017;169:1029-41.e16.

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