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.

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.[9]

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

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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. 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 three classes levodopa, 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 dyskinesias by 4–6 years of treatment with levodopa, 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 DYSKINESIAS AT VARIOUS STAGES OF THE DISEASE?

Wearing off effect (reduced motor activity and re-emergence of parkinsonian symptoms before the next dose 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

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**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/destination     | Pain                    |
| Micrographia             | Fatigue                 |
| Hypomimia                | Erectile dysfunction     |
| Reduced arm swing        | Dementia                |
| Abnormal glabellar tap   | Hallucination/anxiety/psychosis |
| Dysphagia/dysarthria     |                         |
| 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). |
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. 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. 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.

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,

### 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:          | Melatonin or Clonazepam                        |
| Insomnia, excessive daytime sleepiness, REM sleep behavior disorder | Recent: Topical dopamine agonist rotigotine improves sleep. |
| Neuropsychiatric:       | Pimavanserin (5HT2A inverse agonist), Quetiapine, Clozapine |
| Cognitive impairment:   | Rivastigmine                                    |
| Dementia                |                                                |
| Autonomic:              | Fludrocortisone, Droxidopa, Midodrine          |
| Orthostatic hypotension | Oxybutinin, Solifenacin, Mirabegron, Tolerodine |
| Urinary dysfunction     |                                                |
| Erectile dysfunction    | Sildenafil, Tadalafil                           |
| Excessive salivation    | Topical atropine, Botulinum toxin              |
**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 to reduce alpha-synuclein levels and risk of PD[15][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] |
| Neurotrophic factors                | GDNF (glial cell line derived neurotrophic factors) | Neuroprotective therapies due to its neuroprotective effects, has emerged as a putative treatment option for PD[19] |
| 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[20] |
| Stem cell therapy                   | -                                          | Grafting of pluripotent stem cells that provides a new source for dopaminergic progenitor cells is currently undergoing trials |

**Table 5: (Continued)**

| Treatment strategy                  | Agent                                      | Comment                                                                 |
|-------------------------------------|--------------------------------------------|-------------------------------------------------------------------------|
|                                    |                                            | 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[21] 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[22] |

**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.

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