Review Article

Parkinson's disease : diagnosis and management

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Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disorder best characterized by the motor symptoms of tremor, rigidity and bradykinesia. The presentation of PD varies based on the stage of illness and often diagnosis in the early stage is challenging, requiring an astute clinical eye and knowledge of possible differentials. Patients in the advanced stage frequently develop motor complications which significantly add to the morbidity of the disease. Non-motor symptoms also play a crucial role in the overall management of PD disease complex and should be appropriately addressed. Treatment has to be individualized, bearing in mind several factors such as age of the patient, stage of illness, cost of medication, etc. Non-pharmacological treatment approaches are crucial for holistic management of PD.

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Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder first described in 1817 by James Parkinson, a 19th century English physician in "An essay on the Shaking Palsy"[1]. PD is seldom observed prior to 50 years of age and shows a 5-10-fold increase beyond the 6th decade[2]. A recent study reported an incidence rate of 37.55 per 100,000 women and 61.21 per 100,000 men above the age of 40[3,4]. The incidence rates of PD gradually increase from 3.26 per 100,000 between the age of 40-49 years to 103.48 above the age of 80 years[4]. The prevalence of PD in India has been reported to be lower than other countries and ranges between 6 and 53 per 100,000[5,6].

PD has frequently been considered as a geriatric disease with an average age at onset of 55-60 years. However, approximately 5-10% of patients develop symptoms prior to the age of 50 years and are referred to as early onset PD (EOPD)[7]. The cut-off age for EOPD is variable and ranges between 40 to 50 years. EOPD may be further subdivided in to juvenile PD - age at onset (AAO) < 20 years and young onset PD (YOPD) – AAO between 21 to 50 years. Several studies have reported a higher prevalence of PD in men[8]. A neuroprotective role of estrogen has been suggested as a possible explanation for the lower prevalence in women[8,9].

PD occurs secondary to loss of dopaminergic neurons in the substantia nigra pars compacta and widespread a-synuclein accumulation[10]. The resultant dopaminergic loss within the basal ganglia leads to the characteristic motor symptoms associated with PD.

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Although the exact etiology of PD is uncertain, older age and neurotoxins are established risk factors. Over the past decade several specific causative genes and susceptibility factors have been identified. PD secondary to genetic abnormalities comprises approximately 5-10% of patients with PD and are frequently observed in patients with EOPD or juvenile PD[11]. The genes unequivocally linked with monogenic, heritable autosomal dominant PD are mutations in the alpha-synuclein (SNCA) gene (PARK 1) and Leucine-rich repeat kinase 2 (LRRK2)gene (PARK8)[12]. Mutations in Parkin (PARK2), PINK1 (PARK6), DJ-1 (PARK7), and ATP13A2 (PARK9) are implicated in autosomal recessive PD[12]. Several studies have suggested that genetic forms of PD in India may differ from those in western countries[6].

Editorial Comments :

- **Parkinson's disease is characterised by tremor, regidity and bradykinesia.**
- **Physician should be aware of both motor and non motor symtoms.**
- **Non phamacological therapy also crucial, apart from drug treatment.**

The clinical features and management of PD vary vastly based on the stage of illness. Patients with PD may be broadly categorized based on the duration of motor symptoms and Hoehn and Yahr (H&Y) stage into:

(1) Early PD:Duration of motor symptoms less than 3-5 years[13,14] and H&Y stage: 1-2[15]

(2) Advanced PD : Duration of motor symptoms more than 5 yearsand H&Y stage: Beyond 3[16]

Patients may also be classified on the basis of the need for dopaminergic treatment[14] and the onset of motor complications[17].

Clinical Features :

Although PD can begin at any age, the onset of symp-

toms is most commonly observed in older adults, with a peak AAO around 60 years. Epidemiological studies in western population have reported an average AAO of 59.6±10 years[18]. Similarly, the AAO in Asia has been reported to range from 60-69 years[19]. The average AAO of PD in the Indian population has been reported to be 51.1±11.8 years, which is earlier in comparison to reports from other countries[20]. Several studies have consistently reported a higher prevalence of PD in men.

Establishing a diagnosis of PD is relatively straightforward in a vast majority of patients, however, in some patients it can prove to be challenging. Being able to identify core features of the disease and awareness of finer nuances specific to PD are helpful in avoiding misdiagnosis.

Classically, PD is associated with rest tremor, bradykinesia and rigidity, and this triad has become the sine qua non of PD[21]. The International Parkinson Disease and Movement Disorder task force has suggested three stages of PD[22] (Fig 1) :

(1) Preclinical PD: Neurodegeneration has started; however, the patient is asymptomatic.

(2) Prodromal/ premotor PD: The patient does not have clinical PD as per diagnostic criteria but has clinical signs or symptoms suggestive of neurodegeneration.

(3) Clinical/ motor PD: The patient has bradykinesia with either rest tremor, rigidity or both.

Besides the motor symptoms, patients with PD develop a variety of non-motor symptoms (NMS), a few of which may antedate the motor symptoms by several years. NMS have been established as part of the disease process and have been established as prodromal markers[23]. A holistic approach incorporating both the motor symptoms and NMS is vital to arrive at a definitive diagnosis of PD. Early in the course of illness, patients may report a multitude of vague and non-specific symptoms (Table 1).

Table 1 — *Non-specific features in the early stage of Parkinson's disease*

(1)	Lack of energy and easy fatigability
(2)	Clumsiness of hands and a change in handwriting
(3)	Difficulty concentrating and thinking (bradyphrenia)
(4)	Dragging of a foot or tripping after walking a distance
(5)	Sleep disturbances and vivid dreams
(6)	Constipation, decreased perception of smell and seborrheic dermatitis
(7)	Change in voice- hypophonia, inability to achieve a high pitch
(8)	A feeling of inner tremulousness
(9)	Routine activities take longer to complete
(10)	Myalgia, arthralgia, cramps or vague sensory complaints

Patients in the advanced stages of PD tend to develop motor complications, dyskinesia or freezing of gait. Identifying these symptoms is crucial in order to make appropriate adjustments of medication.

Motor Symptoms :

The United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank Criteria requires the presence of bradykinesia along with rigidity, tremor at rest or postural instability for the diagnosis of PD[21].

Tremor :

Tremor is a presenting symptom in up to 70% of patients with PD. Usually, the tremor is asymmetrical at onset and is a 4 to 6 Hz rest tremor. In the early stages, the tremor may be intermittent and only appear during periods of stress. On occasion, the tremor may also be an action tremor which is observed while a limb is held against gravity or while executing voluntary movements. An isolated head, jaw or trunk tremor is unlikely in the early stages of PD and an alternate diagnosis should be considered in such a situation.

Bradykinesia :

Bradykinesia is a general term used to describe an overall slowness and poverty of body and limb movements, and is the most disabling component of PD. In the early

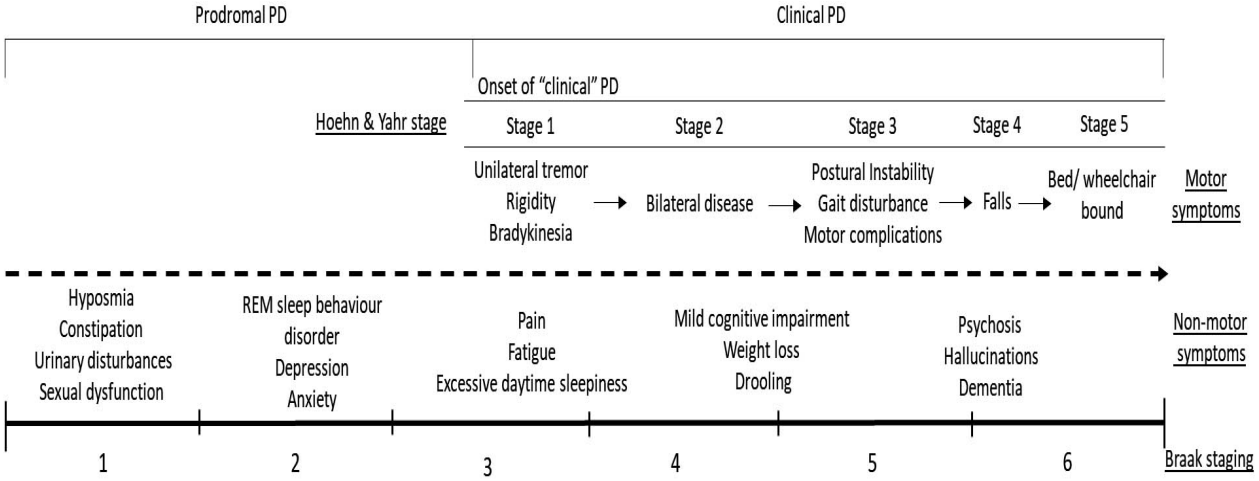

Fig 1 — Natural history of Parkinson's disease

stages of PD, bradykinesia may be discreet and limited to distal muscles of hand. This usually manifests as micrographia or slow finger tapping. Bradykinesia may also be observed in other body parts and patients may have reduced blink rate, hypomimia (reduced facial expression), hypophonia (reduced volume of voice), and a subtle, asymmetric reduction in arm swing. Bradyphrenia, a slowing of the thought process, may often be misinterpreted as dementia especially in older patients. Patients often report a significant increase in the time taken for completion of activities of daily living. Generalized bradykinesia observed in older patients may be attributable to comorbidities or normal age-related slowing.

Rigidity :

Rigidity is reported by patients as muscle stiffness and contributes to muscle pain, aches, fatigue and clumsiness of hands. It is assessed as the degree of resistance to passive movement of limbs. In the early stages of PD, the rigidity is often asymmetric, subtle, affects appendicular musculature and shows variability during the course of the day. Mild rigidity may be detectable by voluntary movement of the contralateral limb during examination (Froment's maneuver). Bradykinesia and rigidity frequently affect the same limb. As the disease progresses, several other regions and other joints get involved which result in a stooped posture. Pre-existing joint problems must be ruled out prior to evaluation, since joint pain secondary to arthritis may also lead to an increase in tone which may be misinterpreted as rigidity.

Postural Instability and Gait Disturbance :

Impairment of gait and balance are common in advanced PD and seldom observed in early PD. In the early stages, patients have discreet signs in the form of slowing of gait and shortening of stride length, a tendency to trip after walking for a while, difficulty maneuvering narrow lanes and imbalance while walking on toes, tandem walking or walking backwards. Patients may also have slight flexion of the trunk to one side. Significant impairment in the early stages is usually indicative of a different pathology.

In the later stages of PD, these abnormalities are obvious and significantly contribute the morbidity. Patients may have difficulty with gait initiation and turning, and may develop festination, retropulsion and freezing. Impairment of postural reflexes in the advanced stage leads to falls while standing or walking.

Other causes for postural instability and gait disturbances should be evaluated and ruled out, especially in older patients.

Non-motor Symptoms (NMS) :

NMS play a significant role in PD and are frequently under-reported by patients. A large number of NMS predate the clinical onset of PD and may herald the onset of motor symptoms[24]. NMS have been shown to correlate with the pathological process described by Braak[10], and NMS reported by patients may vary based on the stage of illness.

Sensory symptoms :

Olfactory dysfunction has been well established as a prodromal marker for PD[25] and may prove to be a useful diagnostic tool. Although patients with PD seldom complain of hyposmia, upon specific questioning, 22-70%[26] may report hyposmia and 70-100% test positive for hyposmia[27].

Neuropsychiatric Symptoms :

Patients with PD can present with a spectrum of neuropsychiatric manifestations, ranging from anxiety and depression to psychosis and dementia. The former group being more prevalent in early PD and the latter in advanced PD. Depression and anxiety are commonly observed in early PD and has been reported to precede the onset of motor symptoms in 10-45% of patients[28]. Cognitive impairment may manifest as mild cognitive impairment or in advanced cases as dementia[29]. Psychosis is often observed in advanced PD and visual hallucinations are among the most common psychotic symptoms reported by 22-38% of patients with PD and psychosis[30].

Sleep Symptoms :

These can be broadly categorized into insomnia, parasomnias- REM Sleep Behavior disorder (RBD) and excessive daytime sleepiness (EDS)

RBD : The connection of this NMS with PD has been demonstrated unequivocally and is one of the strongest predictors of PD[23]. RBD has been shown to precede motor symptoms in up to 40% of patients[24]. Patients with a mild form of RBD or those who sleep alone may be unaware of this NMS.

EDS : This NMS has been reported in up to 40% of patients with early PD[31]. Patients must be screened for this NMS while treating with a dopamine agonist (DAs), which frequently causes sudden uncontrollable somnolence.

Gastrointestinal Symptoms :

Gastroparesis and constipation are the most frequently reported gastrointestinal NMS, with a reported prevalence of up to 40%[32]. This plays an important role in drug pharmacokinetics as it leads to erratic drug absorption. Weight loss, drooling and dysphagia can also be present in advanced PD.

Autonomic Symptoms :

Urinary dysfunction[33], sexual dysfunction[32], orthostatic and postprandial hypotension[34] are commonly observed in the later stages of PD.Presence of these symptoms early in the course of illness is unlikely and a different diagnosis should be considered in such cases.

Other symptoms :

Vague, non-specific symptoms such as fatigue, pain and sensory symptoms may also be reported[35].

Motor Complications :

These are symptoms usually seen after 5-6 years of treatment with levodopa, and include motor fluctuations, dyskinesias, and freezing of gait[36].

Motor fluctuations: These include wearing off i.e. gradual loss of efficacy of dopaminergic medication, and unpredictable ONs or OFFs.

Dyskinesias: Involuntary choreiform movements usually seen in the ON stage – peak dose dyskinesia. Dystonic dyskinesias may occur in the OFF state. Myoclonus is an infrequent form of dyskinesia which may be seen in advanced PD.

Freezing of gait:Usually reported as an inability to initiate walking, sudden stoppage while turning or while crossing obstacles and narrow paths[37].

Differential Diagnosis :

Making a diagnosis of PD in the late stages may be relatively easy; however, an accurate diagnosis in the initial stages can be challenging. Accurate knowledge of PD mimics is crucial to avoid a misdiagnosis. It is also imperative to be aware of red flag signs which entirely rule out a diagnosis of PD (Table 2).

Parkinson-plus Syndromes :

Multiple system atrophy-with predominant parkinsonism (MSA-P) :

MSA-P bears a resemblance to PD as it may have an asymmetric onset, rest tremor. However, the key differences lie in the early and prominent autonomic failure which is paramount for the diagnosis of MSA-P[38]. Patients with MSA-P also develop postural instability and dysphagia early in the disease course. Symptoms show poor response to levodopa.

Progressive supranuclear palsy – Parkinsonism (PSP-P) :

The early stage of PSP-P bears a resemblance to PD, as patients present with asymmetric parkinsonism, rest tremor and poor response to levodopa[39]. Features distinguishing PSP-P from PD include supranuclear vertical gaze palsy, early postural instability with backward falls, prominent axial rigidity, dysarthria, dysphagia and subcortical dementia[40].

Table 2 — *Red flagssuggesting a parkinsonian disorder other than Parkinson's Disease*

(1)	Early impairment of postural reflexes
(2)	Early significant abnormalities of balance and gait
(3)	Disturbances in ocular motility
(4)	Autonomic dysfunction unrelated to drugs
(5)	Early cognitive dysfunction
(6)	Cerebellar signs
(7)	Pyramidal signs
(8)	Early hallucinations and delusions unrelated to drugs
(9)	Poor response to dopaminergic drugs
(10)	Rapid progression of the symptoms

Corticobasal Syndrome (CBS) :

CBS mimics PD as it can present with levodopa responsive asymmetric parkinsonism. Symptoms specific to CBS are stimulus sensitive myoclonus, apraxia, alien-limb phenomena and cortical sensory loss, and the patient should be thoroughly examined for them[41].

Normal Pressure Hydrocephalus (NPH) :

Patients with NPH present with shuffling gait, retropulsion and occasionally report rigidity and bradykinesia. Features in favor of NPH include symmetric lower body parkinsonism, gait apraxia, decrease in step height, wide based gait, early cognitive impairment and urinary dysfunction, and poor levodopa response. Imaging findings play a significant role in confirming a diagnosis of NPH[42].

Vascular parkinsonism (VP) :

Patients with VP usually have a short-stepping gait. Distinct clinical features which differentiate it from PD include symmetric onset, early freezing of gait, limited upper limb involvement, absence of tremor and no therapeutic response to levodopa. Patients also exhibit several symptoms secondary to ischemic lesions[43].

Other Differential Diagnosis :

Normal Aging :

A stooped posture, stiffness, slowness of movement and postural instability are commonly observed in the elderly[44]. A kinetic or postural tremor can frequently be observed in a normal elderly person. A false positive Froment's maneuver may be secondary to an increase in tone can occur in a normal healthy elderly person. These symptoms are usually symmetrical, the arm swing and heel strike is normal, gait is wide based and there is no response to levodopa.

Essential Tremor :

ET and tremor dominant-PD are very similar in presentation. ET may be asymmetric at onset; rest tremor may be present at later stages and the Froment's maneuver can also be positive. However, positive family history, head and voice tremor, absence of significant rigidity and bradykinesia aid in differentiating ET from PD[45]. ET and PD can co-exist in a single patient.

Drug induced parkinsonism (DIP) :

DIP is a common cause of secondary parkinsonism. Usually symmetric in onset with a postural tremor, patients may present with asymmetric parkinsonism and rest tremor, which mimics PD[46]. Symptoms usually develop during treatment with drugs like dopamine-depleting agents, dopamine antagonists and antipsychotics. Recovery occurs within 6 months of drug withdrawal[47]. A careful drug history is crucial to diagnose DIP. Imaging may be required to confirm a diagnosis.

Systemic disorders :

Symptoms of systemic illnesses may mimic PD. These include (a) metabolic disorders- hypoparathyroidism, hypothyroidism, acquired hepatocerebral degeneration (b) early-onset and genetic disorders - juvenile Huntington's disease,Wilson's disease, spinocerebellar ataxia types 2 and 3, and neurodegeneration with brain iron accumulation (c) infectious diseases (d) autoimmune diseases - Sjogren's syndrome (e) paraneoplastic disorder (f) space-occupying brain lesions (g)trauma[48].

Diagnosis :

The diagnosis of PD is usually clinical and based on UKPDS brain bank criteria for PD[21] which requires:

(1) Diagnosis of a parkinsonian syndrome

(2) Exclusion based on the criteria provided

(3) Supportive positive criteria to confirm the diagnosis of PD.

Of the supportive criteria, the criterion of levodopa responsiveness is extremely useful for the diagnosis of PD.

Although the diagnosis of PD is essentially clinical, there are occasions wherein symptoms are subtle or confounded by comorbidities and confirmation of a diagnosis requires the use of imaging or ancillary diagnostic tests.

Neuroimaging in early PD helps rule out structural causes of parkinsonism. Molecular imaging methods such as 18F-DOPA PET and DaTscan can help differentiate between PD and clinical mimics[49].

Ancillary diagnostic tests can help complement and strengthen a clinical diagnosis. However, at present with the exception of olfactory testing[23], no clinically useful biomarkers exist. Genetic testing has limited utility as genetic forms account for a very small percentage of cases with PD[50]. However, in cases of EOPD or in those with a positive family history genetic testing may be crucial to confirm a diagnosis. In patients with young onset parkinsonism,Wilson's disease should be ruled out.

Management of PD :

The treatment of PD is primarily symptomatic and theapproach has to be individualized based on the stage of illness, age of the patient and side effect profile. Although the primary aim of treatment is reduction of motor disability, NMS, if present should also be addressed. Prior to starting treatment and during the course of treatment, disease severity should be quantified and staged using validated scales and questionnaires. The commonly used scales are:

(1) Modified Hoehn and Yahr (H&Y) scale: The H&Y scale is frequently used to describe the symptom progression in PD and has five stages ranging from 0 to 5[51](Fig 1).

(2) Unified Parkinson's disease rating scale (UPDRS): This is the most widely used clinical rating scale for PD[52]. Section III of the UPDRS – motor examination, should be routinelyused to quantify the motor symptoms of PD.

(3) NMS Questionnaire (NMSQuest): As discussed earlier NMS play a crucial role in the symptom complex of PD and adequate documentation and quantification is necessary. The NMSQuest is a comprehensive questionnaire which covers 10 domains of NMS and can either be administered by the physician or provided to a patient for self-completion[53].

Several factors which govern the choice of treatment are listed in Table 3. Fig 2 shows a possible approach to treatment of PD.

Pharmacological Management of Motor Symptoms :

The choice of drug has to be based on the age of the patient, symptom causing greatest disability and co-existing NMS. Drugs commonly used in the treatment of PD are summarized in Table 4.

Levodopa :

Levodopa is the gold standard drug for the treatment of PD and no other drug has been shown to match up to the benefits obtained. Levodopa is a precursor of dopamine and is absorbed in the gastrointestinal tract at the level of the small intestine. In the periphery, levodopa is metabolized to dopamine by aromatic acid decarboxylase, and to3-O-methyldopa by catechol-O-methyl transferase (COMT). The peripheral conversion of levodopa significantly reduces the availability of levodopa in the brain. Hence, levodopa is frequently given in combination with decarboxylase inhibitors such as carbidopa or benserazide to reduce the peripheral conversion. The most commonly used preparations in India are levodopa + carbidopa available as regularand controlled release (CR) preparations, and less often levodopa+benserazide.

The treatment may be initiated with either a regular or CR preparation and should follow a "start slow" and "go slow" regimen, i.e. start with a low dose and slowly titrate upward based on the clinical response and adverse effects (Table 5). Levodopa should ideally be consumed either half hour before, or one and a half hours after meals. The most common side effects of levodopa after initiation of treatment include nausea and postural giddiness. Domperidone may be prescribed half hour prior to each dose or the medication may be consumed with a snack.

Table 3 — *Factors determining choice of drugs in Parkinson's disease*

(1)	Age of the patient
(2)	Affordability
(3)	Profile of non-motor symptoms
(4)	Side effect profile of drugs
(5)	Occupation
(6)	Functional disability/ impairment of activities of daily living
(7)	Expectation of quick relief vs the patience to wait
(8)	Presence of systemic illness
(9)	Literacy and knowledge of the disease

Table 4 — *Drugs commonly used in the treatment of Parkinson's disease*

Drug	Starting dose	Usual daily maintenance dose	Side effects
Levodopa/ carbidopa*:	½ tablet once daily **	400–800 mg in 4-6 divided doses	Nausea, postural giddiness
• Immediate release preparation: 100/10mg or 100/25 mg			
Dopamine agonists*:			Daytime somnolence, leg edema, ICD
• Pramipexole	0.125 mg tid	0.75 – 3 mg in 3 divided doses	
• Ropinirole	0.25 mg tid	9 – 24 mg in 3 divided doses	
MAO-B inhibitors:			
• Rasagiline	0.5 mg once daily	1 mg in a single dose	Worsen dopaminergic adverse effects, increase dyskinesia, confusion, hallucinations, serotonin syndrome
• Selegiline	5 mg once daily	5 – 10 mg in a single dose	
COMT inhibitor:			
• Entacapone	200 mg with every dose of levodopa/carbidopa	1600 mg– 200mg with every dose of levodopa/carbidopa	Peak dose dyskinesia
NMDA receptor blocker:			
• Amantadine	50-100 mg once daily	200 mg in 2 divided doses	Hallucinations, confusion, nightmares, ankle edema, livedo reticularis, dry mouth, hyponatremia
Anticholinergics:			
• Trihexiphenidyl	1-2 mg once daily	6 mg in 3 divided doses	Dry mouth, postural giddiness, blurred vision, urinary retention, constipation, confusion
• Benztropine	0.5 mg once daily	6 mg in 3 divided doses	

COMT: Catechol-O-methyl transferase; ICD: Impulse control disorder; MAO-B: Monoamine oxidase type B; NMDA: N-Methyl-D-Aspartate
*Controlled release/ extended release preparations are also available
**See Table-5 for details

CR preparations are beneficial as they have a prolonged half-life and a slower decline in plasma levels and clinical effect. It is helpful for reduction of motor fluctuations and may be used at bedtime to improve mobility during the night. However, CR preparations have a delayed onset of action and need a higher dose in comparison to regular preparations of levodopa. CR preparations should be avoided or discontinued in patients with peak dose dyskinesia.

Prolonged treatment with levodopa will invariably lead to the production of dyskinesias. A daily dose of less than 600mg has been suggested to aid in delaying the onset of motor complications [54]. Additional agents such as DAs or monoamine oxidase type B (MAO-B) inhibitors should considered if a higher dose of levodopa is required.

Dopamine agonists :

DAs may either be used as adjunct treatment in advanced PD or as monotherapy in early PD. These are especially useful when patients on prolonged levodopa treatment start to develop motor complications. DAs can either be ergot derivatives – bromocriptine, lisuride, pergolide and cabergoline or non-ergot derivatives- pramipexole, ropinirole, rotigotine and apomorphine. Non-ergot DAs are preferable owing to the side effect profile of the ergot group.

DAs must be started at a very low dose with slow increase in the dose, for e.g. pramipexole should be started at 0.125mg tid for a week and gradually increased at 0.125mg per week to a dose of 0.5mg tid. Rotigotine is a unique DA since it can be administered as a transdermal patch and provides continuous drug delivery.

DAs have a troublesome adverse effect profile of daytime somnolence, leg oedema and impulse control disorders[55]. Hence, DAs should be avoided in patients with symptomatic postural hypotension or psychosis and used with caution in those working as heavy machinery operators, drivers, etc.

Monoamine Oxidase Type B Inhibitors :

MAO-B inhibitors are frequently utilized as first-line therapy, especially in patients with mild symptoms. Rasagiline can be used as monotherapy at 1mg/day in early PD and has recently gained popularity owing to its neuroprotective properties and possible utility as a disease modifying agent. Selegiline has been shown to significantly delay the need for initiation of levodopa treatment[56].

Catechol-O-methyl transferase (COMT) inhibitors :

COMT-inhibitors aid in obtaining a steady drug level throughout the day and are used to achieve continuous dopaminergic stimulation, hence they play a crucial role in the management of patients with wearing off phenomenon. They act by inhibiting either central or peripheral COMT. Entacapone is a frequently used reversible peripheral COMT inhibitor and 200mg should be given along with every dose of levodopa. The maximum dose of entacapone is 1600mg/day i.e. 8 tablets. Tolcapone is a central and peripheral COMT inhibitor which is no longer used due to hepatotoxicity. Peak dose dyskinesia is one of the common side effects of entacapone.

N-Methyl-D-Aspartate (NMDA) Receptor Blockers :

Amantadine, is widely used as an antidyskinetic agent in late stages of PD, and may also be used as monotherapy or adjunct therapy in early PD. It can be given at a dose of either 100mg bid or tid. This drug has a wide side effect

Table 5 — *"Start slow" and "Go slow" regimen for a patient with Parkinson's Disease when initiating a treatment with levodopa/ carbidopa (100/25 mg or 100/10 mg) regular formulation*

Time				Days*
8:00 am	12:00 noon	4:00pm	8:00pm	
½	0	0	0	3 to 7 days
½	0	½	0	3 to 7 days
½	½	½	0	3 to 7 days
½	½	½	½	3 to 7 days
1	½	½	½	3 to 7 days
1	½	1	½	3 to 7 days
1	1	1	½	3 to 7 days
1	1	1	1	to continue

* Dose escalation depends on side effect profile. May be accelerated if well tolerated.
This is only a suggested schedule and the timings need to be tailored to patient's sleep-wake pattern.

profile which includes hallucinations, confusion, nightmares, ankle edema, livedo reticularis, dry mouth and hyponatremia.

Anticholinergics :

Trihexyphenidyl and benztropine are inexpensive and low-risk monotherapy options for young patients who are tremor-dominant. Trihexyphenidyl can be started at 2mg once daily and gradually increased to 2mg tid. Benztropine should be started at 0.5mg once daily and gradually increased to 2mg tid. They should be avoided in elderly patients due to common adverse effects such as dry mouth, postural giddiness, blurred vision, urinary retention, constipation and confusion.

Newer drugs :

Several new drugs such as Pardoprunox (SLV-308) and Rytary (IPX066) are in the trial stages and are being explores as possible monotherapies[57]. Safinamide is a reversible MAO-B inhibitor which has been recently introduced and has been shown to prolong ON time without significant dyskinesia.

Pharmacological Management of NMS :

Although motor symptoms are the main features of PD, in a large percentage of patients, the NMS are more bothersome. These symptoms should be given due credence and appropriate treatment must be provided. Treatment of common NMS is provided in Table 6[58-60].

Surgical Management of PD :

Surgical intervention in the management of PD is typically restricted to advanced stages of PD and consists of either deep brain stimulation (DBS) or lesioning procedures.

Deep Brain Stimulation (DBS) :

DBS targeting the subthalamic nucleus is widely accepted for advanced PD with inadequately controlled symptoms. DBS should be considered when a patient needs very frequent doses of dopaminergic drugs, has severe wearing off and dyskinesias, or has a tremor which is poorly

Table 6 — *Pharmacological treatment of Non-motor symptoms in Parkinson's disease*

1. Neuropsychiatric symptoms[58]
   - Depression: Selective serotonin reuptake inhibitors and selective norepinephrine reuptake inhibitors. Tricyclic antidepressants should be used with caution in old patients
   - Psychosis: Quetiapine, olanzepine or clozapine
   - Dementia: Rivastigmine
2. Sleep symptoms[60]
   - REM behaviour disorder: Clonazepam, melatonin
   - Excessive daytime sleepiness: Modafinil
   - Restless leg syndrome: Clonazepam
3. Autonomic symptoms[59]
   - Urinary dysfunction: Anticholinergic drugs - Oxybutinin, alpha-1 agonists and antispasmodics
   - Erectile dysfunction: Sildenafil (caution in patients with orthostatic hypotension, and coronary artery disease on treatment with nitrates)
   - *Orthostatic hypotension: Fludrocortisone, midodrine
4. Gastrointestinal symptoms[59]
   - Constipation: High fibre diet, lactulose
   - Drooling: Anticholinergics (caution in elderly, bladder disturbances and psychosis), intra-parotid botulinum toxin injection
   - Gastroparesis: Domperidone, tegaserod and mosapride
5. Other symptoms[58]
   - Pain usually responds to optimization of dopaminergic treatment

*Non-pharmacological methods such as the use of elastic stockings, an increase in salt and water intake, and gradual change of posture should be tried in orthostatic hypotension prior to starting medication

responsive to treatment. Good response of motor symptoms to levodopa is a mandatory criteria for consideration of DBS[61]. However in patients with severe tremor, patients with inadequate response of the tremor to levodopa can also be considered for DBS. Unpredictable OFF states, severe freezing, gait and balance problems and severe hypophonia unresponsive to levodopa may not improve with DBS. Patients with cognitive impairment, psychosis, autonomic dysfunction, severe psychiatric co-morbidity or systemic illness, and advanced age are relative contraindications to DBS[62]. Appropriate patient selection is a critical step for a successful outcome after DBS. The ability of a patient to afford DBS and the recurring costs involved should also be considered prior to suggesting DBS. It is imperative to explain realistic outcomes of DBS to patients, since several symptoms of PD do not improve after DBS.

Lesioning procedures :

The advent of DBS has significantly reduced the utility of lesioning procedures in PD which was frequently performed in the past. The thalamus (ventral intermediate nucleus), globuspallidusinternus and subthalamic nucleus (STN) were sites commonly used sites in PD. Although this procedure has been shown to produce improvement in some symptoms such as tremor; there presence of major adverse effects has reduced the utility of lesioning in PD. At present the use of lesioning in PD may be limited to thalamic lesioning in patients with treatment resistant tremor dominant PD[63]. Unilateral pallidotomy may be performed in cases with severe dyskinesia. STN lesioning is

avoided due to severe adverse effects such as hemiballismus.

Experimental Therapies :

Although gene therapy and fetal cell transplantation are being explored for the treatment of PD, results are conflicting and extensive trials are needed prior to establishment of these therapies as mainstays of treatment[64].

Non-pharmacological Treatment for PD :

In spite of optimal medical management, patients persist to experience a wide range of symptoms which significantly affect the quality of life. Several non-pharmacological managements such as physiotherapy, yoga, tai chi, cognitive and behavior training, and dance intervention have been shown to produce symptomatic relief [65,66].

FOG which is a troublesome motor complication has been shown to respond to visual or auditory external cues. Visual cues in the form of striped floors have frequently been reported to aid in alleviating FOG[67,68].

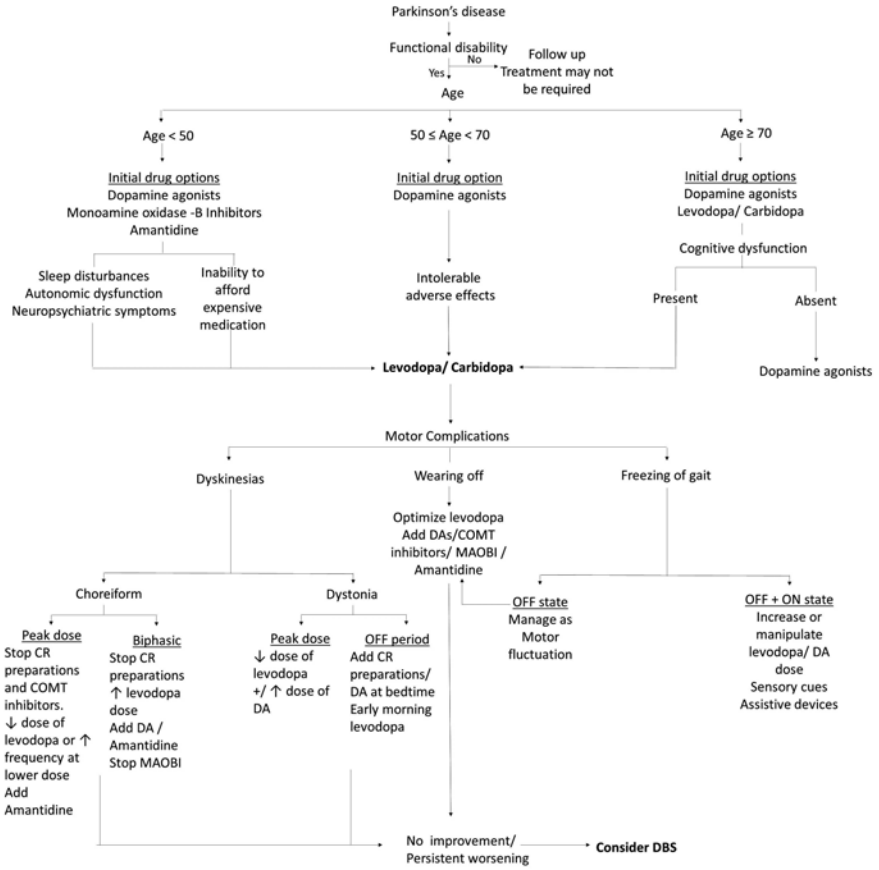

Fig 2 — Approach to treatment approach of Parkinson's disease

Conclusion :

PD is a chronic, neurodegenerative disorder which shows significant variability in signs and symptoms based on stage of illness. Diagnosis of PD in the early stages may be challenging and other diagnosis must be ruled out. NMS often overshadow the motor symptoms and due consideration must be given while planning treatment.

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