INTRODUCTION
Parkinson’s disease (PD) is the second most common neurodegenerative disease, affecting 1% of the population over 55 years of age. This disease is characterized by the loss of ~50–70% of the dopaminergic neurons in the substantia nigra, a profound loss of dopamine (DA) in the striatum, and the presence of intracytoplasmic inclusions called Lewy bodies (LB).

PARKINSONISM AND PARKINSON’S DISEASE
Parkinsonism is a syndrome characterized by one or more of the four cardinal symptoms: (1) rest tremor; (2) rigidity; (3) hypokinesia and (4) postural instability. Parkinson’s disease is the most common disorder, which presents with parkinsonism. Drug-induced parkinsonism, progressive supranuclear palsy (PSP), multiple system atrophy (MSA) are some of the other conditions, which present with parkinsonism.

PREVALENCE OF PARKINSONISM IN INDIA
Very few studies are available on the prevalence of PD in India. Different studies have shown that the crude prevalence rate (CPR) of PD is 14 per 100,000 in the north India, 27 per 100,000 in south India and 16 per 100,000 in east India. However, in one study of Parsis in Mumbai revealed a CPR of 328 per 100,000.

This is exceedingly higher compared to CPR in the rest of India, but is comparable to the prevalence in the western countries. One study from Bangalore showed that the prevalence is higher in rural (41 per 100,000) compared to urban (14 per 100,000) population and also that it is more common in men compared to women. A study of residents aged 65 years or more living in old age homes, showed that 24% of them had parkinsonism.

DIFFERENTIATING PARKINSON’S DISEASE AND OTHER CAUSES OF PARKINSONISM

Clinical Features
Rest tremor with bradykinesia and/or rigidity, particularly when asymmetric favors the diagnosis of PD. Absence of rest tremor, symmetry of findings, early falls, early autonomic dysfunction, early vertical gaze palsy and early dementia suggest other causes of parkinsonism such as MSA, PSP, etc.

Therapeutic Response to Levodopa
Good response to levodopa (LD) strongly suggests PD. There is little or no response to LD in MSA and PSP. Unified Parkinson Disease Rating Scale (UPDRS) is a useful tool to assess LD response. An improvement of 30% or above in the scale after LD/carbidopa (CD) challenge is strongly suggestive of PD. This test has a sensitivity of 71% and specificity of 81% to make an eventual diagnosis of PD after 2 years. Apomorphine, a DA agonist may also be used as a challenge but it is not available in India.

Therapeutic response to LD while strongly suggestive of PD, it cannot always differentiate PD from other causes of parkinsonism. Short-term response to LD may be seen in PSP. Hence long-term response to therapy must be assessed. Persistent response for several years definitely points to a diagnosis of PD. Levodopa induced dyskinesias, which are common after 5 years of therapy, occur only in PD.

Limitations of the Above Approach
The above approach, based on clinical features and therapeutic response, is generally useful in the vast majority of patients. However, this approach does have its limitations. In two studies of clinical-pathological correlation, only 76% of patients with a clinical diagnosis of PD actually met the pathologic criteria of PD. Others had pathological changes suggestive of other causes of parkinsonism.

Pathological Approach
There is a considerable overlap between pathological changes seen in PD and those seen in other causes of parkinsonism. For example, many patients with a clinical diagnosis of typical PD have LB in the multiple regions of the brain apart from basal ganglia. Hence, there is controversy as to what exactly should be the pathological criteria to diagnose PD.

Genetic Approach
About 10% of patients with PD have specific mutations. There are significant differences in the clinical features and pathological changes even among patients with one particular mutation. Given that only a minority of patients with PD have specific mutations and that for a particular mutation, there is considerable heterogeneity in the clinical and pathological features, a genetic approach to identify PD is not feasible.

Imaging Studies
Computed tomography (CT) and magnetic resonance imaging (MRI) are normal in patients with PD and of little value in diagnosing PD. Brainstem and cerebellar atrophy suggest MSA. Imaging studies are useful to rule out diseases such as normal pressure hydrocephalus (NPH), chronic subdural hematoma (SDH) and slow-growing brain tumors, which can present with features resembling parkinsonism.
Multiple cerebral infarcts with clinical history of recurrent stroke suggest vascular dementia.

**EARLY DIAGNOSIS OF PARKINSONISM**

In patients presenting with rest tremor, the diagnosis is usually made early. Before the tremor becomes manifest, the patient may feel an inner sense of tremulousness. This is often misinterpreted as a functional symptom. The patient with hypokinesia and rigidity often presents atypically. Shoulder pain or shoulder stiffness is sometimes the presenting symptom. Some patients present with poor sleep and pain in the neck and back, as rigidity of trunk muscles prevents the patient from turning in bed during sleep, thus causing awakening and pain in the neck and back. The above observations are useful in making early diagnosis.

**ANIMAL MODELS OF PARKINSONISM**

Several animal models of parkinsonism exist, 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are the most widely used. The 6-OHDA and MPTP are toxins, which induce a disease resembling parkinsonism in animals. They produce an oxidative stress and cell death of dopaminergic neurons, mimicking the pathogenetic events in PD, leading to pathology and symptomatology resembling parkinsonism.

Several drugs were able to slow the progression of PD in animal models, and subsequently, evaluated in humans as neuroprotective therapy. Drugs used in parkinsonism can be divided into two types:

1. Neuroprotective therapy, which delay the progression of the disease.
2. Symptomatic therapy, which provides just symptom relief.

**Neuroprotective Therapy**

Selegiline, a selective monoamine oxidase-B (MAO-B) inhibitor, was shown to delay the development of disability in several studies. It delayed the time to addition of LD to control symptoms. This was thought to be due to the neuroprotective effect of selegiline. However, post-hoc analysis of these studies has shown that the delay in the need for LD was due to symptomatic benefits from selegiline rather than to true neuroprotective effect. Recently, long-term clinical follow-up of Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism (DATATOP) study has also made it clear that selegiline therapy does not halt disease progression.

Like selegiline, ascorbic acid and alpha tocopherol slowed the progression of PD in animal models but did not show protective effect in humans. Several other drugs have been tried as neuroprotective agents including rasagiline, rituxol, neuroimmunophilin, coenzyme Q10, glial-cell line-derived neurotrophic factor (GDNF) but have little or no benefit. A few anti-apoptotic drugs have been tried, again with no benefit.

**Symptomatic Therapy**

**When to Initiate Symptomatic Therapy in Parkinson’s Disease?**

Symptomatic therapy should be initiated when the disease is causing functional impairment. Several factors should be considered in deciding whether the disease is causing functional impairment. These include:

- The effect of the disease on the dominant hand
- The extent to which the disease interferes with work, activities of daily living, or social and leisure function
- The presence of significant bradykinesia or gait disturbance
- The patient’s personal philosophy regarding the use of drugs.

The decision should be taken after a full discussion with the patient. A brief period of drug therapy may help the patient to understand the benefits and side effects of therapy, and thereby, take a well-informed decision. In short, the decision to start therapy should be based on the individual needs of the patient.

The major drugs available for symptomatic therapy include:

- Levodopa
- Monoamine oxidase-B inhibitors
- Dopamine agonists
- Catechol-O-methyltransferase (COMT) inhibitors
- Anticholinergic agents
- Amantadine.

In addition, low-dose estrogen may be helpful as adjunctive therapy in postmenopausal women.

**What should be the Initial Drug for Symptomatic Therapy?**

Approximately 70% of patients with PD will require symptomatic therapy within 2 years of disease onset. Less potent therapies such as selegiline, rasagiline and amantadine may be useful for initial therapy, but LD or DAs are the choices when more potent therapy is indicated. The choice between LD and DAs for initial therapy remains controversial. There is universal agreement that LD is the most potent drug but there are concerns that it might be toxic to dopaminergic neurons and that it promotes the development of motor fluctuations (MF).

**LEVODOPA AND MOTOR COMPLICATIONS**

Levodopa is the most effective anti-Parkinson drug. However, up to 50% of patients on LD for 5 years’ experience MF and dyskinesia. These symptoms are, especially, common in patients with onset of PD before 50 years of age. They are unique to LD, and are not produced by the other anti-Parkinson drugs.

Patients typically experience a smooth and even response to the early stages of LD treatment. As the disease advances, however, the effect of LD begins to wear off about 4 hours after each dose, and symptoms reappear but resolve as the next dose takes effect. Motor fluctuations are alterations between periods of being “on”, during which the patient enjoys a good response to medication, and being “off”, during which the patient experiences symptoms of their underlying Parkinsonism. Different types of “off” may occur as the following:

- **Wearing off** is the most common type of MF. It refers to the predictable return of parkinsonian symptoms in the hours before the next dose as the plasma level of the drug falls below the critical level.
- **On/off** is the unpredictable reappearance of parkinsonian symptoms at a time when central levels of anti-Parkinsonian drugs are expected to be within the target of therapeutic range.
- **Delayed on** is delay in the onset of symptom relief after a dose.
- **Dose failure** is a complete failure to develop a favorable response to an incremental dopaminergic dose.
- **Protein-related offs** occur when the transport of LD across the intestinal wall is impeded by competition for facilitated transport by large amounts of neutral amino acids.

**Dyskinesia** consists of abnormal involuntary movements that are usually choreic or dystonic but, when more severe, may be ballistic or myoclonic. It usually appears when the patient is “on” (peak-dose dyskinesia).

**Painful dystonia** may occasionally occur when the patient is “off”, especially in the morning on awakening, when dystonic intorsion of a foot (usually on the side of greater Parkinsonian involvement) occurs as a withdrawal reaction because of the long interval without medication overnight.

In the large group of patients with early PD studied in the DATATOP study, motor complications occurred in 30% after only
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2 years of treatment with LD. However, in a study of early PD, the prevalence of motor complications was only 20% after 5 years of treatment with LD given in relatively low doses.

Retrospective data from a study of the effect of pramipexole and LD on early PD [the Comparison of the Agonist Pramipexole with Levodopa on Motor Complications of Parkinson’s Disease (CALM-PD) study] also suggest that the earlier occurrence of MF in the course of PD is associated with higher cumulative LD doses and higher cumulative LD-equivalent doses (i.e. LD plus the DA agonist pramipexole).

Given that the occurrence of motor complications is dose related, only the lowest effective dose of LD should be used in any patient.

Levodopa: Neurotoxic or Neuroprotective?

There is a concern that oxidative metabolism of LD may lead to damage of dopaminergic neurons from oxidative stress. The evidence regarding potential effects of LD on dopaminergic neurons is summarized by the following observations:

- In vitro, LD is toxic to cultured DA neurons. In contrast, LD does not damage DA neurons in tissue culture in the presence of glial cells, in normal humans or in intact animals.
- In a retrospective neuropathologic study of patients with PD, the cumulative lifetime dose of LD did not correlate with disease pathology as measured by neuronal cell counts in the substantia nigra or by LB density in the cortex and substantia nigra.
- One experimental study found that LD increased neuronal damage in animals with partial injury to dopaminergic neurons. However, this was not confirmed in subsequent reports.

A 1998 consensus conference reached the following conclusions, which remain relevant today:

- There is no evidence that LD causes neuronal death in animal models of Parkinsonism.
- The relevance of in vitro studies of LD toxicity to clinical use of LD is highly uncertain.
- There is no evidence that chronic administration of LD exacerbates the degenerative process in PD.
- Late motor complications arise due to progressive degeneration of DA neurons.

Data from the Levodopa Therapy in Parkinson’s Disease (ELLIDOPA) trial suggest that LD, rather than being neurotoxic, either slows the progression of PD or has a prolonged benefit even after the drug has been stopped. On the other hand, single-photon emission computed tomography (SPECT) imaging data from a substudy of 116 patients supported observations from two previous studies that LD treatment is associated with a greater decline in basal ganglia uptake of DA. The substudy used SPECT to assess striatal DA uptake by measuring [123I] 2 beta-carbomethoxy-3 beta-(4-iodophenyl) tropine (beta-CIT) uptake, and showed that patients taking LD had a greater reduction in nigrostriatal DA transport compared with those on placebo. Once again, the question of LD toxicity versus LD-related down regulation of the DA transporter receptors could not be resolved.

In conclusion, the debate over the potential neuroprotective versus neurotoxic effects of LD remains unresolved, but the weight of the evidence accumulated to date shows that long-term use of LD is not a hazard, especially in the light of its superiority over all other pharmacotherapies. Further clinical trials are needed to determine the effects of LD on the progression of PD. In the meantime, LD remains the most effective therapy for PD, and should be introduced if there is sufficient compromise of quality of life or functional ability to warrant treatment.

Levodopa Therapy: Practical Points to Optimize the Benefit

Absorption of LD does not change with progression of the disease. Amino acids in protein-rich diet can compete with LDs entry across the blood brain barrier and reduce its concentration in the brain. This could reduce the effect of LD; therefore, it is best to take LD on an empty stomach.

Patients taking LD for the first time should take each dose with a meal or snack to avoid nausea, a common early side effect. Patients with more advanced disease, especially those with MF, often notice that a dose of LD is more effective if taken on an empty stomach 30 minutes before or 1 hour after meals due to reduced competition with other amino acids for gastrointestinal absorption.

Levodopa and CD tablets dissolved in ascorbic acid solution reduce symptoms and increase “on” time when compared with the standard LD/CD tablet.

The controlled-release (CR) preparation of LD is useful to prolong the “on” period during sleep. Absorption of CR preparation is unpredictable, and therefore, its use is less helpful to manage MF during the day. Second, if the CR preparation is used all through the day it collects and causes dyskinesias toward the end of the day. The CR preparation is useful at bed time as it allows patients to turn in the bed during sleep, and might reduce falls while going to the rest room at night.

The usual practice is to titrate to the lowest LD dose that produces a useful clinical response. This varies from patient to patient, but at the start, it is typically in the vicinity of 300–600 mg of LD daily. The vast majority of patients with idiopathic PD will enjoy a significant therapeutic response to moderate doses of LD (300–600 mg daily).

Complete absence of response to a LD dose of 1,000–1,500 mg/day suggests that the original diagnosis of PD may be incorrect and that one of the other Parkinsonian syndromes, such as MSA, PSP or vascular Parkinsonism should be considered.

DOPA AGONISTS: WHEN AND TO WHOM?

The dopamine agonists (DAs) are a group of synthetic agents that directly stimulate DA receptors. The drugs include bromocriptine, pramipexole, ropinirole, rotigotine and injectable apomorphine.

Dopamine agonists were initially introduced as adjunctive treatment for advanced PD complicated by reduced LD response, MF, dyskinesia and other adverse effects of LD. However, the hypothetical concern that free radicals generated by the oxidative metabolism of DA contribute further to the degeneration of dopaminergic neurons has prompted some investigators, despite lack of conclusive evidence, to advocate the early use of DAs as LD-sparing strategy.

With this approach, treatment with LD can be postponed and saved for a later time in the course of the disease, when disability worsens and the less effective agonists no longer provide adequate benefit. This strategy is based upon the unproven concept that the long-term duration of a given patient’s responsiveness to LD is finite and that the drug, like money in a savings or retirement account, should be rationed. However, whether reduced responsiveness to LD over time is due to a decline in drug response or progression of underlying PD is currently uncertain.

Given the potential that DAs are associated with fewer MF and the evidence that there is a higher incidence of LD-related dyskinesia in young-onset PD, some experts suggest using DAs as initial treatment for PD in patients younger than age 60, and using the more effective LD in patients 60 and older, although other factors should be weighed in making this treatment decision.

Unlike CD-LD, these drugs are direct agonists that do not require metabolic conversion, do not compete with amino acids for transport across the gut or into the brain and do not depend upon neuronal uptake and release. An additional advantage over immediate-release forms of LD is the longer duration of action of most of these agents.

Pergolide and cabergoline should not be used for PD because of the risk of valvular heart disease.

It is reasonable to initiate therapy with a DA in younger patients (age < 65 years) with PD, and with LD in elderly patients (age > 65 years).
years). However, there are exceptions to these general rules, and all treatments should be individualized. Levodopa is the drug of choice if symptoms, particularly those related to bradykinesia, seriously threaten the patient’s lifestyle.

The choice between the three dopa agonists should be based on adverse effects because the benefits are similar. Some patients may benefit from all three equally; some may get adverse effects from one not the others. Switching can be done rapidly, using a ratio of 1:5:10 for pramipexole: ropinirole: bromocriptine.

In deciding between LD and dopa agonists as initial therapy, the cost of these agents should be kept in mind. The cost of DA agonists is five to ten times that of Dopa-CD.

**ROLE OF ANTICHOLINERGIC DRUGS IN PARKINSON’S DISEASE**

Dopamine and acetylcholine are normally in a state of electrochemical balance in the basal ganglia. In PD, DA depletion produces a state of cholinergic sensitivity so that cholinergic drugs exacerbate and anticholinergic drugs improve Parkinsonian symptoms.

Anticholinergic drugs are most useful as monotherapy in patients under age 70 with disturbing tremors, who do not have significant akinesia or gait disturbance. They also may be useful in patients with more advanced disease, who have persistent tremor despite treatment with LD or DAs.

**ROLE OF AMANTADINE IN PARKINSON’S DISEASE**

Amantadine is an antiviral agent that has mild anti-Parkinsonian activity. Its mechanism of action is uncertain; it is known to increase DA release, inhibit DA reuptake, stimulate DA receptors and it may possibly exert central anticholinergic effects. It has N-methyl-D-aspartate (NMDA) receptor antagonist properties that may account for its therapeutic effect by interfering with excessive glutamate neurotransmission in the basal ganglia.

In early uncontrolled clinical trials, two-thirds of patients receiving amantadine monotherapy showed an improvement in akinesia, rigidity and tremor. Subsequent controlled studies demonstrated that it was more effective than anticholinergic drugs for akinesia and rigidity. The benefit induced by amantadine appears to be transient in some patients; it is best used as short-term monotherapy in those with mild disease. Amantadine is of little benefit when added to LD, although the addition of LD to amantadine causes significant additive improvement.

Amantadine in divided doses of 200–400 mg a day may reduce the intensity of LD-induced dyskinesia and MF in patients with PD. Although the published randomized trials on amantadine in advanced PD are limited by serious methodological flaws and small numbers of patients, experience has shown that individual patients with advanced PD who have MF and dyskinesia can benefit dramatically, at least for a while, from the addition of amantadine to a regimen of LD.