ABSTRACT:

Parkinson’s disease (PD) is a progressive disorder, which however can be treated satisfactorily with a judicial combination of medical and surgical treatment. In the past 2 decades there have been significant advances in the development of new drugs and surgical treatment for PD. While levodopa still remains the best drug for adequate relief of motor symptoms of PD, several recently introduced drugs such as dopamine agonists (ropinirole, pramipexole and rotigotine), COMT inhibitor (entacapone), and MAO-B inhibitor (rasagiline) have significant roles to play in management of PD, especially in patients with motor complications. Finally, there is strong evidence to suggest that selected patients of PD with motor complications benefit from deep brain stimulation (DBS) of bilateral subthalamic nuclei.

Parkinson’s disease (PD) results from premature, progressive degeneration of neurons in the brain. The primary area of brain affected in PD is substantia nigra, from where neurons proceed and innervate another area of brain known as striatum. Dopamine is the neurotransmitter produced by these neurons and dopamine concentration of striatum depends on the integrity of the substantia nigra. The manifestations of PD occur when there is a loss of approximately 60-80% of the dopamine producing cells of the substantia nigra.

PD was first described in 1817 by James Parkinson, a 19th century English physician in a pamphlet entitled “An essay on the Shaking Palsy”. PD is usually a disease of the elderly, characterized by tremor of hands and legs, slowness of movements (bradykinesia), stiffness (rigidity) of limbs and body, and later in the disease by poor balance and frequent falls while walking. PD is now recognized as one of the commonest neurological disorders to affect people over the age of 55 and as many as 8% of patients may be diagnosed before the age of 40.

With increased longevity and health awareness more number of PD patients are seen in the hospitals and clinics throughout the world. In the past one decade, there have been major advances in understanding the cause of PD, and its medical and surgical management. PD is a unique progressive neurodegenerative disorder where there is an effective treatment to ameliorate the symptoms, at least in the early part of the disease, and with good medical care patients may have a normal life span.

The average age of onset of symptoms in PD is 55 years, and the course is slowly progressive over the next few decades. The initial symptoms may be intermittently present especially during stress. The cardinal manifestations of PD are tremor at rest, rigidity, bradykinesia, and abnormalities of posture, gait and balance. Any combination of tremor, rigidity or bradykinesia may be present in early PD; gait and balance problems are usually late features. Apart from the motor problems, patients with PD may have several non-motor symptoms throughout their lifetime, which include constipation, dysphagia, sleep disturbances, fatigue, pain, sensory discomfort, cramps, and very commonly depression.

Response to adequate dose of dopaminomimetics is often considered to support a diagnosis of PD. Alternatively, when the response to dopaminomimetics is not very obvious or doubtful, worsening of patient’s problems by stopping of dopaminomimetics may again support a diagnosis of PD.

Before starting treatment of PD, other causes of parkinsonism should be ruled out by appropriate investigations. The disorders which may mimic PD include progressive supranuclear palsy, corticobasal degeneration, diffuse Lewy body disorder, vascular parkinsonism, drug-induced parkinsonism, etc.

This review discusses the management of PD. While there are new drugs and surgeries for treatment of PD (Table-1), most of the older drugs also play a major role in treatment of PD.

As of now, there is only symptomatic treatment of PD. With the judicial use of available medical and surgical treatments, the life of PD patients can be made more comfortable until the advanced
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PLANNING OF TREATMENT:

Though most patients will need treatment at some time, there is great individual variability and not all need treatment in the early stages. It is generally agreed that initiation of drug treatment for PD should be done only when there is functional disability. The lowest effective dose should be used for as long as possible. These strategies probably help in postponing drug-induced complications. Relaxation exercises, change of occupation to less-stressful jobs, reduced working hours, or even voluntary retirement, may help to postpone initiation of treatment.

MEDICAL TREATMENT OF PD:

The following medications are available for medical treatment of PD.

A. Levodopa preparations:

Even with advent of newer drugs, levodopa still remains the cornerstone for treatment of PD, and virtually all patients experience a clinically significant benefit. In the brain, levodopa is converted to dopamine. Peripheral decarboxylase inhibitors - carbidopa or benserazide is added to prevent its breakdown in other parts of body. The most common preparation used in India is Levodopa+Carbidopa, which is available in immediate release (regular) and controlled release (CR) preparations. Levodopa dose is reduced by about 75% by adding 75-100 mg carbidopa per day to levodopa and it reduces nausea. The preparation is given one half hour or more before, or one hour or more after meals to achieve best results. The absorption of levodopa is impaired by high protein content in diet and this may result in reduced efficacy or erratic absorption leading to motor fluctuations. In this situation low/balanced protein or protein redistributed diet should be considered.

The treatment can be started with a regular or CR preparation. Though the latter has a delay in onset of action and needs an increased dose of about 30% compared to regular preparation of levodopa, it reduces periods of immobility, peak dose dyskinesia, wearing off effects and unpredictable motor fluctuations (ON/OFF attacks).

Levodopa is the drug of choice for initiation of treatment in elderly patients (more than 70 years) with PD, those with cognitive dysfunction, sleep disturbances, hallucinations, or those who want quick improvement in symptoms. The initial dose need to be very small and gradually increased every week. Domperidone 10mg tablet taken ½ hour before each dose of levodopa can prevent nausea and vomiting. When using CR preparations, some patients may need booster dose of ½ to 1 tablet of regular levodopa/carbidopa in the morning or late afternoon for quick relief of PD symptoms. Unless severe parkinsonian symptoms dictate the use of levodopa, it is ideal to avoid late evening and nighttime doses, as these may cause disturbed sleep, hallucinations, and bad dreams, especially in advanced disease and those with dementia.

In a typical patient with early PD, a total daily levodopa dose of 300-400 mg in 3-4 divided doses is usually adequate to manage PD symptoms. Patients who do not respond adequately even with a dose of 1,000 mg of levodopa per day probably has other causes of parkinsonism rather than idiopathic PD. As disease progresses, the dose of levodopa need to be increased. There is a progressive increase in the prevalence of drug related motor fluctuations over time and half of patients experience weaning off and a third experience dyskinesias within 2 years of therapy. The patient initially develops “predictable motor fluctuations” (ON / OFF). Approximately an hour after taking medicine, patient starts improving and gradually attains his best period (ON state). At this time he may develop dyskinesias. After 3-4 hours, his symptoms start reappearing (wearing off). In this situation, if there are no dyskinesias, dose of levodopa can be increased or it may need to be administered more frequently. However, if dyskinesia is present, other drugs such as dopamine agonists and amantadine (discussed below), should be introduced, and the dose of levodopa is reduced.

Motor fluctuations of PD and their treatment

1. Wearing off refers to predictable return of Parkinsonian symptoms in advance of the next scheduled anti-parkinsonian dose.

Adjust Levodopa dose and inter-dose interval

1. Shorter interval
2. Smaller increments
3. Liquid Levodopa / Carbidopa

Add COMT inhibitor

Add Dopamine Agonist

Table 1: Newer treatment modalities in Parkinson’s Disease

<table>
<thead>
<tr>
<th>Medication</th>
<th>Description</th>
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<tr>
<td>A. Medical Treatment:</td>
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<tr>
<td>a. Dopamine agonists:</td>
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<tr>
<td>i. Pramipexole</td>
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<tr>
<td>ii. Ropinirole</td>
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<td>iii. Rotigotine (Patch)</td>
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<td>iv. Apomorphine injection (subcutaneous)</td>
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<td>b. Catechol-o-methyl transferase (COMT)inhibitor:</td>
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<tr>
<td>i. Entacapone</td>
<td></td>
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<tr>
<td>c. Monoamine-oxidase-B (MAO-B) inhibitor:</td>
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</tr>
<tr>
<td>i. Rasagline</td>
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<tr>
<td>ii. Zydis selegiline</td>
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<tr>
<td>d. Continuous duodenal delivery of levodopa/carbidopa</td>
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<tr>
<td>B. Surgical Treatment:</td>
<td></td>
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<tr>
<td>Deep brain stimulation of bilateral subthalamic nuclei</td>
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Add Rasagiline / Selegiline

2. Dyskinesias

1. Peak dose dyskinesias are usually choreiform and stereotypical movements present at the peak of the therapeutic response.
   - Optimize dose and interval of levodopa
   - Smaller increment and shorter interval
   - Add Amantadine
   - Surgery
   - Lower dose of levodopa and add dopamine Agonist
   - Atypical neuroleptic – clozapine reduces levodopa induced dyskinesias.

Diphasic dyskinesias

Large amplitude dyskinetic movements of the lower body during the time of increasing and decreasing LDopa levels.

- More frequent or higher doses of LDopa and dopamine agonists to produce a more continuous on state.
- Avoid CR forms of LDopa and COMT inhibitors and switch to regular LDopa.
- Surgery.

Off period dystonia usually occurs in the more seriously affected foot in the morning before the first daily doses and sometimes reappears during weaning off.

- Chew or crush the 1st dose of LDopa, take with carbonated beverage
- Add dopamine agonist
- Add Baclofen
- Add anticholinergic agents
- Botulinum Toxin injection.

Recently, a new formulation of levodopa/carbidopa solution for duodenal infusion is available and is discussed below.

B. Dopaminomimetics:

Dopaminomimetics are recommended as initial therapy for healthy and cognitively intact people younger than 70 years. Dopaminomimetics act directly on the dopamine receptors and provide symptomatic benefits as adjuncts to levodopa or as monotherapy in early disease, especially in young individuals. There is evidence that in newly diagnosed patients with PD, if these drugs are started alone or in combination with levodopa, the onset of motor fluctuations and dyskinesia can be delayed. However after 3-5 years of monotherapy with dopaminomimetics, most patients will require levodopa.

There are two categories of dopamine agonists-ergot and non-ergot agents. The former include bromocriptine, pergolide, cabergoline and the latter include the newer agonists such as ropinirole, pramipexole, and rotigotine. The ergot derivatives have a potential of causing pulmonary fibrosis and cardiac valvular disease and therefore not preferred. Bromocriptine and pergolide are not in use anymore for treatment of PD. Carbergoline is a long-acting drug and can be given once a day. It can be introduced at a dose of 0.05 mg and titrated to a maximum of 5 mg once a day.

Apomorphine, a non-ergot agonist, is the oldest dopamine agonist. It has similar efficacy as levodopa, with equal affinities for D2, D3 and D4, which are greater than for D1. It is available in injectable form and given subcutaneously for rapid, though short lasting improvement of motor symptoms of PD. It is a “rescue drug” for PD.

The newer dopamine agonists are pramipexole, ropinirole and rotigotine, which have highest affinity for D2 subfamily (highest for D3 receptor), with no (ropinirole), very little (pramipexole) or agonistic (rotigotine) activity for D1 receptors. Pramipexole and ropinirole are available in Indian market and are currently the most used dopamine agonists for treating PD in India. Both can be used as initial monotherapy or as an add-on drug to other dopaminomimetic drugs in PD. The drugs are started slowly (ropinirole at 0.25 mg three times a day and pramipexole 0.125 mg three times a day) and gradually increased to doses of 9 to 24 mg/day for ropinirole and 1.5 to 4.5 mg/day for pramipexole. Because of its strong D3 affinity, pramipexole may be effective in the treatment of some patients with depression. Ropinirole is rapidly and fully absorbed, reaching peak levels in 1 to 2 hours and is unaffected by food. Ropinirole should be used with caution in patients with hepatic failure and pramipexole in patients with renal failure.

Rotigotine is the most recently approved non-ergoline dopamine agonist for treatment for PD and is available as a transdermal patch which needs to be changed every 24 hours. Patches are available in 3 sizes: (i) 10 cm2 with 4.5 mg of drug, releasing 2 mg/24 hours; (ii) 20 cm2 with 9 mg of drug, releasing 4 mg/24 hours; and (iii) 30 cm2 with 14.5 mg of drug, releasing 6 mg/24 hours.

The side-effect profile of dopaminomimetics is similar to levodopa and can cause nausea, vomiting, orthostatic hypotension, bad dreams, hallucinations psychiatric problems, cardiac dysfunction, and, pleural or retroperitoneal fibrosis. The latter side effect is seen only with the ergot-derived drugs like bromocriptine, pergolide, and cabergoline, and manifest as cough and breathlessness. Therefore patients with lung disease should not receive these drugs and before starting these drugs chest x-ray should be taken. Ropinirole and pramipexole have been reported to cause sudden onset of daytime sleepiness and therefore should be used with caution in those who drive or work in dangerous situ-
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Recently two new MAO B inhibitors were approved

Selegiline, a MAO-B inhibitor has been used for many

**C. Anticholinergics:**

Trihexyphenidyl and benztrpine are anticholinergic drugs which may help relieve early symptoms of PD by correcting an imbalance between dopamine and another neurochemical—acetylcholine in the brain. These are mainly helpful for tremor and minimally beneficial for bradykinesia and rigidity. In elderly people side effects may preclude using at high doses. Dry mouth, postural dizziness, blurred vision, retention of urine (caution in those with prostatic hypertrophy), confusion, and constipation are the usual side effects. Anticholinergics can be used as monotherapy in tremor-dominant PD or as adjunct to other drugs. In patients with drooling of saliva, these drugs may help reduce saliva secretion and thus drooling. Trihexyphenidyl is most commonly used and started as one 2mg tablet/day gradually increased over days to the maximum tolerable dose (usually 6-12 mg in 3-4 divided doses per day).

**D. Amantadine:**

The exact mechanism of action of amantadine is unknown and it probably stimulates release of dopamine and blocks acetylcholine and NMDA receptors. It is a mild anti-PD drug, which can be used as a monotherapy in mild PD or as an adjunctive therapy. Dose is 100 mg 2-3 times a day. It may have some beneficial effects on dyskinesias. Side effects include confusion, red mottling on feet and lower legs (livedo reticularis), swelling of legs, low body sodium, and should be used with caution in patients with renal disease.

**E. Enzyme inhibitors:**

These groups of drugs increase the level of levodopa by preventing its breakdown. These are basically of two types: (i) Monoamine oxidase-B inhibitor (MAO-B inhibitors), and (ii) Catechol-o-methyl transferase inhibitor (COMT-inhibitors).

**i. MAO-B Inhibitors:**

Selegiline, a MAO-B inhibitor has been used for many years in treatment of PD, either as a monotherapy in early PD or as an add-on therapy. It prolongs the action of levodopa and is given as 5mg orally twice daily (with breakfast and lunch). It may cause hallucinations, confusion and bad dreams, and should not be taken during the later part of the day. It was thought to have a neuroprotective effect and delay the need for levodopa therapy. Though it may be a good adjunct to levodopa when patient develops motor fluctuations, there studies, which show that patients taking selegiline may experience cardiac side effects.

Recently two new MAO B inhibitors were approved for PD: an orally disintegrating selegiline (Zydis, a new formulation of the oral form of selegiline), and rasagiline, which is a novel second-generation agent. Both these drugs are irreversible MAO inhibitors. Thus, the functional half-life does not coincide with the pharmacologic half-life. Rasagiline is a more potent inhibitor of MAO type B, and at a dose of 0.5 mg/day the enzyme is fully inhibited in a week. Rasagiline is now used treating patients with early PD as a monotherapy and as an add-on therapy in advanced PD. Zydis selegiline is approved only for treatment of motor fluctuations. Both are given once a day, an advantage for patients that also improves compliance.

**ii. COMT-inhibitors:**

Tolcapone, a COMT inhibitor was first introduced in 1997 as an adjunct to levodopa in the treatment of PD patients with wearing off symptoms. It has a greater COMT-inhibitory property than entacapone which was introduced soon after. Tolcapone is not routinely used anymore for treatment of PD due to its potential fatal hepatotoxicity. Entacapone is peripheral COMT inhibitor which inhibits the peripheral metabolism of levodopa, thereby increasing its availability to the brain, and increasing the plasma levodopa elimination half-life by about 50%. Clinical trials have shown increased “ON” time, decreased “OFF” time, and improvement of the motor scores in patients of PD with motor fluctuations. It is given as 200 mg tablet with each dose of levodopa/carbidopa, up to 1,600 mg/day and is helpful for patients with wearing off symptoms. It can cause excacerbate levodopa-related side effects especially peak dose dyskinesias, cause diarrhea and urinary discoloration. It should not be given in patients with troublesome peak-dose dyskinesias.

**F. Continuous duodenal delivery of levodopa/carbidopa:**

This is a more physiologic way to deliver levodopa and is a potential therapy to treat severe motor fluctuations in PD. Recently a new levodopa formulation (Duodopa) has provided a new opportunity for continuous administration by enteral infusion and achievement of a more continuous plasma levels than oral administration of levodopa. Recent studies have reported reduction of both dyskinesia and off time in PD patients treated with duodenal levodopa infusion. The levodopa infusion is administered via a permanent catheter implanted into the duodenum via a percutaneous endoscopic gastrostomy (PEG) under local anaesthetic. The drug administration is controlled by a pump.

**G. Surgical treatment for Parkinson’s disease:**

In the past two decades, stereotactic surgery has established a definitive role in management of selected patients of advanced PD. Surgery for PD is usually considered when the medications have become less effective over time, or side-effects, such as dyskinesias have reached a stage to sig-
nificantly impair the ability of the patient to move about unimpaired. At this stage, usually different categories of anti-PD medications have been given a sufficient trial, and increasing dosage results in worsening of side effects.

Surgeries for PD are usually of two types: (a) lesional stereotaxy which includes thalamotomy, pallidotomy and subthalamotomy, and (ii) deep brain stimulation (DBS) of thalamus, pallidum or subthalamus. The type and site of operation depends on several factors which include (i) types of symptoms addressed, (ii) cost, (iii) availability of expertise both during operation and following surgery.

For all types of surgeries for PD, patient selection criteria are relatively uniform. The patients should have idiopathic PD for at least five years, have disabling hypokinetic fluctuations, dyskinesia or tremor despite optimal medical therapy, excellent levodopa-responsiveness of at least the akinetic-rigid state, best ‘ON’ H&Y stage of ≤ III, normal cognitive status, no major psychiatric illness, and good general health condition. The best results of surgery are obtained for younger patients.

The best site for DBS is bilateral STN stimulation, which improves all cardinal symptoms of PD which are responsive to levodopa. Moreover this stimulation allows an average reduction of dopaminergic medication by 65%. There is a risk of worsening of depression after surgery and this may need adequate treatment with SSRIs. Bilateral pallidal stimulation is also equally effective except that patients continue to require pre-operative anti-PD medications doses and the energy required for effective pallidal stimulation is about 2-3-fold higher than values previously reported subthalamic or thalamic stimulation. Thalamic DBS helps to treat only tremor symptom in PD and is considered as an option only in tremor-dominant PD, especially for older patients with little akinesia and slow progression of disease.

Lesional surgeries are less preferred than DBS because of higher risks and non-reversibility of the procedures. Ventro-intermediate nucleus (ViM) lesion of the thalamus is highly effective (>85%) in either completely or near-completely suppressing contralateral tremor. Unilateral pallidotomy is effective in improving contralateral motor symptoms of PD and reducing dyskinesias in around 30% of patients. Though there is also initial benefit in ipsilateral and midline symptoms, these benefits are usually lost after the first years. There are only few studies on subthalamotomy in PD as a less expensive alternative to DBS. There is potential risk of hemiballism or hemichorea.

H. Potential hope of newer treatments in Parkinson’s disease:

There are ongoing research to develop drugs with less side effects, better way of delivering drugs and drugs with different mechanisms of action (such as neuroprotection). There is research on the beneficial effects of transplantation of fetal nigral cells in brain, which has the potential to sur-

vive and produce dopamine. Finally, several genes have been identified responsible for causing familial young-onset PD, and further research holds promise of discovering the exact defect and its treatment.

I. Principles of Management of Motor Complications in PD:

Motor complications appear in approximately 50% of patients on levodopa therapy for more than 5 years. These occur as a result of progression of the disease process and the cumulative effect of prolonged treatment with dopaminergic drugs, especially levodopa.

Management of motor complications in PD is difficult and treatment should be individualized for each patient. The general guidelines for two common problems are:

i. Suboptimal clinical response, wearing-off phenomenon, delayed “ON” or no “ON” without dyskinesias or minimal dyskinesias:
   a. Strategies include optimizing the current dosage of anti-PD medications, adding entacapone, changing over to controlled-release preparation of levodopa, or adding a MAO-B inhibitor, amantadine, or a dopamine agonist to the current regime.
   
ii. Redistributing dietary protein

   iii. Considering surgery for PD

   iv. Adding atypical neuroleptics such as clozapine, haloperidol, or risperidone

   v. Considering options of continuous drug delivery such as subcutaneous apomorphine or duodenal levodopa,

   vi. Adding atypical neuroleptics such as clozapine, and finally

   vii. Considering surgery for PD.

J. Other aspects of management of PD:

Patients with PD, especially in advanced stages have several non-motor manifestations which need to be treated and often is a challenge to the physicians. These include management of sleep disturbances, anxiety, depression, psycho-
sis and other psychiatric problems, constipation, drooling of saliva, dysphagia, postural hypotension and other autonomic dysfunctions, etc. The discussion on management of these problems is beyond the scope of this review. Regular exercise, gait, speech and respiratory therapies, counseling of patient and caregiver, and emotional, social and often financial support will remain the most important aspects of management of advanced stages of PD. (Table 2).

In summary, with advent of newer drugs and stereotactic surgery, there is hope for better management of PD and improving the quality of life of the patients and their caregivers. Since there are inter-individual variations in response to treatment, side-effect profile, and course of the disease, treatment should be tailored for each patient. Levodopa is still the most effective and affordable drug. Surgical treatment is costly, and expertise is available in only a few centres in India. It is best reserved for patients with moderately advanced PD, who fails adequately to respond to medications, have side-effects like dyskinesias, or have severe tremor. Finally, at all stages of PD, care should be given to management of several non-motor symptoms of the disease and providing emotional and psychosocial support.

REFERENCES


