Title	Update on the management of parkinson's disease
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Citation	Hong Kong Practitioner, 1998, v. 20 n. 1, p. 20-32
Issued Date	1998
URL	http://hdl.handle.net/10722/45074
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Update On Management Of Parkinson's Disease

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Summary

Parkinson's disease is a chronic disabling condition with specific histopathological findings. No cure is yet available although treatment response can be remarkable. Family physicians are often faced with problematic issues on diagnosis and therapy when managing patients with Parkinson's disease. Levodopa is still the mainstay of treatment but its long-term use can be associated with considerable side-effects. We advocate the use of dopamine agonists as de novo therapy in younger onset patients. The application of stereotactic functional surgery has great potential in the treatment of Parkinson's disease. (HK Pract 1998;20:20-32)

摘要

帕金氏病是一種慢性障礙性疾患,具特異性組織病理檢驗表現。目前藥物治療能對帕金氏病有顯著效果,但可惜至今尚未有治本之方。家庭醫生時常在帕金氏病的診斷與治療關鍵中面對困難和抉擇。雖然左旋多巴在長期使用中可能產生相當多副作用,但仍然是現時主要用藥。本文提倡重新考慮對治療帕金氏病的年青患者使用多巴胺結抗劑。立體定位性手術對帕金氏病的療效有極大的潛質。

Introduction

The prevalence of Parkinson's disease (PD) is about 1 in 800, representing a patient load of almost 8000 in Hong Kong. PD is a chronic neuro-degenerative disease and no cure has yet been found. The cause is not known. We present an overview on the diagnostic and therapeutic issues that family physicians have to face in the day-to-day management of patients with PD. Some novel therapeutic approaches, in particular stereotactic functional surgery, are discussed.

Diagnosing Parkinson's disease

The cardinal signs of PD are rigidity, bradykinesia, tremor, and postural abnormalities. All these features are usually, but not always, present. The presence of upper body bradykinesia is essential for diagnosis.[1] The typical rest tremor is described as pill-rolling, with a frequency of 3-6 Hz. Postural instability, falls, and freezing tend to be late features. Early symptoms, such as muscle ache, fatigue, and constipation, are vague and non-specific and can therefore be easily overlooked.

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Dementia is not a feature of PD until the late stage. However, patients with PD may develop a subcortical type of cognitive impairment, characterised by apathy, slowness of thought, lack of motivation and, blunting of drive.

The gold standard for the diagnosis of PD relies on histopathological findings with the typical features of substantia nigra pars compacta degeneration (**Figure 1**) and loss of pigmentation, and the presence of intraneuronal Lewy bodies (**Figure 2**). Clinical examination may not be entirely reliable in differentiating PD from other parkinsonian syndromes. Up to 1/4 of cases diagnosed clinically as PD by neurologists turned up to be incorrect at post-mortem examination.[2,3]

Although PD is the commonest cause of parkinsonism, other causes ought to be considered (**Table 1**). Dopamine antagonistic drugs, such as neuroleptics, antihistamines, prochloperazine, and metoclopramide, can induce secondary parkinsonism and very often exacerbate parkinsonian features in PD. Vascular pseudoparkinsonism due to cerebral atherosclerosis usually shows a different pattern of involvement from PD. Their gait and postural stability are more affected than the upper limb functions. In diffuse Lewy body disease, early dementia is a prominent feature. Wilson's disease must be excluded in early-onset PD. The "parkinsonian syndromes" include multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). Their initial presentation may be similar to PD.

In MSA, neuronal loss and gliosis without Lewy bodies occur in a

Figure 1: Transaxial section across the mid-brain of a patient with Parkinson's disease showing unilateral substantia nigra depigmentation
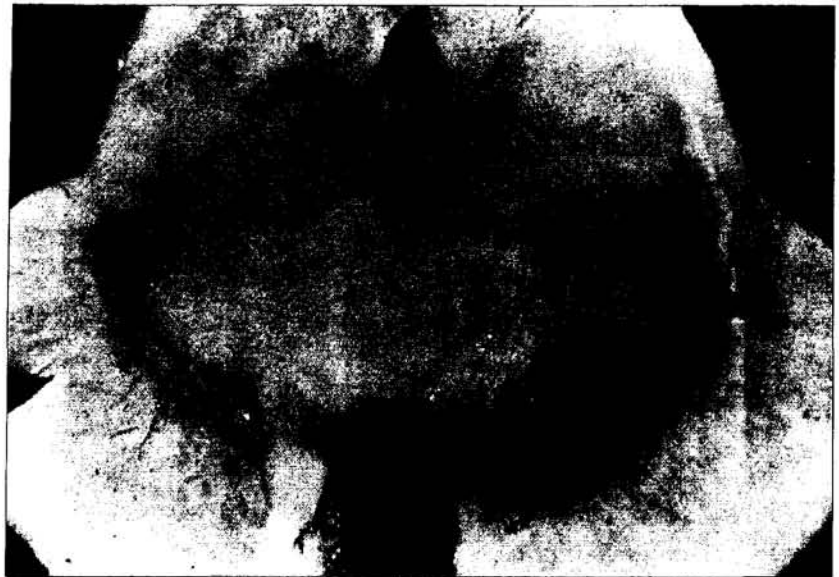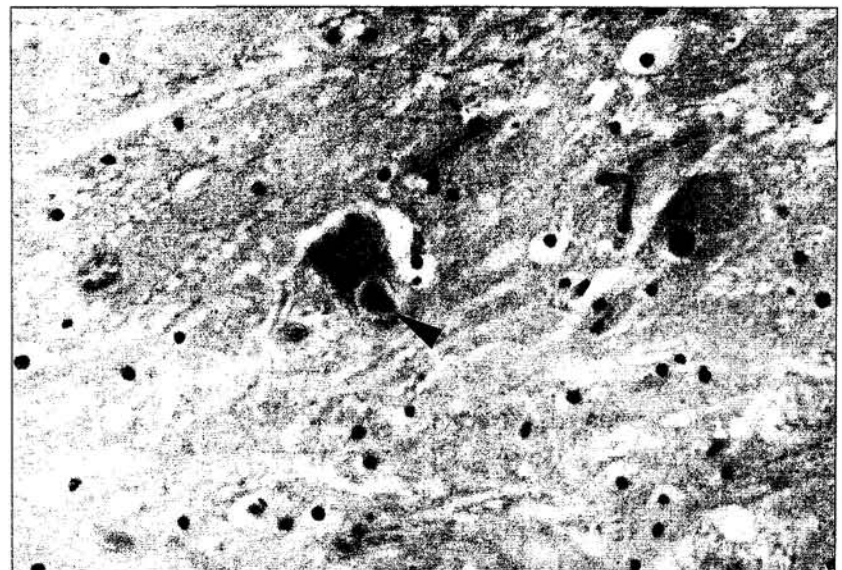

Figure 2: Inclusional Lewy body (arrow) forming a halo appearance within a neuromelanin-containing neuron

multiplicity of other structures, e.g. substantia nigra, globus pallidus, inferior olives, cerebellum, corticospinal tract, etc. Almost all the patients have parkinsonian features and autonomic dysfunction. The typical parkinsonian pill-rolling tremor is exceedingly rare in MSA. Cerebellar and pyramidal features are present in up to 35% and 60% of patients with MSA respectively.[4,5] There are several clinical subtypes classified according to the predominant impairment in addition to the parkinsonian features:

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1) Shy-Drager syndrome presents with autonomic failure,

2) Striatonigral degeneration presents with pyramidal spasticity, and

3) Olivoponto-cerebellar degeneration presents with cerebellar ataxia.

Median age of onset is 53 to 55 and the median survival is 7.3 to 7.5 years.[5,6] However, early disability is common with over 40% of patients becoming non-ambulatory five years after the onset of motor symptoms.[5]

PSP, also known as Steele-Richardson-Olszewski Disease, is an akinetic-rigidity predominant parkinsonian syndrome characterized by early postural instability and falls, axial rigidity, bulbar dysfunction, and a prefrontal-type of dementia.[7,8] The classical sign is a limited downward gaze. The median age of onset is 63 and the median survival is 5.6 years.[7]

Assessing adopaminergic responsiveness to levodopa is useful in differentiating PD from other parkinsonian syndromes. Over 70% of PD have excellent response to levodopa. Failure to respond suggests, but does not confirm, an alternative diagnosis. Diffuse Lewy body disease also respond to levodopa but prominent visual hallucinations and psychosis are often precipitated. Vascular pseudo-parkinsonism is typically refractory to levodopa.[9] Only 50% of MSA[10] and 38% of PSP[11] improve with levodopa, but usually with moderate and transient response. Facial and neck dystonias are commonly induced. Apomorphine given subcutaneously can be used as an indicator of dopaminergic responsiveness.[12]

Reduced putaminal 18F-Dopa uptake on positron emission tomography (PET)[13] is a specific finding in PD. Single-photon emission computerised tomography (SPECT) with iodine-123 labelled ß-CIT,[14] iodobenzamide,[15] and iodo-lisuride[16] are also useful in detecting early cases of PD and quantifying the disease severity. However, the application of these techniques is often limited to research centres.

For practical considerations, a diagnosis of idiopathic PD is unlikely if dementia, postural instability and falls occur at an early stage, and cases which are refractory to treatment. Features against a diagnosis of PD are summarised in **Table 2**.

Table 1: Differential diagnosis of Parkinsonism

1) Parkinson's disease (Idiopathic Parkinsonism)

2) Secondary (symptomatic) Parkinsonism

Postencephalitic – encephalitis lethargica

Drug-induced – neuroleptics, anti-emetics (prochlorperazine, metoclopramide), anti-histamines

Toxic – copper (Wilson's disease), carbon monoxide, manganese, MPTP

Traumatic – "Punch-drunk" syndrome

3) Multiple system atrophy

4) Progressive supranuclear palsy

5) Lewy body dementia

6) Corticobasal degeneration

7) Pseudoparkinsonism – atherosclerosis, "normal-pressure" hydrocephalus

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Table 2:   Features suggesting an alternative diagnosis to idiopathic Parkinson's disease :

1. Modest to poor response to levodopa / apomorphine

2. Rapid deterioration

3. Early dementia

4. Early falls

5. Prominent autonomic symptoms

6. Gaze palsy

7. Cerebellar signs

8. Pyramidal signs

Pharmacotherapy

Therapeutic approaches to PD are subjected to many controversies, in particular, whether treatment could influence its progression. As far as pharmacotherapy is concerned, there are two categories of treatment to be considered:

1. Neuroprotection

At present, there is no conclusive evidence that progression of PD can be delayed. Tocopherol (vitamin E) was shown to be ineffective in neuroprotection.[17] The role of monoamine-oxidase B (MAO-B) inhibitors is still controversial.[18,19]

2. Symptomatic Treatment

The objective is to maintain independent functioning for as long as possible.

Levodopa

Levodopa is the mainstay and most potent drug for treating PD. The features of PD manifest when 60-80% of nigrostriatal neurons are degenerated with 90% reduction of striatal dopamine. Levodopa enters the striatum and is converted into dopamine by l-aromatic amino acid decarboxylase and replenishes the deficient store.

Levodopa is combined with a dopa-decarboxylase inhibitor (DDI) to minimise its peripheral dopaminergic side-effects and increase its concentration in the central nervous system. The DDI in Sinemet and Madopar are carbidopa and benserazide respectively. Levodopa should be introduced slowly with dose incrementations every six to twelve weeks depending on the clinical response.

In the initial stage of PD, a stable reversal of almost all its manifestations can be obtained with levodopa. This is the therapeutic "honeymoon period". Exogenous dopamine source can generate a storage in the remaining nigral neurons that is sufficient to maintain a steady supply to the striatal receptors. The gradual loss of dopaminergic terminals diminishes the capability to synthesize, store, release and reuptake dopamine.

After some years of levodopa treatment, a significant proportion of patients will develop complications, which represent a complex interaction between the long-term drug effects and disease progression. Motor fluctuations are major problems in younger patients, and neuro-psychiatric symptoms tend to occur in elderly patients.

Since the introduction of levodopa, several unique treatment-related motor fluctuations were recognized,[20] which develops in approximately 50% of patients after five years of treatment. A "benign" pattern of predictable oscillations with end-of-dose wearing-off usually progresses to the more "malignant" random swings. This picture is further complicated by the occurrence of dyskinesia.[21]

With long-term levodopa, a therapeutic threshold gradually emerges with an all-or-none clinical response across a certain levodopa level. Above this threshold, the patient remains more or less responsive and increasing the dosage will not improve the quality of therapeutic response. The threshold persists and remains almost unchanged during chronic levodopa treatment. This finding can be explained by the following mechanism. Disease progression results in a reduction of presynaptic dopamine storage terminals so that the ability to buffer fluctuations in levodopa level is lost. Besides the striatum, uptake and conversion of levodopa to dopamine also take place in the endothelial and glial cells. However, these extra-striatal sites lack the appropriate control of storage and release of dopamine. Their contribution increases as more neurons in the substantia nigra degenerate, so that dopamine is released intermittently and in large quantity as soon as they are synthesized from their substrate. The synaptic dopamine concentration is therefore directly dependent on the availability of levodopa. Clinically, the patient will experience a predictable response soon after a dose of levodopa, but will deteriorate towards the end of it when the drug level is below therapeutic threshold. The first symptom is usually early morning akinesia. Later, tremor and bradykinesia occur regularly in a close temporal periodicity to the timing of levodopa dosage.

In at least 15% of levodopa-treated patients, motor fluctuations become increasingly abrupt, with sudden and unpredictable off periods. The off-period can be complicated by distressing positive symptoms, such as dystonia, sensory, autonomic and psychiatric symptoms. Dose failure is an advanced stage of response fluctuation when one or more

succeeding doses do not reverse the parkinsonian symptoms. The exact mechanism for these unpredictable swings is unknown. They may be due to pharmacodynamic changes which lead to altered interactions between dopamine and the striatal receptors. Relatively small fluctuations in cerebral levodopa and dopamine concentrations may have a large effect on drug response. Peripheral pharmacokinetic factors may also contribute to these swings.

Dyskinesia can be classified into:

1) Peak-dose dyskinesia, which is often choreic and ballistic,
2) Low-dose dyskinesia, which is typically dystonic and painful, and
3) Diphasic dyskinesia, with mixed pattern of chorea, ballismus and dystonia.

The occurrence of dyskinesia is due to a complex interaction between the fluctuating striatal dopamine level and its differential stimulation on the subtypes of receptors, including agonistic and antagonistic, that distributes abnormally in the degenerating striatal pathways.

To manage peak-dose dyskinesia, frequent administration of levodopa is only effective initially. The small, frequent dosage may not achieve a therapeutic level to produce a clinical response. Moreover, the duration of response is reduced. During chronic levodopa therapy, the threshold for production of peak-dose dyskinesia decreases, sometimes to below the therapeutic threshold. The therapeutic window of levodopa thus narrows to a state when motor response always

coexist with dyskinesia. For some patients, peak-dose dyskinesia may not cause significant functional disability despite its alarming clinical appearance. Dose reduction improves dyskinesia only at the expense of motor deterioration, which is often more disabling.

A third of chronic levodopa users develop painful dystonia as a manifestation of low-dose dyskinesia. Withholding levodopa will eventually lead to its cessation. However, drug holiday of levodopa is no longer recommended since a fatal neuroleptic malignant-like syndrome can be precipitated. The addition of muscle relaxants and anticholinergics can sometimes be helpful in painful dystonia.

Diphasic dyskinesia is linked to a critical levodopa plasma level and emerges at the transition between rising and falling phases of drug concentration. The typical pattern is dyskinesia-improvement-dyskinesia (D-I-D). Management is difficult. Patients may remain in a continuous dyskinetic state if only an intermediate levodopa level is achieved. Frequent high doses of levodopa which exceed the therapeutic threshold are needed to overcome this problem.

Motor fluctuations form an additional disability which goes beyond that of the original disease. It was postulated that the large-amplitude, unphysiological swings in levodopa levels produced by conventional therapy contribute to these long-term complications by inducing postsynaptic dopamine receptor hypersensitivity. The maintenance of stable peripheral

and central levodopa concentration may, therefore, be important in reducing motor fluctuations. There are several strategies to achieve a constant levodopa level.

Differential actions of intermittent levodopa on dopaminergic receptor subtypes lead to downregulation of the direct pathway and upregulation of the indirect pathway. This imbalance results in dyskinesia. Continuous duodenal levodopa infusion[22,23] that avoids drug level oscillations had been shown to restore this balance. However, long-term infusion therapy is impractical as well as uncomfortable for the patients.

Controlled-release delivery systems of levodopa (Sinemet CR, Madopar HBS) aim at modifying the pharmacokinetic profile by producing a more steady drug level. The peak levodopa level is brought down by about 1/3 and the trough level is approximately doubled. The bioavailability of levodopa is reduced by about 25% with these preparations and the total levodopa dosage has to be increased accordingly. In the short-term, motor fluctuations and dose frequency can often be reduced. Some patients may find it troublesome when they switch from conventional to controlled-release preparations because the onset of clinical effect can be delayed for over one hour. Supplements of conventional levodopa is often required.

Protein in food and neutral amino acids in blood compete for carrier system with levodopa.[24] Protein reduction or redistribution may increase the efficacy of oral levodopa by

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achieving a favourable balance of absorption and transport. In advanced PD, gastric emptying can be an important rate-limiting step in levodopa absorption.[25] Prokinetic agents without dopamine antagonistic properties, such as domperidone and cisapride, are useful both for improving drug absorption and alleviating drug-induced emesis by promoting gastric emptying.

Levodopa-induced cognitive and neuropsychiatric problems are common in the elderly patients. They typically describe faces and figures on the wall. Insight is often preserved and the hallucinations can be well-tolerated. Sometimes, more sinister hallucinations and full-blown psychosis can be precipitated. Mental symptoms will respond to reduction of levodopa dosage at the expense of motor deterioration. If it is not possible to reduce the levodopa dosage, clozapine, an atypical neuroleptic with low propensity for inducing extrapyramidal side-effects, can be added. Clozapine also exerts a dose-related suppression of levodopa-induced dyskinesia [26]. However, fatal agranulocytosis had been reported in association with clozapine so that close haematological monitoring under specialist supervision is required when this drug is prescribed. The dose of Clozapine should be increased gradually as patients may develop tiredness and increased salivation. The dosage required to settle drug-induced psychosis in PD is usually much less than that needed for schizophrenia.

It has been postulated that the unphysiological dopaminergic response from levodopa therapy might form a source of oxidative stress in the central nervous system. Up till now, there is no firm evidence that levodopa can accelerate neuronal death in human. However, we know that levodopa benefits patients with PD by extending their life-expectancy and improving their quality of life.[27,28]

Dopamine Agonists

Dopamine receptors can be classified by their transduction mechanism into either D1- like (D1 & D5) and D2- like (D2, D3 & D4). Bromocriptine and pramipexole stimulate D1- and D2- like receptors respectively, while pergolide stimulates both. A combination of D1- and D2-like receptors activation might be of greater benefit in preventing motor fluctuations and dyskinesia than activation of individual receptors alone.

Using dopamine agonists as monotherapy may provide adequate therapeutic effect especially in young-onset cases. Progression of disability may be delayed for over two years.[29] Their long half-life may prolong the therapeutic response of levodopa and reduce the associated motor fluctuations and dyskinesia. Their long-term role in delaying motor fluctuations is unknown. The dosage should be gradually increased. A rapid increase in dosage results in side-effects such as nausea, vomiting, and postural hypotension. The levodopa dosage may be reduced after introduction of dopamine agonists.

Apomorphine is a potent non-ergot derivative dopaminergic D1 and D2 agonist. The development of new delivery systems permits a reintroduction for future practical usage. It is effective in reversing end-of-dose wearing-offs and the associated non-motor positive symptoms. A reliable response begins 5 to 15 minutes after subcutaneous injection and lasts for a mean of 60 minutes. In general, 1 to 3 mg is given two to six times a day. Alternatively a continuous subcutaneous infusion mini-pump can be used. Apomorphine is especially indicated in patients with predictable motor fluctuations and who are capable of anticipating their onset with a booster dose. The therapeutic benefits of apomorphine can be maintained for more than five years.[30] Prophylactic domperidone is necessary to prevent nausea, which will wear off after several months as tolerance to the peripheral effects of apomorphine develops.

Anticholinergic drugs

These agents work by blocking the striatal muscarinic receptors to reduce excessive cholinergic activity. Anticholinergic drugs are more useful for parkinsonian tremor than rigidity or akinesia. In mild PD, anticholinergics can be used as sole therapy with 20% functional improvement. In more advanced disease, they are useful for levodopa-induced dystonia. Their use in the elderly is limited by their side-effects, which are related to their antimuscarinic properties. Faecal impaction, urinary retention, and acute glaucoma can be precipitated. Elderly patients are particularly prone to drug-induced hallucination and confusion[31] and hence should be used with caution in the elderly. Anticholinergic agents should be tapered very slowly since abrupt withdrawal can result in acute deterioration of parkinsonism.

Monoamine-oxidase B inhibitors

MAO-B is responsible for 80% of the striatal MAO activities involved in the breakdown of dopamine. Selegiline (L-deprenyl, Jumex) at doses below 20 mg/day inhibits MAO-B selectively. It is given twice daily in the morning and at noon. Evening doses may precipitate insomnia and nightmare. There is no definite evidence that progression of disease can be delayed with selegiline.

Amantidine

Presynaptically, amantidine enhances release of stored dopamine and inhibit its reuptake. Postsynaptically, it increases the affinity of dopamine receptors. Its efficacy is similar to that of the anticholinergics. The recently demonstrated N-methyl-4-D-aspartate (NMDA) antagonistic property of amantidine has renewed its clinical interest as a potential neuro-protective agent in the glutamate pathway.

Cathechol-O-methyl-transferase inhibitors

Cathechol-O-methyl-transferase (COMT) is involved in the methylation of levodopa to 3-O-methyldopa, and dopamine to 3-methotyramine. By blocking these two pathways with COMT-inhibitors, the level of dopamine in the striatum can be increased. Moreover, 3-O-methyldopa competes with levodopa for cerebral uptake and may also antagonise the action of levodopa and dopamine. Entacapone acts peripherally. Tolcapone exerts an additional effect at the synaptic level by penetrating the blood-brain barrier. Initial studies of COMT inhibitors have shown their efficacy as adjunctive therapy to levodopa.[32,33]

L-threo-dihydroxyphenylserine

Progression of disease will cause more gait instability and freezing episodes. These manifestations are related to noradrenergic or serotonergic pathways rather than the dopaminergic system, so that conventional agents are less effective. L-threo-dihydroxyphenylserine (L-DOPS), which increases cerebral noradrenaline, has been used for specific treatment of freezing episodes.

Role of family physicians in managing Parkinson's disease

Patient counseling is an essential part of managing PD including the discussion of disease prognosis, treatment options and potential complications. It should be emphasised that although PD cannot be cured, effective treatment is available and life expectancy can be close to normal.

There is no consensus on the best treatment plan for PD. Generally speaking, anti-parkinsonian therapy needs to be individualised to the specific patient. The trend is to use dopamine agonist and withhold levodopa at the start of treatment in younger-onset patients[34,35] unless their side-effects are intolerable. In the early stages of the disease, anticholinergics, selegiline and dopamine agonists may be sufficient for many months, although their efficacy is much less than levodopa. We generally use the controlled-release rather than conventional preparations when levodopa therapy is initiated.

A shared-care approach with neurologists is indicated for young onset patients, those with atypical features, and when control of the disease becomes difficult.

Patients with a younger age of disease onset have a slower progression of disease, better initial levodopa response, but earlier and more frequent response fluctuations.[36] They have many years of disease and treatment ahead, making the balance of therapeutic decisions much more difficult. It is our practice to introduce dopamine agonists as initial therapy for patients whose age of onset is below 60.

Surgical treatment

Fetal mesencephalon transplantation

Replacement of dopamine-producing cells with fetal mesencephalon grafts is still undergoing experimental assessment. Many questions about the techniques remain unanswered, including the optimal amount of fetal tissue needed, the best site for implantation, and the requirement for immunosuppressants.

Stereotactic functional neurosurgery

With the advent of high resolution neuro-imaging devices and more precise

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Table 3: Stereotactic neurosurgery – therapeutic effects			
Lesioning procedures :	**Thalamotomy**	**Pallidotomy**	**–**
Deep brain stimulation:	**Vim**	**GPi**	**STN**
Tremor	+ + +	+ +	+ + +
Rigidity	+	+ +	+ + +
Akinesia, gait	0	+	+ + +
Dyskinesia	+	+ +	+ +
Off-period dystonia	0	+ +	+ + +

Vim – ventralis intermedius

GPi – globus pallidus internus

STN – subthalamic nucleus

0 – no response; + + + – maximum response

These stereotactic procedures, particularly DBS, are highly promising in improving the quality of life of patients with advanced PD. Their therapeutic effects are summarised in **Table 3.** ■

localising techniques, stereotactic functional neurosurgery with high levels of precision can now be carried out. Generally, surgery for PD involves three main steps. Firstly, the anatomical target is defined stereotactically with neuro-imaging techniques. Then, electrophysiological assessment is performed by the insertion of stereotactic intracranial probes to identify the target nucleus and avoid nearby structures. The final step is thermolytic lesioning of the target or implantation of deep brain stimulating electrodes. The stimulating electrodes are connected to a programmable pulse generator which is placed in a subcutaneous pocket under the clavicle like a cardiac pace-maker. Stimulating variables can be altered by an external programming.

Thalamotomy is an ablative technique for control of tremor but does not ease bradykinesia or rigidity. Pallidotomy is helpful in ameliorating all cardinal features of PD as well as levodopa-induced dyskinesia, and was shown to produce favourable functional outcomes.[37,38] The effects of thalamotomy and pallidotomy are predominantly on the contralateral side so that symptoms in patients with generalised disease cannot be totally abolished. Bilateral lesioning procedures are rarely performed because of the significant side-effects including speech and cognitive impairment.

Recent advances have been made in deep brain stimulation (DBS) of various target nuclei. The exact mechanism of action of DBS is still not entirely understood. The effects of DBS are immediate and reversible when the stimulation stops. Stimulation of the ventral intermediate (Vim) thalamic nucleus abolishes tremor[39] while stimulation of the subthalamic nucleus (STN) or globus pallidus internus (GPi) improves all cardinal features of PD.[40] DBS can be performed bilaterally or combined with various lesioning techniques.

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Key messages

1. It is important to identify reversible causes of parkinsonism, such as drug-induced parkinsonism and Wilson's disease.

2. Although Parkinson's disease is not curable, many effective treatments are available. Treatment strategies should be tailored to the individual patient.

3. In younger onset patients (i.e., below 60), consider starting dopamine agonists first, although levodopa-based medications are still the most efficacious.

4. Surgical treatment is a promising option for selected patients.

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