Assessing and managing Parkinson's disease

Parkinson's disease is relatively common: the prevalence is over 1% in those older than 55 years, rising with age to nearly 5% in people over 85.[1] Antiparkinsonian treatment improves quality of life. Management involves collaboration between the patient, carers, GP, allied health professionals and neurologist.

NEIL MAHANT
MB BS, FRACP
VICTOR S.C. FUNG
MB BS, PhD, FRACP
JOHN G.L. MORRIS
DM(Oxon), FRACP

Dr Mahant is Neurology Fellow, Department of Neurology, Westmead Hospital; Dr Fung is Staff Specialist and Director of the Movement Disorders Unit, Department of Neurology, Westmead Hospital; Associate Professor Morris is Clinical Associate Professor, University of Sydney, and Head, Department of Neurology, Westmead Hospital, Westmead, NSW.

Assessing a patient for parkinsonism

History

Typically, patients with parkinsonism complain of tremor and impairment of hand function, with difficulty writing, doing up buttons and brushing teeth. They may describe weakness, but none is apparent on examination. When there is no tremor, it is easy to overlook the diagnosis. Always consider idiopathic Parkinson's disease in a patient presenting with stiffness of the shoulder or dragging of one leg; this presentation is often misdiagnosed in patients with younger onset Parkinson's disease.

Examination

The diagnosis of parkinsonism is often apparent as the patient walks into the room and sits down. There is a quality of stillness about the patient – with slight loss of facial expression, quietness of the voice and lack of normal gesticulation. This lack of animation may be mistaken for depression, particularly if no tremor is present. When assessing the patient, attention should be paid to:

- gait
- rest tremor
- rigidity
- akinesia.

Gait

Gait is the single most useful test for parkinsonism. Loss of or reduced arm swing, initially on one side, is one of the earliest manifestations. Later, the stride shortens and the posture becomes flexed. Paradoxically, the stride may quicken, causing a hurrying ('festinating') quality. This is usually associated with impairment of balance, which is tested by pulling the patient backwards by the shoulders ('retropulsion'). However poor the balance, the base of the gait in parkinsonism remains narrow, and broadening of the base raises the likelihood of a different disease entity, such as normal pressure hydrocephalus or vascular parkinsonism (see 'Differential diagnoses' on page 18).

IN SUMMARY

- **The diagnosis of Parkinson's disease depends on a careful history and examination. Investigations are done to exclude other disorders.**
- **It is useful to divide the syndrome of parkinsonism into two groups: idiopathic (Lewy body) Parkinson's disease, where the response to levodopa is good, and atypical parkinsonism, where the response to levodopa is usually poor.**
- **Levodopa remains the most effective treatment for Parkinson's disease; however, long term complications are common.**
- **Dopamine agonists and catechol-*O*-methyl transferase (COMT) inhibitors are useful in the management of levodopa-related dyskinesia and fluctuations.**

Diagnosing Parkinson's disease

Core criteria for idiopathic Parkinson's disease

An akinetic–rigid syndrome with:

- Asymmetrical onset
- Rest tremor
- Good and sustained response to levodopa
- Slow progression

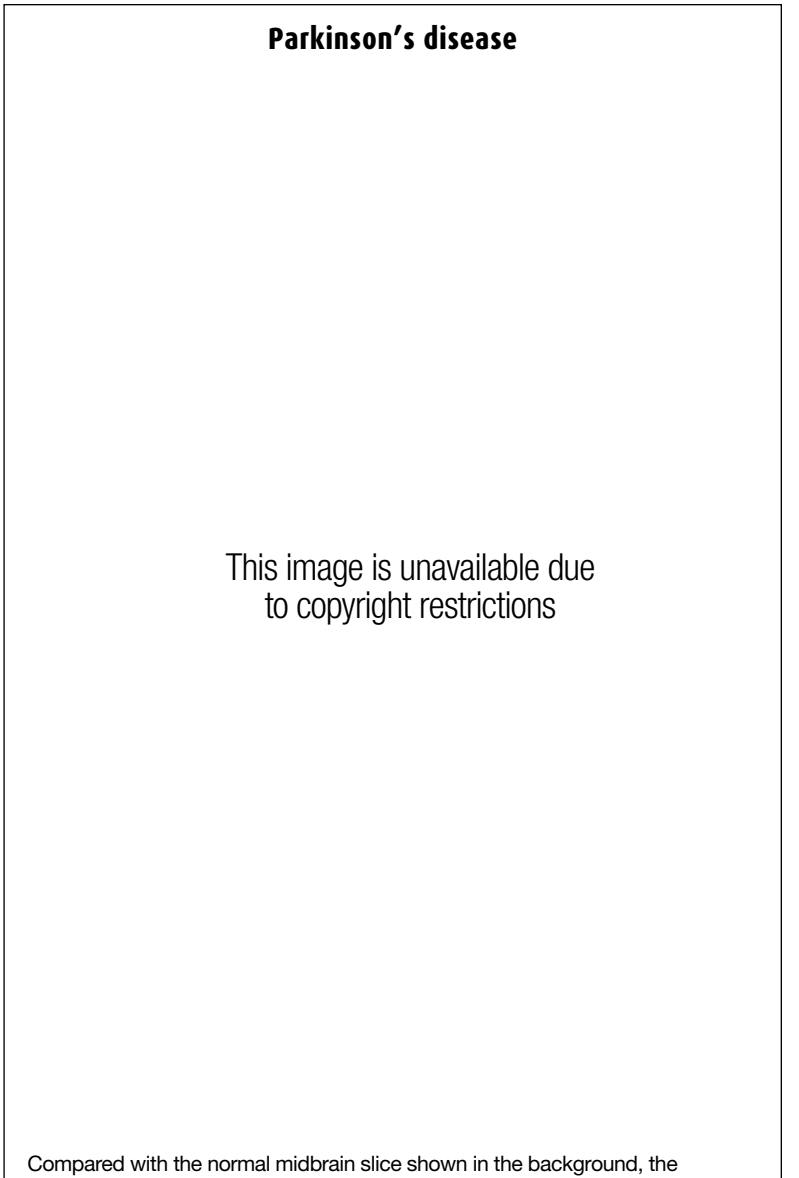
Clinical clues to other diagnoses*

Consider other diagnoses if there is:

- Exposure to neuroleptics or antiemetics (drug-induced parkinsonism)
- Early postural instability and falls (progressive supranuclear palsy, multiple system atrophy, vascular parkinsonism, normal pressure hydrocephalus)
- Early dementia (dementia with Lewy bodies, Alzheimer's disease, vascular parkinsonism)
- Truncal rigidity or dystonia (multiple system atrophy, progressive supranuclear palsy)
- Isolated postural tremor (essential tremor)
- Autonomic dysfunction (multiple system atrophy)
- Rapid or stepwise progression (multiple system atrophy, progressive supranuclear palsy, vascular parkinsonism)
- Onset before 50 years (Wilson's disease)
- Exclusively unilateral signs (structural lesion)

* Some alternative diagnoses are listed in parentheses as a guide.

Parkinson's disease



Compared with the normal midbrain slice shown in the background, the midbrain from a patient with Parkinson's disease shown in the foreground has a paler substantia nigra, signifying loss of pigmented dopaminergic neurons. The diseased neurons on the right contain Lewy bodies and neurofibrillary tangles.

Rest tremor

Rest tremor in the hands is the most recognisable feature of idiopathic Parkinson's disease. It is best seen when the patient is seated with his or her hands resting on, but not clasping, the thighs. It increases when the patient performs 'serial sevens' (serial subtractions of seven, as in the Mini Mental State Examination) and usually disappears on voluntary movement of the arm. It is also seen during walking. The tremor may resume, after a brief pause, when the arms are held outstretched.

Rigidity

Rigidity is an increased resistance to passive movement. It is the same throughout the range of motion and is likened to bending a lead pipe. Often a tremor is also palpable during the testing of tone, giving rise to so-called cogwheeling. Rigidity is tested by flexing and extending the wrist or elbow or rotating the hand; it is accentuated when the patient repeatedly raises and lowers the other arm at the shoulder ('activation').

Akinesia

Akinesia refers to impairment of the initiation,

speed and amplitude of voluntary movement. It is best tested by getting the patient to repetitively tap his or her fingers and thumb (Figure 1) or make alternating piano playing movements of the index and middle fingers (Figure 2). The movements are usually slow and of reduced amplitude, and the amplitude progressively decreases as the task continues.

Possible diagnoses when a patient has parkinsonism

Idiopathic Parkinson's disease

Parkinson's disease (strictly known as idiopathic Parkinson's disease) is defined as the clinical syndrome of parkinsonism with the pathological findings of neuronal loss and Lewy bodies in the substantia nigra; thus the diagnosis can be made with certainty only post mortem. The box on page 17 summarises criteria that help to make the diagnosis. Even using strict diagnostic criteria, Parkinson's disease is misdiagnosed in up to 25% of cases.[2] The most common misdiagnoses revealed at post mortem are progressive supranuclear palsy, multiple system atrophy, Alzheimer's disease and vascular parkinsonism.

Approximately 5 to 10% of people with idiopathic Parkinson's disease experience early onset parkinsonism: they develop symptoms before the age of 40 years.[3]

Differential diagnoses

Recognising causes of parkinsonism other than Parkinson's disease is important to guide treatment and allow a more accurate assessment of prognosis. Clinical clues that a patient may have a variant of Parkinson's disease are summarised in the box on page 17.

Neurodegenerative conditions that mimic Parkinson's disease include multiple system atrophy, progressive supranuclear palsy and dementia with Lewy bodies. A history of falls or cognitive impairment within a few years of presentation or early marked autonomic dysfunction should alert you to the possibility of one of these variants. Mild extrapyramidal features are common in the later stages of Alzheimer's disease.

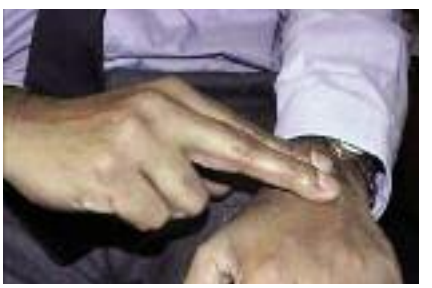
Vascular parkinsonism usually presents with gait disturbance and mild cognitive impairment. The gait is shuffling, often with prominent freezing, but it differs from that of Parkinson's disease because it is on a broad base.

Normal pressure hydrocephalus has a similar broad based gait to that of vascular parkinsonism and is accompanied by incontinence and cognitive impairment.

Drug-induced parkinsonism occurs with neuroleptics (e.g. haloperidol, fluphenazine, chlorpromazine, trifluoperazine), antiemetics (e.g. prochlorperazine, metoclopramide) and dopamine depleting drugs (e.g. tetrabenazine). These medications all antagonise the action of dopamine and should be withdrawn before making a diagnosis of Parkinson's disease. It may take months for improvement to occur.

Wilson's disease should be considered in any patient whose symptoms start before the age of 50 because Wilson's disease may present with parkinsonism and copper chelation may be lifesaving.

Figures 1a and b. Hand opening and closing. In Parkinson's disease the movements become progressively smaller, but this may take several repetitions to occur. To observe this sign, encourage the patient to continue to fully open and close the hand as quickly as possible.



Figures 2a and b. Two finger taps. Impairment of tapping one finger then the other, like playing a trill on the piano, is a sensitive sign of motor disorders. In Parkinson's disease the movements are performed with difficulty. Other disorders, such as a pyramidal tract lesion, may produce the same sign.

Investigations

The results of routine investigations and neuroimaging are normal in idiopathic Parkinson's disease. Cerebral MRI may be indicated to exclude alternative diagnoses. Neurophysiological studies (e.g. to further assess tremor or autonomic function) may be useful in selected cases. Serum copper and caeruloplasmin levels and urinary copper excretion should be measured in early onset cases.

Prognosis

No treatment has been shown to arrest or slow the neurodegenerative process in

Parkinson's disease. The median duration of the disease is about 12 years. However, the rate of progression in individual patients is highly variable and many patients live with their illness for 20 to 30 years or more.

Common treatment issues in early idiopathic Parkinson's disease

The box below outlines the medications used in the management of Parkinson's disease.

Which drug to start?

Drug treatment is indicated if there is significant disability. In the doses tolerated by most patients, levodopa (Kinson, Sinemet, Madopar) remains the most effective drug for reversing the motor

Medications used in Parkinson's disease

Levodopa

Levodopa is converted to dopamine in the brain. It is combined with a peripherally acting decarboxylase inhibitor (carbidopa in Kinson and Sinemet; benserazide in Madopar) to reduce conversion to dopamine outside the brain. This decreases nausea and increases the bioavailability of levodopa. Levodopa is absorbed from the small intestine but not the stomach. Standard release, controlled release (Sinemet CR, Madopar HBS) and dispersible (Madopar Rapid) formulations are available.

Side effects include nausea, postural hypotension and hallucinations.

Dopamine agonists

Dopamine agonists stimulate dopamine receptors in the striatum directly, bypassing the necessity for dopamine production. Three oral dopamine agonists are available through the PBS: bromocriptine (Bromohexal, Bromolactin, Kripton, Parlodel), pergolide (Permax) and cabergoline (Cabaser).
All are ergot derivatives. The PBS does not currently fund the non-ergot agonists pramipexole and ropinirole.

Bromocriptine and pergolide have relatively short half-lives, and require two to three doses a day. Cabergoline has a very long half-life, and takes one to two weeks to achieve steady state.

Ergot-related fibrotic complications occur in up to 3% of patients, including retroperitoneal and pleuropulmonary fibrosis and constrictive pericarditis. Patients should be monitored every three to six months with auscultation of the chest and heart and measurement of inflammatory markers such as ESR. Fibrosis should be considered in the differential diagnosis of urinary symptoms, breathlessness or chest pain.

Other side effects include nausea, postural hypotension, hallucinations, confusion and exacerbation of dyskinesias.

COMT inhibitors

These drugs inhibit catechol-O-methyl transferase (COMT), and thus delay the breakdown of levodopa and extend its duration of effect. They do not have any independent antiparkinsonian action. Entacapone (Comtan) has a similar half-life to levodopa, and they are generally taken together. Tolcapone is not freely available in Australia because of rare reports of severe hepatic toxicity, but it is available through the Special Access Scheme or from overseas.

COMT inhibitors discolour the urine. The most common adverse events are due to an accumulation of levodopa (manifesting, for example, as dyskinesias, confusion, hallucinations) and may necessitate a reduction in the daily levodopa dose. Diarrhoea is an uncommon side effect.

Amantadine

Amantadine (Symmetrel) has anticholinergic and antiglutamate effects. It reduces the severity of levodopa related dyskinesias in some patients.

Most patients develop livedo reticularis, which is a mottled discolouration of the skin. Other side effects include confusion, delirium, peripheral oedema, postural hypotension, dry mouth and leucopenia.

Anticholinergics

Anticholinergics (benztropine [Cogentin], benzhexol [Artane] and biperiden [Akineton]), once the main treatment, now have a limited role in the treatment of Parkinson's disease. They have a mild antiparkinsonian effect but cause memory impairment, hallucinations and urinary retention, particularly in the elderly.

Domperidone

Domperidone (Motilium) is the treatment of choice for nausea in the setting of parkinsonism. Unlike other antiemetics, it does not cross the blood–brain barrier and is therefore safe in Parkinson's disease. It has a role in treating dopamine-receptor-mediated nausea and postural hypotension.

Selegiline

Selegiline (Eldepryl, Selgene), a monoamine oxidase B inhibitor, inhibits breakdown of levodopa and dopamine in the brain. It also has a weak antiparkinsonian effect when used as monotherapy, but it may exacerbate levodopa-related dyskinesias. It interacts with many medications, including opiates, selective serotonin reuptake inhibitors and other antidepressants. Concomitant use of other monoamine oxidase inhibitors (e.g. moclobemide, phenelzine, tranylcypromine) is contraindicated.

symptoms of Parkinson's disease. However, several recent trials have shown that initiating treatment with a dopamine agonist, adding levodopa only if required, significantly reduces the incidence of dyskinesias, and to a lesser extent motor fluctuations, after two to five years of follow up.[4] These studies leave open the possibility that initiating treatment with levodopa, with early introduction of agonists as a levodopa-sparing strategy (e.g. once patients require treatment beyond 450 mg/day of levodopa) will confer the same benefits.

With the above facts in mind, we recommend the following approach. In younger patients with relatively mild disability, treatment should begin with a dopamine agonist, such as bromocriptine (Bromohexal, Bromolactin, Kripton, Parlodel), pergolide (Permax) or cabergoline (Cabaser). In patients with an older age at onset and in patients with more significant disability, treatment should begin with levodopa and then a dopamine agonist added once doses of more than 450 to 600 mg/day of levodopa are needed.

Levodopa is started at 50 to 100 mg three times a day and then increased over three to six weeks to 300 to 450 mg/day. Dopamine agonists should be used with care in older patients, who are more prone to side effects such as hallucinations, psychosis and postural hypotension.

Nausea due to levodopa or dopamine agonist

Stimulation of dopamine receptors in the area postrema of the brainstem (the 'vomiting centre') causes nausea and vomiting. Nausea is managed by taking levodopa with food, to slow the rate of absorption, and by combining the levodopa with carbidopa or benserazide. Domperidone (Motilium) may be added if needed for nausea. The antiemetics metoclopramide and prochlorperazine should not be used in parkinsonism.

Issues in mid and later stages

For the first few years of the disease, the response to treatment is often good and side effects are minimal and manageable. After this 'honeymoon period', levodopa-related motor fluctuations and dyskinesias become increasingly likely, and aspects of the disease emerge that are not improved by levodopa.

Motor fluctuations

Antiparkinsonian medications, especially levodopa, have short and long duration responses. The long duration effect may last for days, but it is prominent only in the early stages of the disease. The short duration response mirrors the blood level of dopa. After an oral dose, the peak plasma concentration occurs usually within an hour and the half-life is about 90 minutes.

Several types of motor fluctuations are described:

- end of dose deterioration
- early morning and end of dose dystonia
- dose failure
- yo-yoing
- severe 'offs'.

End of dose deterioration

This refers to re-emergence of parkinsonian symptoms three to four hours after taking the tablets. Eventually this deterioration may occur after one to two hours. The first step is to increase the dose frequency of levodopa. The next step is to add a dopamine agonist or a catechol-*O*-methyl transferase (COMT) inhibitor such as entacapone (Comtan).

Early morning and end of dose dystonia

This manifests as painful twisting of the foot occurring at the end of a dose cycle

Functional neurosurgery

Interest in functional neurosurgery has increased over the last five to 10 years. There are two approaches: the ablation of a small volume of brain tissue or the implantation of an electrode for high frequency stimulation. The aim of both is to inhibit an overactive structure such as the globus pallidus or subthalamic nucleus.

The indications are evolving, including disabling dyskinesias, motor fluctuations or tremor due to clinically definite, levodopa-responsive idiopathic Parkinson's disease. Subthalamic stimulation produces a similar effect to levodopa and allows a more sustained benefit. The levodopa dose can usually be reduced, occasionally to zero. Pallidal surgery (pallidotomy or pallidal stimulation) is efficacious primarily for drug-induced dyskinesias (improving contralateral and ipsilateral dyskinesias in about 90% and 50% of patients respectively). Thalamic surgery reduces tremor, but is not recommended in Parkinson's disease because it does not improve other aspects of the disease. There are potential complications and irreversible side effects with all forms of surgery.

The assessment, surgery and postoperative care are complex, and should be done with the co-operation of neurologists and neurosurgeons with expertise in the field. Functional neurosurgery is not covered by Medicare, and the stimulators cost over $20,000.

Functional neurosurgery for movement disorders holds great promise, and there are ongoing studies attempting to better define the indications and improve outcomes. Future developments may include the implantation of stem cells or local delivery of growth factors.

Acknowledgement: We thank Dr Richard G. Bittar and Professor Nicholas W.C. Dorsch, Department of Neurosurgery, Westmead Hospital, Sydney, for their contribution to the text above.

or before the first dose of dopa in the morning. It may be accompanied by marked akinesia. It is relieved by a further dose of levodopa. Early morning dystonia may respond to the use of Sinemet CR in the evening, or taking small doses of levodopa during the night. Both forms of dystonia may improve with the addition of a COMT inhibitor or dopamine agonist.

Dose failure

It is not uncommon for a dose of levodopa to have no effect, often after a heavy meal or emotional upset. This is due to a failure of levodopa to leave the stomach and pass to its site of active absorption in the proximal small bowel. This problem is lessened by encouraging patients to take the levodopa on an empty stomach and to avoid heavy meals, especially in the middle of the day.

Changing from standard levodopa to a dispersible formulation (e.g. Madopar Rapid) is useful in some patients. The sustained-release preparations of levodopa are often not effective in this setting.

Yo-yoing

This unpredictable alternation between 'on' and 'off' states is often difficult to manage. A period of observation by a nurse or doctor skilled in this area may lead to useful changes in the way the drugs are given.

Severe 'offs'

Some patients experience very severe 'off' periods, when they become almost immobile. These may occur quite suddenly. A useful drug, particularly in younger patients, is apomorphine (Apomine Injection), a dopamine agonist that is as potent as levodopa. It is administered by subcutaneous injection by the patient or a carer. Its main indication is as rescue therapy for severe 'offs'. A response occurs within five to 10 minutes, and the benefit lasts for about an hour. Admission to hospital is needed to establish the effective dose. Apomorphine causes severe nausea, and pretreatment with domperidone is necessary.

Levodopa-induced dyskinesias

Approximately 40% of patients with Parkinson's disease will have involuntary movements within five years of commencing treatment, with higher rates in patients with younger onset disease.[5] Most patients who are responsive to levodopa will develop dyskinesia if enough levodopa is given. The timing of the dyskinesias in relation to dosing with levodopa is important in differentiating between the types (Figure 3).

Peak dose dyskinesias

Peak dose dyskinesia, the commonest type of dopa-induced dyskinesia, occurs 30 to 60 minutes after taking levodopa, when the blood level is highest. Twisting, writhing, bobbing movements are seen in the trunk and limbs, less commonly in the face. Surprisingly, the patient is often unaware of the movements. Lowering the dose of levodopa lessens the movements, but often at the cost of worse parkinsonian symptoms. Most patients prefer to twist than to shake. Amantadine (Symmetrel) is often helpful in reducing the severity of peak dose dyskinesias.

Diphasic dyskinesias

Diphasic dyskinesia occurs as the patient is turning 'on' (as the levodopa level rises) and again when turning 'off' (as the level falls). It may consist of painful focal dystonic movements, generalised dyskinesia or both. These are difficult to treat. Sometimes the addition of a COMT inhibitor or long-acting dopamine agonist improves the situation.

Severe, unresponsive dyskinesias

Stereotactic neurosurgery (see the box on page 20) is worth considering in patients who benefit from levodopa but suffer severe dyskinesias, provided there is no evidence of cognitive impairment.

Late features that are not improved by levodopa

Falls

Levodopa often does not improve balance, and patients with postural instability may fall more frequently during periods of mobility induced by levodopa. Physiotherapists and occupational therapists can help with strategies for preventing falls and in gait and balance retraining.

Speech problems

Speech problems sometimes become

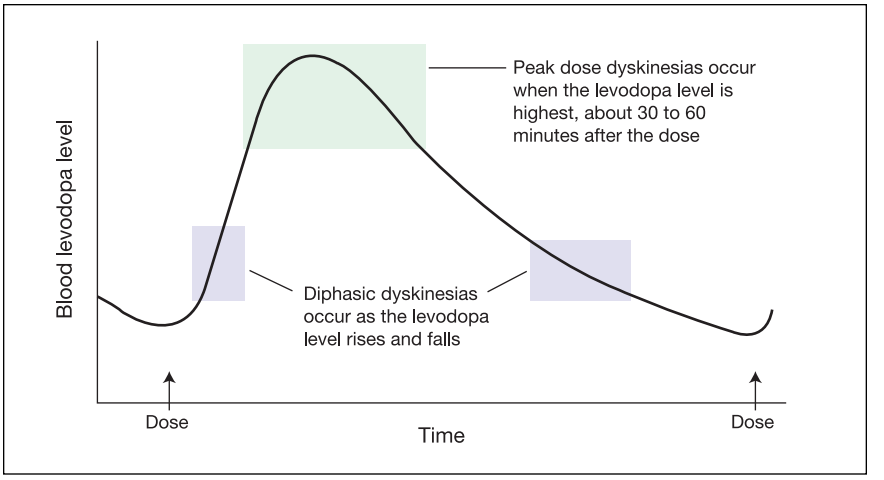


Figure 3. Dyskinesias tend to occur at different times during the levodopa dose cycle. Patients are 'off' when the levodopa level is at its lowest, and 'on' when the level is above a therapeutic threshold, which is approximately the level where diphasic dyskinesias occur.

unresponsive to levodopa. Speech therapy with the Lee Silverman technique is of particular benefit.[6]

Postural hypotension

Postural hypotension is made worse by levodopa and dopamine agonists. Ensure that the patient has an adequate salt and fluid intake. Elevating the head of the bed is worth trying. Compression stockings are not well tolerated. Fludrocortisone (Florinef) or domperidone can be used if these measures do not help.

Visual hallucinations and psychosis

Visual hallucinations and psychosis are common in older patients and those with advanced disease, usually occurring in the setting of a mild dementia that may not be obvious on meeting the patient. Often they are triggered by intercurrent infection, surgery or the addition of a dopamine agonist, anticholinergic agent or COMT inhibitor. Patients thereafter are best managed on levodopa alone at the lowest dose compatible with reasonable mobility.

Two atypical antipsychotics, quetiapine and clozapine, have relatively little antidopamine effect and are effective in treating psychosis in Parkinson's disease.[7] However, they are available on authority prescription only for the treatment of schizophrenia.

Issues at any stage of the disease

Constipation

Constipation is a common problem in Parkinson's disease, partially because of loss of dopaminergic neurons in the enteric nervous system. Ensure adequate fibre and fluid in the diet and, if necessary, give gentle laxatives. Many patients require enemas.

Depression

In Parkinson's disease, there is a significantly increased incidence of depression, which is independent of, and even overshadows, the degree of motor disability. Depression is a major determinant of quality of life in Parkinson's disease.[8]

Heightened awareness of the possibility that depression is present and early intervention are needed. If medical therapy is required, selective serotonin reuptake inhibitors are generally well tolerated, though some patients experience worsening in their parkinsonism. There is still a place for tricyclic antidepressants, particularly in those patients who cannot sleep.

Driving

Austroads recommends that patients with parkinsonism 'should not drive if capacity to control the vehicle is impaired', and it advises referral for neurological assessment.[9]

Most patients with uncomplicated parkinsonism manage driving perfectly well in the early stages of the disease. If the spouse raises concerns, or if the patient wishes to continue to drive even in the presence of advanced disease, referral to a trained driving assessor is helpful. Patients with dementia should be strongly discouraged from driving.

When to refer

We recommend referral to a neurologist to confirm the diagnosis and guide initial management. Once therapy has been initiated and stabilised, there is a 'honeymoon period' of several years when visits to the neurologist can be infrequent. Once major problems associated with advanced Parkinson's disease emerge, patients need to be seen on a regular basis. Much can be gained from a multidisciplinary approach involving nurses, physiotherapists, occupational therapists, speech therapists and social workers.

Future developments

The assessment and management of Parkinson's disease are developing rapidly. Areas of progress include diagnostic imaging using SPECT with specific dopaminergic radioligands. Pharmaceutical advances include the development of transdermal dopamine agonists and medications targeting other neurotransmitter systems. Stereotactic neurosurgery has a promising future, particularly deep brain stimulation targeting the subthalamic nucleus.

Conclusion

Antiparkinsonian treatment improves quality of life. Levodopa remains the mainstay of management, but complications occur and can be difficult to manage. Other drugs and surgery are largely introduced to deal with these complications. MT

References

1. de Rijk MC, Breteler MM, Graveland GA, et al. Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. Neurology 1995; 45: 2143-2146.
2. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55: 181-184.
3. Schrag A, Ben Shlomo Y, Brown R, Marsden CD, Quinn N. Young-onset Parkinson's disease revisited: clinical features, natural history, and mortality. Mov Disord 1998; 13: 885-894.
4. Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. JAMA 2000; 284: 1931-1938.
5. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001; 16: 448-458.
6. Ramig LO, Sapir S, Countryman S, et al. Intensive voice treatment (LSVT) for patients with Parkinson's disease: a 2 year follow up. J Neurol Neurosurg Psychiatry 2001; 71: 493-498.
7. Friedman JH, Factor SA. Atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease. Mov Disord 2000; 15: 201-211.
8. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 2000; 69: 308-312.
9. Assessing fitness to drive. 2nd ed. Sydney: Austroads, 2001 (can be downloaded from www.austroads.com.au/publications.html).