The art of treating Parkinson disease in the older patient

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BACKGROUND Parkinson disease (PD) is a neurodegenerative disorder that increases sharply after the sixth decade. There are many disorders in the elderly that exhibit some parkinsonian signs that can be confused with PD.
OBJECTIVE This article discusses the diagnostic and management issues of PD in the elderly patient.
DISCUSSION Levo-dopa (L-dopa) therapy is the cornerstone of treatment for PD in the elderly. After 5–8 years of treatment, motor complications such as fluctuations and dyskinesia usually occur and adjunct therapy may be required. Dopamine agonists can be used to smooth out motor fluctuations and amantadine is sometimes useful for dyskinesia. However, the adverse drug effects of adjunct therapy in the elderly are more common than with L-dopa alone, and risks need to be weighed up against benefits. Nonmotor complications including dementia, psychosis, depression, autonomic dysfunction and somnolence are common and require special attention. Late stage problems such as aspiration, difficulties with activities of daily living or recurrent falls require a multidisciplinary approach. Anitcholinergic drugs such as benztropine and benzhexol are best avoided because of the high risk of major side effects.

Parkinson disease (PD) is a common debilitating neurological disorder that increases sharply after the sixth decade. To date, there is no cure. The cornerstone of treatment is Levo-dopa (L-dopa) therapy. However, late complications including motor fluctuations and dyskinesia tend to occur after a period of 5-8 years following the initiation of L-dopa. Adjunctive therapies for control of late complications include the addition of a dopamine agonist, selegiline, catechol-o-methyltransferase (COMT) inhibitor or anticholinergic drug. However, in older patients (due to the high prevalence of dementia, dysautonomia and depression) these adjunctive therapies may cause unacceptable side effects because of their adverse drug profiles (Table 1). Therefore what is acceptable practice for treatment of PD in younger patients (<70 years old) may be quite different in older patients (>70 years old).

Making the diagnosis

Before consideration of treatment, an accurate diagnosis of PD is essential. Wrong diagnosis may result in little response to treatment or, worse still, may cause unwanted side effects. The clinical diagnosis of PD requires two out of the three cardinal signs, namely:

- resting tremor
- bradykinesia, and
- rigidity.

Postural instability is another criterion often mentioned in literature. As it occurs commonly with increasing age and in other conditions, its use as a diagnostic criterion in older people is somewhat limited. Other helpful supportive features include:

- expressionless face
- speech problems including hypophonia and dysarthria
- gait – reduced arm swing, flexed posture, freezing and festination
- loss of fine motor skills such as writing (resulting in micrographia)
- eye – reduced upward gaze, positive glabella tap and decreased eye blinking, and
- excess sweating and seborrhoeic skin.

In older patients there are a wide range of diseases that exhibit parkinsonian features, making diagnosis difficult (Table 2). Although L-dopa responsiveness can be used as a clue for differentiation, it is

important to be aware that some non-PD conditions such as Lewy body dementia and multisystem atrophy may respond positively to L-dopa, at least initially.[1] Other helpful tips in distinguishing PD from differential diagnoses include:

- asymmetric onset (especially true for people who develop PD before the age of 70 years), and
- the presence of a classic 4–6 Hz tremor at rest.

Table 1. The 4Ds that affect treatment issues of PD in elderly

- Dementia – use of anticholinergics is limited because of risk of delirium
- Postural hypotension (dysautonomia) – implication in treatment options, especially as most PD treatment tends to cause or exacerbate it
- Co-existence of depression is common and needs to be addressed
- Dyskinesia and motor fluctuations occur in late disease and are difficult to treat

Resting tremor is infrequent in other causes of parkinsonism. However, it must be noted that the tremor is absent in about one-quarter of classic PD cases and it occurs less commonly with the older onset age group. The tremor may also increase with anxiety or stress and sometimes some patients may only have postural kinetic tremor but not resting tremor. The main treatment strategies for PD include:

- increase in dopaminergic stimulation
- decrease in cholinergic stimulation, and
- decrease in glutamatergic stimulation.

Levo-dopa in the elderly

Levo-dopa remains the most potent medication for bradykinesia and rigidity in the elderly. It should be considered early for treatment in older patients if gait or functional independence is affected. There has been constant debate about its early use especially in younger patients with regards to potential neuronal toxicity (secondary to oxidant stress resulting from dopamine metabolism) and possible predisposition to late motor complications, namely dyskinesia and fluctuations. However, the neuronal toxicity theory has not been confirmed by recent, better designed studies.[2] In elderly PD patients with reduced life expectancy, the issue of neuronal toxicity may not be as important when balanced against functional independence provided by early commencement of L-dopa therapy.

Dosage

The dosage for L-dopa in the elderly is much less than in younger patients. The safest way of initiating treatment is to commence patients on half a tablet of either Sinemet 125 or Madopar 125 twice a day. If response is inadequate, the dose can be slowly titrated upward according to the clinical response. Levo-dopa can also be given as a slow release formulation. However, a longitudinal study has failed to show any difference between short acting and long acting preparations in terms of reduction in long term motor complications.[3]

Table 2. Distinguishing Parkinson disease from its differential diagnosis

Disease and rigidity	Bradykinesia	Tremor	Dementia	Other features responsiveness	L-dopa antipyschotic	Sensitivity to
Parkinson disease	• Yes • Limb	Yes	More common in the late onset		Yes	+
Drug induced	• Yes • Limb	No			No	++
PSP	• Yes • Axial	No	Yes, early	Loss of conjugate gaze (esp. downward)	No	
Lewy body dementia	• Yes • Axial	No	Yes, early	Hallucinations	Yes, initially	+++
Vascular	• Yes • Limb	No	Yes in some	Pyramidal signs	No	+
Multisystem atrophy	• Yes	No	Yes	Pyramidal, cerebellar signs (OPCA) Dysautonomia (SDS)	Yes, initially	

PSP: progressive supranuclear palsy
OPCA: olivopontocerebellar atrophy/degeneration
SDS: Shy-Drager syndrome
Axial rigidity: rigidity mainly involving vertebral column
Limb rigidity: rigidity mainly involving upper and lower limbs
Bradykinaesia and rigidity are grouped in one column as they are both considered as 'negative' symptoms as compared to tremor 'positive'

Neuroprotective agents

Selegiline has been found useful in some studies.[4,5] However, follow up studies failed to confirm neuroprotection.[6,7] In fact, there has been some debate about selegiline having adverse effects on mortality[8] although a meta-analysis disagreed with this suggestion.[9] Data regarding the use of selegiline in the elderly is limited.

Motor complications

As the disease progresses, motor complications (fluctuations and dyskinesia) may occur (Table 3, Figure 1).

Treatment of fluctuations

After a number of years, the duration of responsiveness to L-dopa becomes shortened and this phenomenon is termed the 'wearing off' reaction. Strategies to combat this are to:

- increase absorption by taking L-dopa on an empty stomach either at least 30 minutes before meals or at least 45 minutes after meals (this may cause nausea)
- increase in L-dopa dosage

If these two approaches fail or cause unacceptable side effects:

- consider adding an adjunctive therapy (eg. dopamine agonist) to smooth out motor responsiveness.

Dopamine agonists

Bromocryptine and pergolide are both ergot derivatives that have dopamine agonist properties. However, they are both associated with retroperitoneal fibrosis. Cabergoline is also a dopamine agonist and appears to be efficacious. These drugs should be used cautiously and the dosage increased gradually over a 4–8 week period to an optimal level. If dyskinesia occurs, reduction in L-dopa dosage may be required. Motor score improvement is seen in around 20–35% of patients.[10]

Although a dopamine agonist may resolve or reduce late motor complications, its benefit has to be balanced against potential risks in the elderly. The main adverse effects in older people are:

- postural hypotension
- delirium, and
- nausea and vomiting.

If side effects are unacceptable or cannot be resolved, the drug may need to be withdrawn.

Catechol-o-methyltransferase inhibitors

Catechol-o-methyltransferase inhibitors (COMTI) metabolise L-dopa and dopamine centrally and peripherally. Inhibition of the metabolism will result in prolonged half life of circulating L-dopa. Tolcapone and entacapone are two available drugs but tolcapone has been withdrawn from many countries due to hepatotoxicity. Only entacapone is available in Australia. Side effects include:

- worsening of dyskinesia
- gastrointestinal upset such as nausea or diarrhoea, and

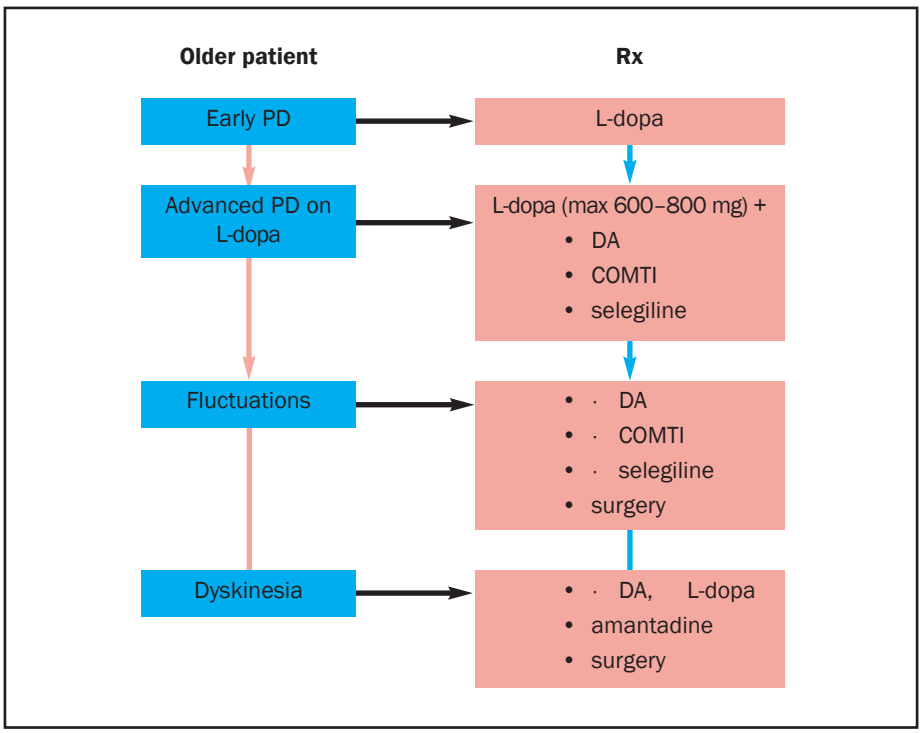

Figure 1. Summary of treatment

Table 3. Efficacy of treatments for motor complications[24]

	Efficacious	Likely efficacious	Insufficient data
Rx	Pergolide	Apomorphine	CR L-dopa
	Ropinirole	Bromocriptine	Selegiline
	Pramipexole	Cabergoline	Anticholinergics
	Entacopone		
	Tolcapone		
	Amantadine*		
		Likely efficacious	**Insufficient data**
Surgery		Unilateral pallidotomy[21]	Fetal transplants
		Bilateral DBS (GB and subthalamic nucleus)[22]	

* Effective for dyskinesia, others are efficacious for fluctuations

• confusion.

Each tablet has to be given together with each dose of L-dopa. The dosage of L-dopa may need to be reduced should dyskinesia occur. Motor score improvement is around 10%.[9,10] The reduction in 'off' time ranges from 1–3 hours per day which is similar to a dopamine agonist.[10,11]

Treatment of dyskinesia

In PD, dyskinesia is a peak dose effect of L-dopa causing chorea or choreodystonia. Dopamine agonists sometimes help by allowing a reduction of L-dopa dosage; COMT inhibitors tend to worsen dyskinesias.

Amantadine, 100–300 mgs per day, may reduce dyskinesia through the inhibition of glutamate mediated neurotransmissions via the blockade of brain n-methyl-d-asparate receptors. Anticholinergic side effects may limit its usage. Another option is to use low dose propanolol 20 mg three times per day, which has been shown to have some potential. For pure dystonia, which does not respond to L-dopa adjustment, anticholinergics may be helpful; again risk of side effects need to be balanced against benefits.

Pallidotomy or deep brain stimulation (pallidal and substantial nigra) may be considered. However, in general, patients over 70 years of age have less favourable outcomes due to higher complications in morbidity and mortality.

Tremor management

A mild resting tremor that does not impact on function will not warrant treatment. When the tremor is severe or affecting function, L-dopa is the first line treatment in the frail elderly. However, the responsiveness is not as good as for rigidity and bradykinesia. Although anticholinergics such as benztropine and benzhexol may be useful in managing tremor, the risks of side effects such as delirium (confusion), hallucinations, dry mouth, worsening prostatism, constipation and blurred vision in the elderly usually outweigh the benefits. In patients with cognitive impairment, anticholinergic drugs must be avoided.

Case study – Mrs H T

Mrs H T, aged 75 years, had well controlled PD. She was admitted to hospital with abdominal pain. While in hospital her antiparkinsonian medication was ceased and she developed marked parkinsonian symptoms. Despite recommencement of treatment and a rehabilitation program, progress was very slow. Further assessment confirmed that she was also suffering from depression. She was treated with a SSRI and her PD symptoms improved to pre-admission level, with no change in PD treatment.

Amantadine has no effect on tremor and propanolol may reduce postural tremor and also help with tremor amplitude in anxious patients. Clozapine may be beneficial but the mechanism is unclear. However, adverse effects of agranulocytosis, myocarditis and cardiomyopathy has limited its use.

Nonmotor complications

Dementia

Evidence is limited in this important aspect of treatment. Only one small randomised control trial has shown that donezepil is useful in improving cognition in demented parkinsonian patients.[12] Another randomised trial has shown that rivastigmine is useful in dementia with Lewy bodies.[13] However, there is a theoretical concern of the cholinergic system antagonising the dopaminergic system. Anticholinergics and dopamine agonists should be avoided in patients with dementia because of the risk of increasing confusion.

Psychosis

Two randomised control trials have shown that clozapine is useful for psychiatric symptoms such as visual hallucinations.[14,15] However, concerns about its adverse effects (eg. agranulocytosis) over-rides its benefit. Other atypical antipsychotics may be tried. These include quetiapine, olanzapine and risperidone. At higher dosage, risperidone can worsen parkinsonism. Likewise, there have been reports on olanzapine causing agranulocytosis albeit less frequently than its predecessor clozapine.[16]

Depression

Depression affects about 40% of PD patients.[17] An unblinded study has shown selective serotonin reuptake inhibitors (SSRIs) to be useful.[18] Lithium on the other hand may worsen parkinsonism. Co-existent depression may significantly affect PD symptoms and rehabilitation efforts (see Case study).

Autonomic dysfunction

Symptomatic orthostatic hypotension occurs in 15–20% of PD patients.[19] It is important to recognise as patients can have devastating results such as falls. Orthostatic hypotension can occur as part of autonomic dysfunction, but can also occur as a side effect of many PD treatments. When symptomatic and troublesome, fludrocortisone may be considered. If systolic hypertension co-exists, a useful drug to consider is pindolol. Other autonomic problems such as constipation, neurogenic bladder and sexual dysfunction can all occur and should be treated accordingly.

Somnolence

Excessive day time sleepiness and sleep attacks commonly occur in PD patients who are on dopamine agonists. The prevalence has been estimated to be as high as 50%.[20] It is likely to be a class effect but has been reported more with nonergot dopamine agonists than with ergot dopamine agonists and L-dopa. Therefore, the patient should be warned about safety issues such as driving when on such medications.

Treating advanced PD – multidisciplinary approach

Although there is a shortage of randomised trials to support multidisciplinary care for advanced PD patients, patients who have aspiration,

Table 4. Principles for management of PD in the elderly

- Doses should be started low and raised gradually
- Lack of L-dopa responsiveness may be due to inaccurate diagnosis
- Falls, decline in ADL and aspiration are common problems. Referral to geriatricians and a multidisciplinary approach is required
- Be aware of polypharmacy, poor adherence and doctor shopping

problems with the activities of daily living or recurrent falls, should benefit from assessment and appropriate interventions from allied health professionals. Medications alone may not suffice in this group of patients (Table 4).

Conclusion

Levo-dopa therapy is the treatment of choice in elderly patients with PD. Doses should be started low and slowly titrated against motor response. Lack of L-dopa response may mean other differentials of PD. Dementia is more common in elderly patients with PD, and the use of anticholinergics is contraindicated owing to the risk of worsening confusion. Postural hypotension may limit the use of adjunct therapy such as a dopamine agonist. Coexistent depression is common and needs to be addressed appropriately.

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