Putting the patient first:
Should general practitioners start people with probable Parkinson's disease on levodopa while awaiting diagnostic confirmation?

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Background
Parkinson's disease poses challenges for timely diagnosis and specialist care, particularly in rural areas.

Objective
This paper aims to assist general practitioners (GPs) who wish to collaborate with their patient with probable Parkinson's disease to improve access to appropriate medication when there might be a delay in obtaining a confirmatory diagnosis from a Parkinson's disease specialist. The feasibility and rationale for commencing levodopa as well as an approach to initiating and monitoring its response are discussed. The importance of educating patients and caregivers, encouraging exercise and building a multidisciplinary team to optimise care is also discussed.

Discussion
The literature supports early levodopa initiation in probable Parkinson's disease to improve a patient's quality of life. The presented approach offers GPs effective management strategies that enhance patient care and mitigate the risks of delayed treatment.

PARKINSON'S DISEASE (PD) is a neurodegenerative condition that contributes to a high disease burden and decreased quality of life (QoL). It typically presents in older adults, although 10–15% are younger than age 60 years. Approximately 219,000 Australians live with PD, and prevalence is rising.[1] The exact pathogenesis of PD remains unclear but is characterised by the accumulation of protein aggregates and gradual loss of dopaminergic neurons.[2]

General practitioners (GPs) are often the first clinician people with PD (PwP) present to and are well placed to recognise the likely diagnosis and manage the initial manifestations.[3] Non-motor symptoms such as anxiety, depression, hyposmia and rapid eye movement sleep behaviour disorder often present in primary care several years before the cardinal motor features of bradykinesia, rigidity and tremor.[4] By the time these motor symptoms manifest, PwP have typically lost at least half of their dopaminergic neurons in the basal ganglia.[5]

Pharmacological management of PD aims to treat symptoms by increasing dopamine levels, as there are currently no disease-modifying medications for PD.[6] First-line treatment usually involves levodopa, a dopamine precursor that significantly, quickly and typically improves function and QoL.[7] Although there are no national Australian PD guidelines, local standards are based on UK National Institute of Health and Clinical Excellence (NICE) guidelines, which recommend that people with suspected PD be referred to a movement disorder specialist *without* initiating treatment.[8] This practice is ideal when patients can access a neurologist or geriatrician promptly, as dopaminergic treatment might mask the Parkinsonian features and decrease diagnostic accuracy. However, in an imperfect health system, long delays waiting for specialist review are common,[9] especially in rural and regional Australia. Diagnostic delays lead to lack of treatment for several months or years, contributing to decreased QoL and increased risk of complications such as falls and fractures.[10]

The solution? A pragmatic trial of levodopa

How, then, can we resolve this tension between needing to wait for specialist diagnosis and needing to improve a patient's symptoms? Should GPs pragmatically trial levodopa with their patients *before* specialist diagnosis? We acknowledge this idea goes against dogma, but it recognises the practicalities of working within an imperfect health system and might provide a solution that is less risky than leaving PD untreated.

So, what is the evidence for such a perspective? First, levodopa is generally considered a safe drug[11] and observational data show that PwP who receive early dopaminergic medication have significantly better QoL over the first 18 months than those who remain untreated.[12] Extending these findings to symptomatic individuals awaiting diagnosis provides a rationale for starting medication when symptoms impair functioning[13] to preserve independence and QoL.[14] Second, levodopa has a short half-life of 1–3 hours[15] and can be withheld overnight before specialist review so as not to mask the clinical signs. This 'defined off' method is often used in research studies[16,17] and the 'long duration effect' of levodopa is unlikely to hinder diagnosis.[18]

There are several levodopa 'myths' that are worth addressing too; for example, the long-held belief that levodopa is neurotoxic and hastens PD progression has motivated some physicians and PwP to postpone treatment,[19] despite strong evidence this is incorrect.[20] Another common notion is that levodopa's benefits decrease over time and should be 'saved' for later stages, but this is unfounded and the apparent reduced efficacy simply reflects PD progression.[21] Furthermore, delaying levodopa treatment does not reduce motor fluctuations such as dyskinesias.[22] A large body of literature confirms that the decision to initiate levodopa should be driven by factors such as clinical need, patient preferences, functional disability and QoL impairments.[23–25]

But what if the GP misdiagnoses PD and inadvertently gives levodopa to someone for another cause of Parkinsonism? Well, the risks remain low,[26] and lack of response to levodopa might help differentiate PD from, for example, vascular Parkinsonism, drug-induced Parkinsonism and rarer causes of atypical degenerative Parkinsonism.[26,27] The lack of other specific treatments for these conditions and subset of patients that will transiently benefit from levodopa further justifies an early pragmatic trial.[28,29] Additionally, levodopa therapy often benefits patients with dementia with Lewy bodies.[30] These findings collectively challenge the rationale behind delaying levodopa therapy in individuals with clinical features suggestive of PD.

CASE

You have been caring for Fran, a woman aged 78 years, for three years after she transferred from another practice. She has multiple health issues including hypertension, atrial fibrillation, congestive cardiac failure, a transient ischaemic attack, history of falls over the last four years, a pacemaker for chronotropic incompetence and hypothyroidism managed with thyroxine. Her fatigue and tendency to fall have been attributed to cardiac issues. Fran lives alone with support from her daughter, a nurse, who lives next door.

You undertake a health assessment where she reports a six-month progressive history of right-hand shaking. Your observations and Fran's daughter's report note that Fran's affect has blunted and she has no right arm swing when walking. You find she has a resting tremor and cog-wheel rigidity in her right arm but no obvious bradykinesia. You suspect she has Parkinson's disease.

You refer her to the local neurologist, but after three months of appointment unavailability and Fran's continuing deterioration, you decide to trial levodopa. If Fran agrees to a trial of levodopa, while understanding you might be wrong about her diagnosis, the following tips will assist you in doing this as you seek to improve Fran's mobility, tremor and a degree of her fatigue and therefore her QoL.

Levodopa: Start low, go slow

Regarding trialling levodopa, a low initial dose with slow titration generally minimises side effects. A low dose would be, for example, levodopa 50 mg combined with benserazide, a dopa-decarboxylase inhibitor, 12.5 mg (brand name Madopar 62.5) once daily for a week, increasing to twice daily for a week, then to three times daily. Symptoms to warn your patient about are nausea and lightheadedness related to a drop in blood pressure. These symptoms usually disappear in a week or two, but if they are problematic, then slow the titration down (eg increasing by 50 mg every two weeks). Gradually increase to 100 mg of levodopa three times daily according to patient response. Many people will not benefit from a dose lower than this. Aim for the lowest sufficiently therapeutic dose.

While recognising other drug classes can be commenced in PD, such as dopamine agonists and monoamine oxidase (MAO) inhibitors, levodopa consistently shows the fewest side effects and gives the best improvement in motor function and QoL.[31] Avoid concurrent use of dopamine-blocking drugs (eg anti-emetics: metoclopramide, prochlorperazine, antipsychotics) or oral iron as these inhibit levodopa absorption. Check your medical prescribing software for a full list of possible drug interactions apart from these more commonly encountered ones.

Our team recommends having a care partner or friend attend appointments to provide useful feedback about the PwP's symptoms like anosmia (which does not respond to levodopa) and response to therapy, especially because many PwP might underestimate the degree to which they are affected by bradykinesia and postural changes. Feedback should focus on whether the areas of impaired activities of daily living noted in the history have improved. We recommend recording current pre-levodopa function (eg with handwriting samples or by video-recording their walking or finger tapping) to assess when the patient is 'on' and obtaining benefit from their levodopa. These videos could also support the movement disorder specialist in confirming or refuting the diagnosis. The GP and the PwP should persist in optimising use of levodopa while the PwP waits to see the PD specialist for diagnostic confirmation.

If the diagnosis of PD seems to be confirmed by the patient's response to levodopa, adequate education and support of the PwP is needed. Obtaining a diagnosis of PD can be distressing for the PwP and those who care about them, and counselling should be offered.[32] A clinical nurse consultant in PD is a useful treatment team member to support the PwP and their family with information and advice including how to access other services.[33] Apart from medication, sessions with a speech pathologist, physiotherapist/exercise physiologist and/or occupational therapist with special skills in treating PwP are recommended.[21] Encouraging exercise is especially recommended, noting a recent Cochrane review (2024) that found evidence for the beneficial effects of exercise on reducing the severity of motor symptoms and improving QoL in PwD.[34,35] Access to care

from the wider healthcare team might be facilitated by a GP management plan, and if the PwP is aged <65 years, via the National Disability Insurance Scheme too. It is acknowledged that access to the members of the PwP's care team might be as equally difficult as access to a movement disorder specialist.

In summary, noting access to diagnosis for people with suspected PD can be difficult, and delayed treatment is associated with poor mobility and complications, GPs should consider trialling levodopa to optimise people's function and QoL. The GP and their team can also start the process of building support, providing education and forming a multidisciplinary team around the PwP.

Key points

- GPs are good at spotting probable PD.
- Levodopa is generally safe with few drug interactions and few side effects.
- PwP require support, education and counselling about their diagnosis.
- Exercise is a key part of the management plan for PwP.
- A multidisciplinary team to assist your patient with PD is vital.

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