New and emerging treatments for Parkinson disease

The main aim is to maintain quality of life throughout the illness

World Parkinson's Day commemorates the birth of James Parkinson on 11 April 1755, and it will soon be the 200th anniversary of his description of the "shaking palsy".[1] In this article I highlight some of the advances in Parkinson disease (PD) therapy since the topic was most recently reviewed in the Journal.[2]

The first step: diagnosis

The diagnosis of PD is the first step in its management. Even years after PD is diagnosed, patients report that "satisfaction with the explanation of the condition at diagnosis" continues to have an impact on quality of life.[3] Diagnosis is not always straightforward. In a UK study, only 44% of patients with PD were initially referred to a neurologist, the other patients being referred to general physicians, orthopaedic surgeons, urologists, psychiatrists and rheumatologists. Pain was the symptom that most frequently impaired the recognition of PD, while frozen shoulder, spondylosis, depression and anxiety were among the common misdiagnoses.[4] The 1997 charter of the European Parkinson's Disease Association recommends that all patients be referred to a doctor with a special interest in PD.[5]

Managing non-motor symptoms

Non-motor symptoms, an intrinsic part of PD, have a major impact on quality of life. Anxiety and depression will develop in about 60% of patients with PD; this is twice the rate seen in the general population. The severity of mood disturbance or apathy is the most important determinant of quality of life in patients receiving treatment, having a greater impact than motor impairment.[3,6] It is important to determine whether mood fluctuates with the motor "on" and "off" states and might therefore be responsive to dopaminergic therapy, or is more pervasive and requires supplementary pharmacological or non-pharmacological treatment. Even after accounting for the effects of altered mood, "current feelings of optimism" still have an independent influence on quality of life.[3]

Impaired olfaction, chronic constipation, and rapid eye movement (REM) sleep behaviour disorder (yelling or thrashing about while dreaming) can predate the onset of motor symptoms by years and even decades. Studies are underway to determine whether these features might be used to enable diagnosis of PD in the premotor stage of the disorder.

Selecting the initial therapy

Monoamine oxidase B (MAO-B) inhibitors, dopamine agonists (DAs) and levodopa can be employed in the initial treatment of PD, with each approach having its advantages and disadvantages.[7] As no treatment has been unequivocally shown to either slow or hasten disease progression, the primary goal of therapy should be to restore and maintain quality of life. There is no advantage in delaying therapy if this has a negative effect on quality of life. Initial therapy may influence short- to medium-term outcomes, and should be tailored to the needs of the individual. The MAO-B inhibitor rasagiline may achieve a marginal slowing of disease progression, requires minimal titration and is well tolerated,[8] but its symptomatic effect may not be as great as that of a DA or levodopa.[9] It should therefore be considered for patients suffering only minor disability, or for those for whom rapid amelioration of disability is not required.

"General practitioners play a central role in educating patients ... about optimal therapy"

Early treatment with the DA pramipexole has been shown to reduce the risk of motor complications by 55% over 2 years, compared with levodopa monotherapy; equivalent to treating 4–5 patients with pramipexole instead of levodopa to prevent one additional complication.[10] This benefit, however, needs to be balanced against its potentially serious side effects, especially impulse control disorders which develop in around 17% of patients using DAs,[11] and excessive daytime somnolence that can lead to sleep attacks (sudden or irresistible drowsiness that can lead to falling asleep, including while driving).

Levodopa is the most potent and well-tolerated symptomatic treatment, its drawback being an increased risk of dyskinesia.[12,13] A recent study of more than 1500 patients randomly allocated to initial treatment with an MAO-B inhibitor (selegiline or rasagiline), DA or levodopa showed only very small differences in global outcome at 3–7 years. The best results were achieved with levodopa in terms of mobility and quality of life, and with the levodopa-sparing agents in terms of avoiding dyskinesias.[13] The overall results reinforced the view that any of the three options is a reasonable choice as initial therapy.

Advanced therapies for patients with disabling symptoms

Patients with disabling symptoms who do not respond to adjustments of medication dose should be referred earlier rather than later for consideration of an advanced therapy.

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Only a minority of PD patients who might benefit from an advanced therapy are currently referred for assessment. There is a limit to the relief of severe, unpredictable motor fluctuations that can be achieved by adjusting the dose of standard oral medications, driven in large part by impaired gastric emptying in PD.[14] To allow patients to make an informed decision about their preferred method of treatment, they should ideally be referred to a specialist with broad experience in advanced therapies.

Two advanced therapies, deep brain stimulation (DBS) and levodopa–carbidopa intestinal gel (LCIG, commonly referred to by its trade name, Duodopa [AbbVie]) have been shown to effectively reduce severe motor fluctuations (including dyskinesias) in randomised controlled studies, decreasing "off" time and increasing quality "on" time by an average of 4 to 5 hours per day. Three trials have found that DBS therapy improved quality of life and motor function better than adjustment of medical therapy.[15-17] DBS was approved for treating PD in Australia in 2001, but inequality of access remains a problem. Public funding for the stimulator device is limited in many states, so that the therapy is primarily financed by private health insurance or self-funding. More recently, LCIG therapy for severe motor fluctuations has been shown to confer benefits similar to those of subthalamic nucleus DBS.[18,19] LCIG is delivered as a continuous infusion into the jejunum, bypassing the problem of impaired gastric emptying. Patients need to have a permanent percutaneous endoscopic gastrostomy tube inserted, through which a finer jejunal tube is placed and connected to an external pump that houses the LCIG cassette. LCIG was approved by the Therapeutic Goods Administration in 2008 and has been funded by the Pharmaceutical Benefits Scheme since 2011. There is evidence that LCIG and DBS also improve non-motor symptoms.[20,21] For patients who need an advanced therapy but prefer a less invasive option than DBS or LCIG, intermittent or continuous subcutaneous delivery of apomorphine (a DA without opioid properties) can be an effective alternative,[22,23] but its benefits are less well documented.

Conclusion

There have been significant advances in our understanding of the motor and non-motor symptoms of PD in the past decade. New therapeutic approaches and options are available, and general practitioners play a central role in educating patients about, and facilitating access to, optimal therapy, so that patients can make informed and positive choices.

Competing interests: I have been on advisory boards for Abbott, AbbVie, Allergan, Boehringer-Ingelheim, Hospira, Ipsen, Lundbeck, Novartis, Global Kinetics Corporation, Solvay and UCB, and serve on the editorial boards of *Movement Disorders, NPJ Parkinson's Disease, Movement Disorders Clinical Practice, Journal of Clinical Movement Disorders, F1000Research and Basal Ganglia.*

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