Dopamine replacement therapy with levodopa has been the mainstay of symptomatic treatment of Parkinson disease (PD) for almost 40 years. While this drug remains the “gold standard,” several additional dopaminergic drugs have been introduced to provide alternatives for patients with PD. Practical challenges in the management of PD include determining the point at which drug therapy should begin and with what, the sequence and combination of drugs required as the disease progresses, and the place for parenteral therapy and surgery in advanced disease. Although levodopa offers effective symptom relief at all stages, its risk of inducing motor complications has led many to advocate alternative drugs for initiation in suitable patients. Dopamine agonists and monoamine oxidase (MAO) B inhibitors offer effective relief of the motor features of PD in early and more advanced disease and are associated with a low risk for motor complications. However, they are not as potent as levodopa. Parenteral dopamine agonist or levodopa delivery offers a useful intermediate or alternative to surgery.

The introduction of levodopa for the treatment of PD has led to a significant improvement in both the quality of life and life expectancy of patients, although they continue to experience significant disability that increases as the disease progresses. Current treatments remain focused on the dopamine system. Two evidence-based reviews of PD treatment have recently been published and provide an excellent critical analysis of medical and surgical therapies. Given the range of potential treatments to offer a patient with PD, it is helpful to set these reviews in a pragmatic clinical context and consider how our practice should best reflect these advances to suit the patient in both the short- and long-term.

WHEN TO START SYMPTOMATIC TREATMENT

An important principle for the treatment of PD is that the introduction and use of medication must be tailored to the patient’s individual needs. Many patients may still be working when first diagnosed. Their need for symptomatic therapy will depend on the effect that the disease has on their performance at work and home; their life expectancy, quality of life, and comorbidities must also be considered. The fact that the average life expectancy from diagnosis to death in patients with PD is 17 years serves to emphasize the need for a long-term treatment strategy for most patients, and this should be developed and discussed with the patient at an early stage. The type of drug used initially and subsequently may also be influenced by concern regarding adverse effects and cost.

The duration from onset of neuronal cell dysfunction and death to the emergence of clinical symptoms in PD is not known. In the monogenic forms of familial PD, this may be over several decades. Recent studies using serial imaging in sporadic PD have suggested that the presymptomatic latent period is approximately 6 years. It is not known with certainty how severe nigral dopaminergic loss must be before symptoms emerge, although 60% to 70% degeneration is thought to be an
Fig. 1. Decision pathway for the initiation of drug treatment for Parkinson disease.

approximate threshold. Clinical progression following diagnosis of PD is relatively rapid; in clinical trials, the Unified Parkinson's Disease Rating Scale score deteriorates by 8 to 10 points in the first year, and this is associated with a significant decline in quality of life.2,6

Traditionally, treatment for PD has been withheld until symptoms have sufficient impact on function in the workplace or in social or domestic life. This view arose and developed during the levodopa era and became established teaching but perhaps deserves re-evaluation given the range of new treatments now available. We have proposed that early vs later symptomatic treatment improves motor control and quality of life in the short term and that this benefit is sustained long-term perhaps through a disease-modifying effect on compensatory mechanisms.7 Others consider that it remains better to delay initiation.8

INITIAL THERAPY

Dopaminergic drugs—e.g., levodopa, dopamine agonists, and the MAO-B inhibitors—are the main therapeutic options for the motor symptoms of PD, and all have appropriate supporting clinical data.2,3,9 There are some important considerations in the use of these and in designing the best long-term strategy for a patient with PD (Figure 1).

Producing Effective Symptom Control

Dopaminergic drugs are, to varying degrees, all effective in improving bradykinesia and rigidity in PD while tremor may be more refractory. Levodopa is still the most potent dopaminergic drug, but dopamine agonists can also provide effective control. Two studies of dopamine agonist monotherapy showed that levodopa improved the Unified Parkinson's Disease Rating Scale score by 3 to 5 points more than the corresponding agonist, but motor control was considered satisfactory in both groups by both patient and physician, suggesting that the rating scale did not necessarily capture all the clinical benefit of the agonists.10,11 Monoamine oxidase B inhibitors are effective as monotherapy in early disease and as adjuvant therapy in more advanced disease but are not as potent as levodopa or dopamine agonists.12-15

Delaying Motor Complications

Motor complications include both wearing off and dyskinesias. These develop at a rate of approximately 10% per annum in later-onset PD but at a much faster rate in young-onset PD such that 70% are affected after 3 years.16 Although early dyskinesias may be mild and do not interfere with general activities, they portend the development of more severe complications that can have a significant effect on quality of life.17,18 The cause of motor complications is not entirely understood but appears to be related to, among other factors, the effects of short-duration pulsatile stimulation of a denervated striatum. As a consequence, there has been a move toward developing treatment strategies that involve more continuous dopaminergic stimulation, thereby returning dopamine receptor stimulation to a more constant (physiological) level.19 These include the use of drugs with long half-lives such as the dopamine agonists ropinirole and pramipexole, delaying the introduction of short half-life drugs such as levodopa or alternatively increasing its half-life and developing novel delivery systems.

Individual Patient Characteristics

Chronological age has sometimes been used as a guide by which to recommend the initiation of particular types of therapy in PD. However, other factors may be more important, including life expectancy, comorbidities, quality of life, etc.

An arbitrary age of 70 years has been used as a guide to develop strategies for treatment initiation, although there must always be an emphasis on each individual patient's characteristics. As a general rule, patients younger than 70 years have several years of life expectancy and require good symptom relief with limited risk for drug-related adverse effects in the short and longer term. For these patients with no cognitive dysfunction, the choice of initial drug may lie between a MAO-B inhibitor and a dopamine agonist.

The MAO-B inhibitor selegiline has been shown to provide long-lasting benefit when given early in the course of PD, with improvements in motor and activity of daily living scores persisting 6 to 7 years or more.12,20 Rasagiline is a MAO-B inhibitor recently licensed for the treatment of both early and more advanced PD.13-15 Both selegiline and rasagiline are used as once-a-day oral therapies; selegiline is also available as an oral wafer. Monoamine oxidase B inhibitors are generally well tolerated. Unlike selegiline, rasagiline has no amphetamine metabolites, and this may account at least in part for a low risk for cognitive adverse effects.14,15

Dopamine agonists are commonly given as oral therapy 3 times a day. They provide greater symptomatic improvement than do the MAO-B inhibitors and have a low
risk for the development of motor complications. They are generally well tolerated, but their use may be associated with somnolence, peripheral edema, and cognitive disturbances (eg, hallucinations) as well as behavioral changes, including punding and gambling. Patients with cognitive dysfunction (eg, dementia) are probably better started receiving levodopa and should avoid dopamine agonists because they are more likely to exacerbate these problems. A recent concern has been the association of cardiac valve fibrosis with ergot-related dopamine agonists, eg, pergolide, cabergoline. Patients receiving ergot agonists should be carefully monitored and assessed with echocardiography and switched to alternative therapy if necessary. Data available so far indicate that the nonergot agonists (eg, pramipexole, ropinirole) are not associated with this complication, but continued vigilance is required.

Patients aged 70 to 75 years could also be considered for initiation of a MAO-B inhibitor or dopamine agonist if they are cognitively intact and lack any significant comorbidity. Again, the choice may be driven by the degree of symptom improvement needed. Thus, many of these patients, and also those older than 75 years, are probably best started receiving levodopa. This drug is effective and relatively well tolerated in many of these patients, and also those older than 75 years, are probably best started receiving levodopa. For those already receiving levodopa at some point. For those who have begun receiving an agonist (pramipexole) and supplemented with levodopa to those receiving levodopa alone. It is notable that this study showed that motor function with treatment at 4 years was still better than baseline while quality-of-life analysis showed deterioration from baseline. In patients with early disease, selegiline was able to delay the need for additional therapy for 9 to 12 months. Figures presented in abstract form indicate that 46% of patients with early PD at 2 years and 32% at 3 years still control their symptoms with rasagiline alone. Thus, patients with PD who start receiving an agonist or MAO-B inhibitor will require supplementary therapy with levodopa at some point. For those who have begun receiving a MAO-B inhibitor, the introduction of a dopamine agonist is the logical next step. Those already receiving a maximally effective or tolerated dose of agonist and who require additional treatment may benefit from a MAO-B inhibitor. For most of these patients, levodopa is the subsequent choice (Figure 2).

The emergence of motor fluctuations complicates drug use and scheduling. Wearing-off is often underdiagnosed, and its treatment can significantly improve the motor control of the patient with PD. For those already receiving levodopa who require better symptom control, the total daily dose may be raised by increasing each individual dose and/or dosage frequency. However, this may lead to more pulsatile receptor stimulation and a greater risk of dyskinesias. The addition of a catechol-O-methyltransferase (COMT) inhibitor will decrease the

As PD progresses, the provision of effective symptom control becomes more challenging and additional drugs may need to be added. Long-term follow-up indicates that of those who begin receiving a dopamine agonist, approximately half at 3 years and two-thirds at 5 years will require levodopa supplementation. Quality-of-life analysis at 4 years was similar for those who began receiving an agonist (pramipexole) and supplemented with levodopa to those receiving levodopa alone. It is notable that this study showed that motor function with treatment at 4 years was still better than baseline while quality-of-life analysis showed deterioration from baseline. In patients with early disease, selegiline was able to delay the need for additional therapy for 9 to 12 months. Figures presented in abstract form indicate that 46% of patients with early PD at 2 years and 32% at 3 years still control their symptoms with rasagiline alone. Thus, patients with PD who start receiving an agonist or MAO-B inhibitor will require supplementary therapy with levodopa at some point. For those who have begun receiving a MAO-B inhibitor, the introduction of a dopamine agonist is the logical next step. Those already receiving a maximally effective or tolerated dose of agonist and who require additional treatment may benefit from a MAO-B inhibitor. For most of these patients, levodopa is the subsequent choice (Figure 2).

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gastrointestinal breakdown of levodopa, increase its half-life, reduce "off" time, and increase "on" time and therefore is an effective treatment for wearing off.2,3

Two COMT inhibitors, entacapone and tolcapone, are currently available. The use of the latter is limited by hepatotoxicity, although this can be avoided by plasma monitoring of liver function and discontinuation of the drug if necessary. Entacapone (200 mg) should be administered with each dose of levodopa up to a maximum of 8 times daily in the United States and 10 in Europe. It reduces off time more than placebo by approximately 60 to 90 minutes per day.27 Adverse effects are related mainly to the enhanced action of levodopa and can be managed by levodopa dose reduction. Patients may experience discoloration of their urine, and a small proportion develop diarrhea. Studies are underway to determine if levodopa initiation with COMT inhibition has advantages in motor control and delay of motor complications.

The ELLDOPA (Earlier versus Later Levodopa Therapy in Parkinson Disease) study confirmed that the total levodopa dose is important in determining the risk for motor complications, so consideration should be given to limiting the total daily dose of levodopa and to seeking alternative dopaminergic strategies if possible. For suitable patients who have already begun receiving levodopa, the addition of a dopamine agonist should improve control. The introduction of a MAO-B inhibitor has also been demonstrated to improve wearing off in those already taking levodopa.14,15

**TREATMENT OF ADVANCED DISEASE**

Progression of neuronal degeneration and the emergence of motor complications inevitably lead to complex treatment regimens (Figure 3). Advanced PD is often characterized by poor control of motor features with rapid oscillations between being on, being on with severe dyskinesias, and being off or frozen. Amantadine has demonstrated efficacy in improving peak-dose dyskinesias. The effective dose is 200 to 400 mg per day in 2 divided doses; the severity of dyskinesias may be reduced by 24% to 56% and the effect sustained at 1 year.28,29 Adverse effects can include confusion and livedo reticularis. A proportion of patients with complex disease should be considered for parenteral dopaminergic therapy or surgery.

Intermittent or continuous subcutaneous apomorphine can significantly improve motor control and reduce or sometimes abolish fluctuations.30 Jejunal levodopa infusion can also significantly reduce fluctuations and can be administered via a percutaneous enteral gastrostomy.31 Patients for parenteral therapy need to be carefully selected, but criteria are not as stringent as for surgery. Subcutaneous apomorphine infusions are a cheaper and less invasive option than jejunal infusions, and both are suitable alternatives to surgery.

Surgery for PD has evolved rapidly and now includes destructive lesions and deep brain stimulation. Surgery offers an important therapeutic option for carefully selected patients. Candidates should have a secure diagnosis of PD and have responded well to dopaminergic therapy. Surgery will not benefit those with atypical Parkinsonism. They should be cognitively intact and their disability predominantly related to motor complications. Manipulation of medical therapies should have been attempted to improve control.

Pallidotomy can provide long-term improvement in contralateral dyskinesia and some improvement in bradykinesia and rigidity in patients.32 Deep brain stimulation (DBS) avoids the need to make a destructive brain lesion and can be used for bilateral procedures with relative safety. Also the stimulator can be adjusted to maximize benefits and reduce adverse effects. Deep brain stimulation of the subthalamic nucleus or globus pallidus interna improves all of the cardinal features of PD as well as dyskinesias.33 Long-term studies demonstrate that benefits of DBS persist for more than 5 years of follow-up, although disability still progresses from year to year, reflecting degeneration in nondopaminergic sites.34 Adverse events with DBS can be related to the intracranial procedure, the electrode system, and stimulation. Problems occur in about 2% to 3% of cases and include lead breaks, lead migration, infection, and skin erosion, occasionally requiring replacement of the electrode. One study has shown that subthalamic nucleus DBS can improve motor control and quality of life more than medical therapy.35

**NONMOTOR COMPLICATIONS**

The development of nonmotor symptoms is the result predominantly of neuronal degeneration beyond the dopamine system and is associated with autonomic, gastrointestinal, and genitourinary problems in addition to sleep disturbance, cognitive deficits, and depression.36 They include apathy, anxiety disorders, hallucinations, fatigue, gait and balance disturbances, hypophonia, sleep disorders, sexual dysfunction, bowel problems, drenching sweats, salorrhea, and pain. They cause significant morbidity and impaired quality of life.1 Although drug treatment for their management is limited, there are support-
ive measures and some pharmacological interventions that can be helpful.

Depression, and to some extent apathy, may respond to tricyclic antidepressants or to selective serotonin reuptake inhibitors. Pramipexole has shown some benefit in both depressed patients without PD and depressed patients with PD, although further studies are required to confirm this effect.7 Anxiety and panic attacks may sometimes relate to wearing off and so respond to dopaminergic therapy; additional anxiolytic therapy may be needed. Hallucinations can arise as a consequence of the neuro-pathology of PD and the dopaminergic drugs used in treatment. If they are troublesome, modification of existing therapy is the easiest strategy to reduce or stop hallucinations. Low-dose clozapine can significantly improve patients with PD with psychosis.38 Patients with PD who developed dementia at least 2 years after the appearance of motor features showed a modest but significant benefit for cognitive evaluations with rivastigmine.39 Abnormalities of sleep and daytime somnolence are common in PD, and management includes improving sleep hygiene, treating nocturnal motor problems, managing nocturia, and modifying medication. Modafinil may help some patients with refractory daytime drowsiness,40 although there is conflicting evidence on efficacy. Nocturia can be treated by the use of oxybutynin, tolterodine, or amitriptyline. Anticholinergic drugs may sometimes help sialorrhea but often cause adverse effects. Botulinum toxin can be used for refractory cases.41

**FUTURE PROSPECTS**

Several new dopaminergic and nondopaminergic medications are in development or will shortly become available for patients with PD.52 Two imminent arrivals are the rotigotine dopamine agonist transdermal delivery system (skin patch), already available in some countries, and the once-a-day ropinirole preparation. Both of these dopamine agonist preparations offer the prospect of better control of PD motor symptoms and improved patient compliance. Once-a-day pramipexole is now in phase III study. No drug has yet confirmed any neuroprotective action, although preliminary laboratory and clinical studies have shown promise in some cases.52

**CONCLUSIONS**

Several novel therapies have become available for patients with PD and offer significant benefits in symptom control and long-term adverse effect profile.2,3 The sequence in which these drugs are best used is an important consideration and is dependent on the characteristics of the individual patient. Each phase of PD provides challenges to manage symptoms with the best risk-benefit ratio in both the short- and the long-term.

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