Treatment of Parkinson's Disease

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ABSTRACT: Parkinson's disease is a progressive neurodegenerative disorder that demands a holistic approach to treatment. Both pharmacologic and nonpharmacologic interventions play an important role in the comprehensive management of this disorder. While levodopa remains the single most effective medication for symptomatic treatment, dopamine agonists are playing an increasingly important role. Motor complications of dopaminergic therapy are a significant issue, particularly in patients with more advanced disease who have been on levodopa for several years. All therapeutic interventions must be tailored to the individual and modified as the disease progresses, with the goal of minimizing significant functional disability as much as possible.

RÉSUMÉ: Le traitement de la maladie de Parkinson. La maladie de Parkinson est une maladie neurodégénératrice progressive dont le traitement nécessite une approche holistique. Les interventions tant pharmacologiques que non pharmacologiques jouent un rôle important dans la prise en charge de cette maladie. Bien que la lévodopa demeure la pierre angulaire du traitement symptomatique, les agonistes de la dopamine jouent un rôle de plus en plus important. Les complications motrices de la thérapie dopaminergique constituent un problème important, particulièrement chez les patients en phase avancée de la maladie qui prennent de la lévodopa depuis plusieurs années. Les interventions thérapeutiques doivent être adaptées à chaque patient et modifiées à mesure que la maladie progresse, dans le but de minimiser autant que possible l'invalidité fonctionnelle.

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The major underlying neurochemical abnormality of Parkinson's disease (PD) is a reduction in striatal dopamine content resulting from impaired function in nigrostriatal neurons. Currently effective treatment strategies are aimed at improving the motor impairment which results from reduced dopamine levels, with the primary goal being to improve motor function sufficiently to minimize disability. In patients with early PD, it is important to employ strategies that provide symptomatic benefit, while delaying as much as possible the development of motor fluctuations and dyskinesias. In patients with more advanced disease, it may be necessary to alter treatment in order to minimize motor or behavioural complications that may have already developed. In this paper, our objective is to review current pharmacological and nonpharmacological treatments of PD. Neurosurgical treatment is also of increasing importance in managing these patients but is reviewed elsewhere in this supplement.

PHARMACOLOGIC TREATMENT

A. Symptomatic Therapy

1. Levodopa

Levodopa is an amino acid that is absorbed from the small bowel and subsequently transported by the neutral amino acid transport system across the blood brain barrier into the brain where it is decarboxylated to form dopamine. Other neutral amino acids in the gut and plasma compete for transport. Levodopa is routinely administered in combination with a peripheral decarboxylase inhibitor to prevent its systemic conversion to dopamine, and the nausea and vomiting that can occur from activation of dopamine receptors in the area postrema. This part of the medulla is not protected by a blood brain barrier. In Canada, levodopa is available in combination with the decarboxylase inhibitors carbidopa (Sinemet) or benserazide (Prolopa).

Levodopa is the single most effective drug for the symptomatic treatment of PD. Its use is associated with decreased morbidity and mortality,[1] and virtually all patients with PD experience a clinically significant benefit.[2] Although there has been theoretical concern that levodopa treatment might promote neuronal degeneration in PD through free radical generation, a recent consensus conference concluded that there is no convincing evidence to indicate that levodopa causes or accelerates nigral neuronal cell death in PD patients.[3]

Levodopa is generally started at a low dose that is gradually increased in order to minimize acute side effects such as nausea, vomiting, and postural hypotension. The lowest dose that provides a satisfactory clinical response should be administered.

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In early PD, 300-400 mg per day is usually sufficient, given in three to four divided doses. Patients who fail to respond to high doses of levodopa (1,000 mg/day) are more likely to have another cause of parkinsonism rather than PD, and are unlikely to respond to higher doses or to other dopaminergic drugs. To fully inhibit peripheral decarboxylase (and minimize side effects), a total intake of about 75-100 mg/day of carbidopa is required. If nausea persists, the peripheral dopamine receptor antagonist domperidone, 10-20 mg, given 30 min before each levodopa dose, can be dramatically effective.

2. Levodopa-induced motor complications

Although usually well-tolerated initially, the chronic administration of levodopa is often associated with significant motor complications, the control of which often dominates the management of patients with more advanced PD. The prevalence of motor complications increases with the duration of exposure to levodopa, occurring in approximately 50% of PD patients who have received levodopa for more than five years.[4] These complications are more common in patients with young-onset PD.[5] These complications are mentioned briefly here, and discussed in more detail elsewhere in this supplement.

Motor fluctuations consist of alternating periods of relatively good mobility and response to medication ("on" periods), and periods of significantly impaired motor function ("off" periods) in which there is a suboptimal response to medication. As PD progresses, the response to a single intake of levodopa becomes progressively shorter so that parkinsonian symptoms reappear before the next dose of medication (end-of-dose deterioration, or "wearing off"). With further disease progression, some patients may experience rapid and unpredictable fluctuations between "on" and "off" periods (the "on-off" phenomenon), seemingly unrelated to the timing of antiparkinsonian medication.

Wearing off is likely related to a reduced capacity for storage of dopamine that worsens with disease progression. With the loss of this buffering capacity, brain dopamine levels tend to become more closely related to plasma levodopa levels such that the clinical response becomes linked to the plasma half life of the drug. Unpredictable absorption and transport of levodopa across the blood brain barrier, and variable delays in gastric emptying may also contribute to fluctuations in response, and to the occasional "dose failure" seen in more advanced disease.[6]

The frequent occurrence of wearing-off with immediate-release levodopa led to the introduction of controlled-release levodopa (Sinemet CR).[7,8] Controlled-release levodopa can add 60-90 minutes to the response duration after a single administration,[9] thereby decreasing the disability associated with wearing-off. It should be noted, however, that a dose increase of 20-30% over the immediate-release dose may be required to compensate for the reduced bioavailability of the controlled-release formulation.

Levodopa-induced dyskinesias are abnormal involuntary movements occurring in response to levodopa administration. These movements are typically choreiform, although dystonic features may also be present. Most commonly, dyskinesias appear in a peak-dose pattern, evident during "on" periods, and are a function of too much levodopa. These movements can also occur, however, during "off" periods. "Off" dyskinesias are typically dystonic in nature and are a function of too little levodopa. Dyskinesias can be diphasic, occurring as the patient is beginning to turn "on" and again as they begin to turn "off", but being absent during the peak levodopa effect.[10] With disease progression, dyskinesias may persist throughout the response to a single dose of levodopa, resulting in considerable disability. Once dyskinesias have developed, they are managed with difficulty, although amantadine (Symmetrel) has been shown to have an antidyskinetic effect in some patients.[11]

Because pulsatile stimulation of striatal dopamine receptors appears to be central to the development of levodopa-induced motor complications, the early use of controlled-release levodopa has been postulated to reduce the long-term development of complications. However, a prospective, randomized, double-blind study comparing controlled-release and immediate-release formulations showed no difference in the incidence of dyskinesias and motor fluctuations over five years.[12]

3. Catechol-o-methyl transferase (COMT) inhibitors

Levodopa is peripherally metabolized not only by decarboxylase, but also by COMT. Catechol-o-methyl transferase is a ubiquitous enzyme, sufficiently active so that when levodopa is administered with a peripheral decarboxylase inhibitor, only about 10% of a given dose reaches the brain intact.[13] Entacapone (Comtan) inhibits the peripheral metabolism of levodopa by COMT, thereby increasing its availability to the brain, and increasing the plasma levodopa elimination half-life by about 50%.[14] Double-blind, placebo-controlled trials have demonstrated increased "on" time, decreased "off" time, and improved motor scores in PD patients with motor fluctuations.[15] Unlike its predecessor tolcapone, entacapone is well-tolerated with no evidence of hepatic toxicity. It does have the potential to increase dopaminergic side effects due to increased levodopa availability to the brain, and can be associated with diarrhea and urine discoloration.

4. Dopamine agonists

The dopamine agonists are drugs that directly stimulate dopamine receptors. In Canada, bromocriptine (Parlodel) and pergolide (Permax) have been available for the treatment of PD for many years. More recently, ropinirole (Requip) and pramipexole (Mirapex) have become available. The two newer drugs differ from the older agonists in that they are not ergot derivatives and are relatively selective in stimulating dopamine D2 and D3 receptors. However, the role played by the different receptors in normal motor function is unclear, although it is well-established that drugs that activate D2 receptors have antiparkinsonian effects.

Historically, the agonists have been used primarily as adjuncts to levodopa in patients who have begun to experience motor complications. Bromocriptine, the first agonist to be approved, is an ergot derivative, a D2 agonist, a weak D1 antagonist, and has well-established utility as an adjunct to levodopa, improving parkinsonian disability while allowing a reduction in levodopa dosage.[16,17] Pergolide is also an ergot derived D2 agonist but, unlike bromocriptine, is a D1 agonist. It has been shown to improve motor and activites of daily living (ADL) scores, decrease "off" time, and provide a levodopa-sparing effect in levodopa-treated patients.[18] Placebo-controlled studies have also demonstrated antiparkinsonian and levodopa-

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sparing effects with ropinirole and pramipexole in levodopa-treated patients.[19-22] There are little clinical data to support the use of any one agonist over another. A direct comparison of pergolide and bromocriptine using a crossover design did not demonstrate a significant difference between groups.[23] However, pergolide has been shown to provide antiparkinsonian benefits to patients with advanced PD who no longer respond to bromocriptine.[24] In a comparison of pramipexole and bromocriptine, Guttman et al[20] reported no statistically significant differences between the two agonists.

Evidence is now accumulating that agonists may be effective in early PD as an alternative to levodopa, and that initiation of therapy with an agonist may decrease the development of motor complications. A double-blind comparison of ropinirole with levodopa reported an absolute risk reduction for dyskinesias after five years of treatment of 26% for the ropinirole treated group.[25] More patients had hallucinations (17% vs 6%), leg edema (14% vs 6%), and somnolence (27% vs 19%) in the ropinirole treated group, but dropout rates due to adverse events were no different in the two treatment groups. Similar findings were reported in a double-blind comparison of pramipexole vs. levodopa monotherapy.[26] Motor complications were significantly less common in the pramipexole group (28% vs 51%) at the end of two years. Somnolence, hallucinations, and both generalized and peripheral edema were greater in the pramipexole group. In both of these studies, levodopa provided a significantly greater improvement in motor function than did the agonist, even though study design allowed for the addition of open-label levodopa if there was insufficient symptomatic benefit from the agonist alone. A practice parameter recently published by the American Academy of Neurology has concluded the following: 1) levodopa, ropinirole, and pramipexole are effective in ameliorating motor and ADL disability in patients with PD who require dopaminergic therapy; 2) levodopa is more effective than ropinirole and pramipexole in treating the motor and ADL features of PD; 3) ropinirole and pramipexole treatment results in fewer motor complications than levodopa after 2.5 years of follow-up; and 4) ropinirole and pramipexole treatment is associated with more frequent adverse events including hallucinations, somnolence, and edema.[27]

5. Managing drug-induced adverse events

The major side effects associated with antiparkinsonian medications are produced by activation of dopamine receptors. Levodopa and all dopamine agonists therefore have the same general range of potential side effects. The commonest side effect is nausea and vomiting, readily counteracted with domperidone (Motilium), 10-20 mg, three to four times daily. Postural hypotension is sometimes problematic, and can be managed with pressure stockings, increased salt intake, fludrocortisone (Florinef), 0.1-0.2 mg daily, or the α_1-adrenergic agonist midodrine (Amatine), 2.5-10 mg, three times daily. Bromocriptine and pergolide also have potential adverse effects related to their ergot derivation, including erythromelalgia and pulmonary or retroperitoneal fibrosis, although these are relatively uncommon.

Activation of the D2 receptor family can be associated with the development of hallucinations. These are more common with dopamine agonists than with levodopa alone. They are not usually an issue in early PD, although the early monotherapy studies with ropinirole and pramipexole have reported hallucinations, usually not sufficiently severe for patients to be withdrawn from the study.[25,26] If hallucinations become problematic, the first step is to rule out some other coincident medical problem, such as dehydration, electrolyte imbalance, or a febrile illness. A possible contribution from other medications should be considered and anticholinergic drugs such as antidepressants, bladder antispasmodics and muscle relaxants should be discontinued. Antiparkinsonian drugs such as anticholinergics, amantadine, or selegiline should also be discontinued. If these steps are ineffective, dopaminergic drug dosage should be decreased, starting with dopamine agonists. If hallucinations persist, or if the patient is unable to tolerate a reduced dosage because of increased parkinsonism, an atypical neuroleptic can be administered. Clozapine (Clozaril) is the neuroleptic least likely to produce extrapyramidal side effects, although it does require weekly hematological monitoring because of its potential for inducing agranulocytosis. It has been shown to be effective in reducing drug-induced psychosis in PD when administered at a low dose (6.25–50 mg/day).[28] Many neurologists now prefer quetiapine (Seroquel; 12.5-50 mg/day)[29] because of its lack of extrapyramidal side effects and because it does not require the frequent hematological monitoring of clozapine. Quetiapine, however, has not been evaluated as extensively in PD as has clozapine and does not yet enjoy the same degree of evidence-based support of efficacy. Olanzapine (Zyprexa) is not as effective as clozapine and has been shown to induce worsening of parkinsonism.[30] Other neuroleptics, including risperidone, should be avoided because they are associated with significant extrapyramidal side effects.

Excessive daytime somnolence and “sleep attacks” have been

Table: Treatment options in advanced Parkinson’s disease

Inadequate peak dose response	- increase levodopa intake
	- add dopamine agonist
Wearing off	- change to controlled release levodopa
	- increase levodopa dose frequency
	- add COMTinhibitor (entacapone)
	- add selegiline
Unpredictable on-off	- add dopamine agonist
	- protein redistribution diet
	- consider stereotactic surgery
Peak dose dyskinesias	- discontinue selegiline
	- reduce individual doses of levodopa, administered with greater frequency
	- add dopamine agonist
	- add amantadine
	- consider stereotactic surgery
Diphasic dyskinesias	- change from sustained release to regular levodopa
	- add dopamine agonist
Early morning dystonia	- add controlled release levodopa at bedtime
	- add dopamine agonist

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reported as a potential side effect of dopamine agonists.[31] A recent survey by the Canadian Movement Disorders Group concluded that although sudden-onset sleep without warning is infrequent, excessive daytime sleepiness may be present in up to 51% of independent PD patients without dementia.[32] This survey did not detect a correlation between sleepiness and any specific type of treatment and it is uncertain whether similar symptoms may be present in PD patients who are not receiving medication. It is essential that patients be warned about this excessive sleepiness and the potential risks associated with driving.

Pharmacological management of the patient with advanced Parkinson's disease represents a particularly challenging problem, primarily because of the complications of levodopa treatment noted above. Treatment options are outlined in the Table.

B. Neuroprotective therapy

Ideally, if a suitable drug was available, treatment of PD should slow disease progression. A neuroprotective benefit of selegiline through decreased free radical production was proposed[33] and has been put to clinical trial in the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study. An interim analysis of this trial demonstrated that selegiline reduced the risk of developing disability requiring levodopa therapy by 50%.[34] Palhagen et al[35] reported similar findings. However, in both of these studies, functional disability in the selegiline treated group declined during the two-month washout period, implying that a symptomatic benefit at least partially explained the reduced risk of requiring levodopa. A practice parameter from the American Academy of Neurology has concluded that there is no convincing clinical evidence for a neuroprotective benefit with selegiline.[27]

Dopamine agonists have a well-established symptomatic benefit in PD. An additional neuroprotective effect has also been suggested. Recent studies utilizing functional neuroimaging as a surrogate marker of disease progression have suggested that both pramipexole[36] and ropinirole[37] may be associated with a slower rate of neuronal loss when compared with levodopa treated patients. The relevance of these observations is uncertain, however, given the apparent lack of a significant difference between agonist and placebo in clinical parameters of disease progression in these studies.

NONPHARMACOLOGIC TREATMENT

Although pharmacologic interventions remain the mainstay of treatment, not all the issues facing the person with PD are addressed by medications. Rehabilitation services and psychosocial support can offer coping strategies at all stages of PD and may have an important function in reducing secondary complications arising from the progressive nature of the disease. A multidisciplinary team approach is essential with members of the team varying according to the needs of the individual, and his or her family, changing as the disease progresses and different issues emerge. The overall goal is to allow the individual to achieve the highest possible level of independent function. This level will inevitably change as physical and/or cognitive abilities decline and the effectiveness of medication changes. Each team member helps educate patient and family, each emphasising issues most pertinent to the stage of disability and the speciality of the discipline. Each individual will require a slightly different approach and it is essential that "patient important" problems are identified, allowing patients a sense of control with respect to treatment. At all stages of the disease, it is crucial to emphasize that the goal of treatment, pharmacologic and nonpharmacologic, is not to achieve a "normal" state but rather to achieve and maintain the highest possible level of independent function. Sources of reliable information should be provided, with a cautionary note made regarding uncensored information obtained from the internet.

A. Nursing

An integral member of the multidisciplinary team is a nurse with specialized knowledge of movement disorders. Regular contact allows the nurse to identify needs and act as a liaison between patient, physician, and allied healthcare professionals, helping to reduce the "authority gap" that may exist.[38] The nurse is important in ongoing education regarding the disease process and treatment, and deals with psychosocial concerns and difficulties managing at home. He or she identifies medical concerns that are directly related to PD versus those that are better handled by a family physician. Many patients and families turn to the nurse for emotional and psychological support. This relationship encourages candid discussions about personal, work and family issues. The nurse frequently fields questions regarding the ability to continue working, concerns of caregivers, speech and swallowing difficulties, mobility problems, and social issues. Concerns about sexuality[39,40] may be broached by the nurse, who may then refer to appropriate resources. The nurse is often the most frequent contact for the patient and the family and is invaluable in co-ordinating the care plan.

B. Rehabilitation

It makes intuitive sense that rehabilitation services are helpful in the treatment of PD and, indeed, there is evidence that patients may benefit from physical and occupational therapy (OT) in conjunction with medications.[41,42] However, studies of physical, occupational and speech therapy in PD all suffer from the same limitations, namely small numbers, no consensus as to "best practice" and difficulty in designing large, randomized placebo-controlled trials that would establish, from an evidence-based perspective, the efficacy of interventions.[42-46] Nevertheless, the individual patient often does benefit subjectively from these services.

1. Physical therapy

The role of physical therapy (PT) is to teach strategies for coping with impairment and disability, compensating and adapting as necessary.[47] The goal is to address the symptoms that are amenable to change to minimize secondary complications, and to teach preventative strategies where indicated.[48,49] Physical therapy intervention must be tailored to the individual needs of patients at different phases of their disease and, as with other therapies, must include the goals and priorities of the patient in the management plan. Physical therapy stresses activities that enhance the performance of functional motor tasks, including walking, turning, going from sit to stand, bed mobility, fall prevention, posture, reaching, grasping and manipulating objects, as well as general conditioning, strength and

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flexibility.[50,51] Individuals with PD move with greater ease in the presence of external sensory cues.[52-54] This fact, coupled with the principles of task and context specific learning,[55] helps to guide PT intervention. Detailed descriptions of these interventions are beyond the scope of this review and are described elsewhere.[43,44,56] Not all PTneeds to be part of a formal, hospital-based program. Under the guidance of a therapist, a fitness program can be implemented in community fitness facilities, especially in early PD, and group exercise classes often meet both physical and social needs of people living with PD.

2. Occupational therapy

Working as part of a team, the physical therapist and occupational therapist share a number of common treatment goals, and a coordinated approach, where possible, will maximize the efforts of all involved. Occupational therapy tends to focus on self-care, leisure, work and daily living activities.[57] Physical therapy may overlap where these activities require strength, flexibility and balance. In PD, the goal of OT is to maintain functional independence and, as the disease progresses and abilities decline, to assist individuals and their families to adapt and change strategies to optimize function at the new level. Education and patient and family support are cornerstones of OT intervention at all times. Perhaps the most recognized role of an occupational therapist is that of assessing the need for adaptive equipment. This includes assistive devices for dressing and grooming, washing and bathing, toileting, eating and drinking, ambulation and bed mobility. As abilities become increasingly compromised, a home OT assessment can help to promote a safe environment, ensuring that the home is functionally optimized. The occupational therapist also advises in the areas of energy conservation, relaxation techniques, advocates use of community resources and assists in helping deal with the functional implications of cognitive decline.

3. Speech therapy

The goal of the speech language pathologist is to assist a person in obtaining and maintaining communication skills. In PD, disorders of speech and swallowing are often seen, with a variable response to medication. With progression, the most common problems relate to imprecise articulation (dysarthria), reduced volume and breath control, reduced facial expression and reduced control over rhythm, rate and pitch.[58] A wide variety of speech therapy techniques administered once or twice weekly, emphasizing rate, articulation, rhythm and pitch have been used to address these problems, often with immediate but no sustained improvement. There is recent evidence that the Lee Silverman Voice Therapy (LSVT®) technique that emphasizes improving vocal adduction and overall voice and speech production may result in long-lasting benefit.[59] As with other rehabilitation therapies, speech therapy requires larger and more rigorous studies to illustrate, from an evidence-based perspective, the role it plays in the management of PD.

C. Nutrition

Nutritional needs should not be overlooked. In early PD, no special care needs to be taken other than stressing a well-balanced diet. With disease progression, dysphagia often develops, with aspiration becoming more common in later stages. At this point the patient may be referred to a dietician and/or speech therapist for nutritional counselling and advice on food preparation. In later stages, when the response to medication becomes unpredictable, a low-protein diet is sometimes beneficial, as there is evidence that levodopa absorption is impeded by dietary protein.[60,61] It is important to involve a dietician in such dietary manipulations to ensure that nutritional requirements are met. Adequate hydration must be stressed, particularly in more advanced disease.

D. Psychosocial issues

The diagnosis of PD and the prospect of dealing with a chronic progressive disease present a challenge for both patient and family. The need for formal psychosocial support will vary between individuals. Referral to a professional may assist in equipping the patient and family with coping strategies. Routine screening for depression during regular office visits may identify problems in the early stages and facilitate timely intervention. Anxiety, mental and physical fatigue and sleep disturbances are often present in PD, all impacting on quality of life.[62] There is a need for ongoing assessment and treatment of emotional, social and psychological needs. As PD progresses, the emotional, mental and physical strain placed on family members and caregivers increases. As part of the overall management of patients, it is important to ensure that the caregivers' needs are being met. A patient's ability to cope as he or she loses independence is greatly affected by the ability of the caregiver to deal with the demands of daily life. The ability to cope can be affected by sleep deprivation, economic/financial concerns, and physical stress of caring for a dependent person, as well as the need for home care and respite and the stress associated with the need for nursing home/continuing care placement.[63] Access to community support services will better enable the caregiver, and by extension the patient.

An important source of both social and psychological support can be found in support groups to help meet the needs of the person with PD and the family. The ability to interact with others who have similar experiences has been shown to be beneficial. This can be helpful at all stages of the disease.[64]

Conclusion

Parkinson's disease is a progressive disorder that demands a holistic approach to treatment. Both pharmacologic and nonpharmacologic interventions play an important role in the comprehensive management of people living with PD. These interventions must be tailored to the individual and modified as the disease progresses and with the goal of minimizing significant functional disability as much as possible.

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