

Current concepts in the diagnosis and management of Parkinson's disease

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Abstract

PARKINSON'S DISEASE IS A PROGRESSIVE NEUROLOGICAL disorder characterized by rest tremor, bradykinesia, rigidity and postural instability. The cause is unknown, but growing evidence suggests that it may be due to a combination of environmental and genetic factors. Treatment during the early stage of Parkinson's disease has evolved, and evidence suggests that dopamine agonist monotherapy may prevent the response fluctuations that are associated with disease progression. L-dopa therapy, however, remains the most efficacious treatment. Treatment during the advanced stage focuses on improving control of a number of specific clinical problems. Successful management of motor response fluctuations (e.g., "wearing off," on-off fluctuations, nighttime deterioration, early morning deterioration and dyskinesias) and of psychiatric problems is often possible with specific treatment strategies. Surgical treatment is an option for a defined patient population.

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Parkinson's disease is a progressive neurodegenerative disorder that affects about 100 000 Canadians, according to estimates from the Parkinson Society Canada (www.parkinson.ca/pd/parkinson.html). The condition is associated with a substantial burden of illness and cost to society. A recent study of mortality among affected patients in Ontario showed an overall mortality odds ratio of 2.5 compared with that among age-matched control subjects.¹ With use of the same methodology, physician costs were found to be 1.4 times higher, hospital admissions were 1.4 times more likely, length of stay was 1.2 times longer and drug costs were 3.0 times higher for patients with Parkinson's disease than for control subjects.² In Ontario, the annual crude prevalence of Parkinson's disease from 1993 to 1999 was 3.6 per 1000 population among men over the age of 25 and 3.2 per 1000 among women over 25.² Over 90% of the patients were over 60. There was a 26% increase in the number of patients over this time, which was due in large part to a change in the demographics of the population. This increase in the population of patients with Parkinson's disease may have a large impact on resource use in our health care system. These data suggest that primary care physicians are managing patients with Parkinson's disease much more often than in the past.

Although significant advances have been made in understanding the underlying pathophysiology of this condition, the cause is still unknown and there is no curative

treatment. In this article we review the clinical presentation of Parkinson's disease, the environmental and genetic factors that may be associated with the development of the disease, principles in the management of early and advanced Parkinson's disease, and surgical management. This review is not designed to be complete, and reference to recent articles by Lang and Lozano^{3,4} may provide further insight. Additional information about treatment interventions for Parkinson's disease may be found in the recent review by Rascol and colleagues.⁵

Clinical presentation

The diagnosis of Parkinson's disease continues to be based on presenting signs and symptoms. Tremor is the most obvious clinical symptom and often starts in one extremity and worsens with precipitating factors such as stress, fatigue and cold weather. It may be confused with the more common essential tremor but can be differentiated by noting if the tremor occurs predominantly at rest (Parkinson's disease) or with action (essential tremor). Essential tremor typically occurs in both arms, whereas patients with Parkinson's disease usually have a unilateral tremor that may affect one arm or a leg. Bradykinesia is usually the most troublesome symptom. Patients report slowness in performing their activities of daily living, including dressing, walking and doing household chores. Writing may become micrographic, with a progressively smaller character size as the person continues to write. Watching a patient get up from a chair and walk is helpful. Patients with Parkinson's disease may need to push themselves up, take a longer time to get up or fall backward. Reduced arm swing, flexed posture and a shuffling gait may be very early features of the disease. Rigidity of the muscles on passive movement is characteristic of Parkinson's disease but must be distinguished from the rigidity resulting from upper motor neuron lesions, for example, in patients with a stroke. In Parkinson's disease, passive movement of the joints reveals continuous resistance throughout the entire range of motion, the so-called "lead pipe" rigidity. With upper motor neuron lesions the muscles, after an initial period of rigidity and resistance to movement, suddenly relax or give way, the so-called "clasp-knife" rigidity. Additionally, patients with Parkinson's disease may show a cogwheel type of rigidity. Here the muscles, on passive movement, have a ratchet-like feel. If rigidity and cogwheeling are not

present when the patient is relaxed, the signs may be brought on by having the patient open and close their contralateral hand during the examination.

A focused examination should be performed to evaluate whether a patient has symptoms and signs that may suggest other forms of parkinsonism than Parkinson's disease (Table 1). Evaluation of changes in vertical eye movement is important to rule out progressive supranuclear palsy. Postural blood pressure changes, other autonomic abnormalities, including a history of bladder instability, and cerebellar features such as early gait instability should be assessed to rule out multiple system atrophy. Although falls and swallowing problems are consistent with late Parkinson's disease, if they occur early and are accompanied by a lack of treatment response, they may be suggestive of progressive supranuclear palsy or multiple system atrophy. Early dementia and other features may suggest Lewy body dementia, corticobasal degeneration or vascular parkinsonism. Patients with early onset parkinsonism (aged < 40 years) should always be evaluated for Wilson's disease with measurement of serum copper and ceruloplasmin levels, 24-hour urine collection for copper excretion and slit-lamp examination for Kayser–Fleischer rings.

Confirmation by autopsy is the only definitive diagnostic method. The United Kingdom Brain Bank Criteria have been developed to improve the accuracy of the clinical diagnosis of Parkinson's disease.⁶ This study evaluated the presenting clinical features that predicted autopsy confirmation of the disease in 100 cases. They found that unilateral onset of symptoms with features that included tremor and at least one of bradykinesia and rigidity with a good initial response to L-dopa were the best predictors of the pathological diagnosis. In 24% of the cases, a different neurological disorder was diagnosed at autopsy from that which had been diagnosed during life.

Neurological imaging studies with CT or MRI do not reveal any specific changes related to Parkinson's disease. Many neurologists choose to perform brain imaging tests to rule out conditions that would require a different man-

agement strategy, such as normal pressure hydrocephalus or focal lesions. These conditions are quite rare and usually can be identified by careful clinical evaluation. Functional imaging to assist in the diagnosis of Parkinson's disease has been proposed with either positron emission tomography (PET) or single photon emission tomography (SPECT).^{7,8} These imaging techniques are still considered experimental, and studies to assess their positive predictive value have not been performed to identify their clinical value at the time of initial presentation of patients with early Parkinson's disease. Because current management strategies would not change because of an expedited diagnosis of Parkinson's disease, most experienced clinicians choose to follow the clinical course of the patient and to make treatment decisions based on the individual patient's needs rather than relying on any information obtained from neurological imaging.

Environmental and genetic factors

Although the cause of Parkinson's disease is still unknown, it is widely believed that most cases of idiopathic disease are caused by an interaction of environmental and genetic factors. The primary brain abnormality found in all affected patients is a degeneration of nigrostriatal dopamine neurons, with a loss of pigmented neurons in the substantia nigra (Fig. 1). The remaining neurons contain intracytoplasmic inclusions called Lewy bodies. There is a moderate-to-severe loss of striatal (caudate and putamen) dopamine.⁹

Over the past 20 years, several pathological processes (e.g., oxidative stress, apoptosis and mitochondrial DNA defect) have been identified that might be involved in the pathway leading to the degeneration of nigrostriatal dopamine neurons; however, definitive proof that any one of these processes is critically involved is lacking. There has been speculation that environmental toxins could cause Parkinson's disease, but a specific agent has not been found.¹⁰ Interesting examples of such speculation have in-

Table 1: Differential diagnosis of Parkinson's disease

Diagnosis	Differentiating clinical features
Progressive supranuclear palsy	Oculomotor dysfunction with vertical gaze abnormalities, axial rigidity, falls during the early stages of disease, pseudobulbar palsy, swallowing dysfunction, cognitive impairment, apraxia of eyelid opening, parkinsonism with lack of or transient response to L-dopa, rapid progression, dysarthria
Multiple system atrophy	Postural hypotension and autonomic dysfunction (Shy–Drager variant), cerebellar dysfunction (olivopontocerebellar atrophy variant), parkinsonism with lack of or transient response to L-dopa (striatonigral degeneration variant), falls during the early stages of disease, swallowing dysfunction, rapid progression, neck flexion, myoclonus, dysarthria
Vascular parkinsonism	Lower body presentation with freezing gait during the early stages of disease, pyramidal tract signs, cognitive dysfunction, relative lack of response to L-dopa
Diffuse Lewy body disease	Early dementia, hallucinations with L-dopa therapy, fluctuating level of alertness, sensitivity to extrapyramidal side effects of neuroleptics
Corticobasal degeneration	Apraxia, cortical sensory signs, myoclonus, unilateral presentation, dystonia, cognitive impairment, lack of response to L-dopa

cluded drug addicts taking a compound toxic to dopamine neurons (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP]), viral exposure causing clusters of cases of Parkinson's disease and specific pesticides causing dopamine neuron loss in experimental animals. These clues may be helpful in defining the cause of Parkinson's disease but are unlikely to be the cause of the majority of sporadic cases.

Typically Parkinson's disease is sporadic, and there is no family history of the disease. A number of genetic forms of the disease have been recently discovered, and research into these rare hereditary forms may help to understand the pathophysiology of this condition. Eight genetic loci for monogenic forms of Parkinson's disease or dopa-responsive parkinsonism have been reported (Table 2).¹¹⁻¹³ In autosomal dominant Parkinson's disease pedigrees, 2 missense mutations in the α -synuclein gene (*PARK1*) were identified in several Greek and Italian families and in a German family. Although the 2 mutations appear to be a rare cause of the disease, α -synuclein has received much attention as it is one of the major components of Lewy bodies. In pedigrees with autosomal recessive early onset parkinsonism, a wide variety of mutations in the parkin gene (*PARK2*) were found in about 50% of families, in which at least one of the affected siblings developed symptoms at or before 45 years of age. A large twin study indicated that genetic factors play a major role in the pathogenesis of early onset Parkinson's disease but not of late-onset Parkinson's disease (diagnosed after 50 years of age).¹⁴ No strong evidence for linkage was identified in a genome-wide scan for idiopathic Parkinson's disease.¹⁵ However, another genomic screen for late-onset Parkinson's disease (onset 40-90 years) suggested multiple genetic factors.¹⁶ A recent heritability study in Iceland has suggested a significant genetic contribution to the development of late-onset Parkinson's disease (onset after 50 years) in the population, and a susceptibility locus for Icelandic patients with Parkinson's disease has been reported.^{17,18}

Currently, most studies of the causes of Parkinson's disease are focused on the exciting possibility that the fundamental degenerative process involved in Parkinson's disease might be identical to, or at least overlap with, that in those rare hereditary forms of degenerative parkinsonisms. In this regard, an argument can be made that the known gene defects in

hereditary degenerative parkinsonisms involve an abnormality in the function of the ubiquitin-proteosomal system, a system which is responsible in part for degradation of damaged proteins.¹⁹ This has led to the reasonable speculation that (sporadic) Parkinson's disease might be caused by overproduction of a toxic protein that cannot be degraded by the ubiquitin-proteosomal system or by a defect in this protein-metabolizing system itself leading to selective damage of the nigrostriatal dopamine neurons.

Management

The management of Parkinson's disease is designed to improve the patient's quality of life. Drug treatment is only one of many available options. One must emphasize the appropriate involvement of other allied health professionals

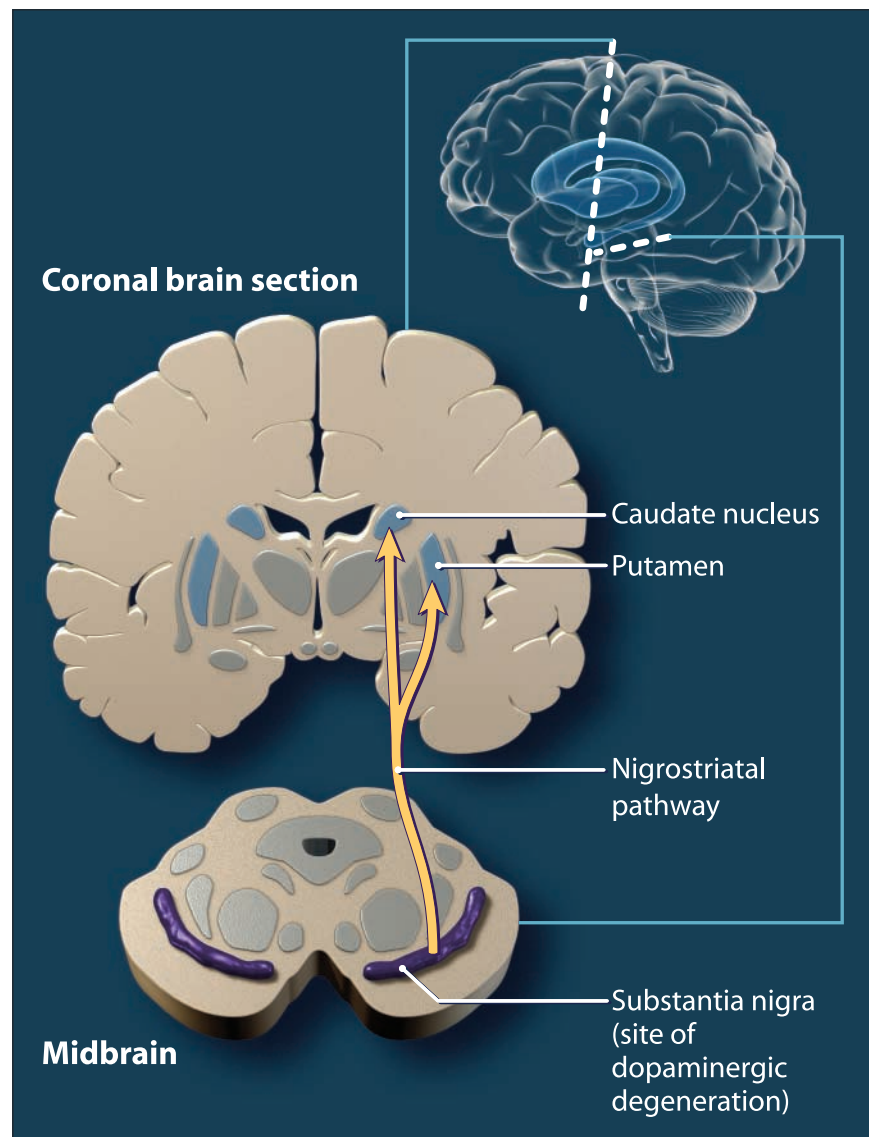


Fig. 1: Coronal section of the brain, showing nigrostriatal pathways and location of selective dopaminergic degeneration in patients with Parkinson's disease.

to help deal with the different needs of patients and their families. Involvement of nurses, social workers and occupational, physiotherapy and speech therapy services will often have a large impact. Patients at different stages of the disease will require different medical therapies as well as other options from a multidisciplinary team dealing with their

condition. The overall objective of medical management is to allow the patient to have as close to normal function as possible without experiencing side effects from therapy. In many cases of early disease, the symptoms are not a problem and treatment is unnecessary. The types of drugs that are used are listed in Table 3.

Table 2: Genetically defined forms of Parkinson's disease and parkinsonism

Gene mutation	Locus	Gene	Inheritance	Lewy body	Clinical characteristics
<i>PARK1</i>	4q21-q23	α -synuclein	AD	Yes	Early age of onset, rapid evolution and dementia
<i>PARK2</i>	6q25.2-q27	Parkin	AR	No (usually)*	Early onset, slow progression, more frequent dyskinesias
<i>PARK3</i>	2p13	Unknown	AD	Yes	
<i>PARK4</i>	4p15	Unknown	AD	Yes	
<i>PARK5</i>	4p14	<i>UCHL1</i>	AD	Unknown	
<i>PARK6</i>	1p35-p36	Unknown	AR	Unknown	
<i>PARK7</i>	1p36	Unknown	AR	Unknown	
<i>PARK8</i>	12p11.2-q13.1	Unknown	AD	No	

Note: AD = autosomal dominant, AR = autosomal recessive, *UCHL1* = ubiquitin carboxy-terminal hydrolase L1.

*On autopsy, one patient with compound heterozygous parkin mutations was found to have Lewy bodies.

Table 3: Drugs used to treat Parkinson's disease

Drug or drug class	Mechanism of action	Side effects	Specific drugs	Typical daily therapeutic dose range	Typical dose frequency
Anticholinergics	Block acetylcholine receptors	Dry mouth, dry eyes, urinary retention, exacerbation of glaucoma and cognitive impairment	Trihexyphenidyl Benztropine Ethopropazine	1–6 mg 1–6 mg 25–100 mg	tid tid tid
Amantadine	Blocks NMDA receptors and acetylcholine receptors and promotes release of dopamine	Cognitive dysfunction, peripheral edema and skin rash	Amantadine	50–200 mg, but caution is required with dose escalation in elderly patients or patients with renal insufficiency	bid
L-dopa	Metabolism to dopamine in cells that contain dopa-decarboxylase	Nausea, hypotension, hallucinations and psychosis, dystonic and choreiform dyskinesias	L-dopa/carbidopa, L-dopa/benserazide, Sinemet CR	100–2000 mg/d as condition advances. Sinemet CR has about 25% reduced bioavailability	From tid to every 2 h
Dopamine agonists	Directly stimulate dopamine receptors	Nausea, hypotension, hallucinations and psychosis, peripheral edema, pulmonary fibrosis (for ergots), sudden onset of sleep	Bromocriptine Pergolide Ropinirole Pramipexole	15–30 mg 1.5–5.0 mg 6.0–24 mg 1.5–5.0 mg	3–4 times/d tid tid tid
Monoamine oxidase (MAO) inhibitors	Block MAO-B receptors to reduce dopamine metabolism	Nausea, dizziness, sleep disorder and impaired cognition	Selegiline	5–10 mg	bid
Catechol O-methyltransferase (COMT) inhibitors	Block peripheral COMT activity to improve L-dopa pharmacokinetics	L-dopa-related side-effect exacerbation, diarrhea, urine discoloration	Entacapone	200 mg with each dose of L-dopa up to 1600 mg/d	With each dose of L-dopa

Note: tid = three times a day, NMDA = N-methyl-D-aspartate, bid = twice a day.

Early Parkinson's disease

Which drug should a physician choose when symptomatic treatment is required for a patient with recently diagnosed disease? Many drugs offer adequate symptomatic improvement, and there is currently debate about which therapy is associated with a lower risk of the problems that may occur as the condition progresses. There are many factors that need to be considered to determine the optimal choice for the individual patient. These include the following:

Level of patient disability

If a patient is having significant problems with his or her activities of daily living, or the patient's ability to work is threatened, L-dopa is probably indicated. Dopamine agonists may be effective for patients with mild-to-moderate disability. If symptoms require minimal treatment, then amantadine or anticholinergic drugs may be considered.

Prevention of response fluctuations

The initial use of dopamine agonists may reduce the risk of developing dyskinesias, "wearing off" and "on-off fluctuations" (see Advanced Parkinson's disease).

Age of the patient

Patients with younger onset (aged < 65 years) are generally able to tolerate medications better and may have a lower risk of side effects. Elderly patients often have more difficulties with cognitive and psychiatric side effects, and physicians should use anticholinergics and amantadine with caution. Dopamine agonists may also be associated with more side effects in elderly patients.

Side-effect profile of the drug being considered

If a patient is concerned about potential drowsiness causing loss of driving privileges, or may not tolerate a change in mental status or already has cognitive impairment, then a dopamine agonist may not be a good choice. Ankle edema may be exacerbated by amantadine or dopamine agonists.

Cost

For patients without health care coverage, generic L-dopa/carbidopa and bromocriptine may be the most affordable.

Unfortunately, no therapies are proven to be neuroprotective or to delay the progression of Parkinson's disease. Initial reports suggested that the monoamine oxidase inhibitor selegiline (Table 3) may reduce the rate of progression of patients with early Parkinson's disease before start-

ing L-dopa therapy.²⁰ The interpretation of the data from the DATATOP study has been debated, and the current consensus is that the observed benefit was most likely due to a mild symptomatic action of selegiline.²¹ Recent practice guidelines from the American Academy of Neurology suggest that there is insufficient evidence to recommend the use of selegiline as a neuroprotective agent.²² Some patients may experience a mild symptomatic benefit but often this is minimal. Side effects of nausea, dizziness, insomnia and cognitive changes make this drug often difficult to use.

Symptomatic therapy is based totally on the requirements of the individual and must be re-evaluated on a regular basis as the condition evolves (Table 3). L-dopa is made into dopamine in the nigrostriatal neurons and remains the most efficacious treatment.²² Essentially all patients with Parkinson's disease will require L-dopa at some point in their disease. Canadian physicians have the choice between standard formulations of L-dopa/carbidopa or L-dopa/benserazide and controlled-release L-dopa/carbidopa. The CR First study examined the effectiveness of the 2 formulations of L-dopa/carbidopa in a prospective 5-year study.²³ Although there is evidence from the animal literature that continuous administration of L-dopa has potential advantages over intermittent dosing, the study did not find any differences between the 2 formulations in reducing response fluctuations. Symptomatic treatment with the immediate-release preparation is less expensive and offers equivalent symptom control. Patients throughout the spectrum of Parkinson's disease have a therapeutic response to L-dopa and if patients are very symptomatic at their presentation or are at risk of losing their job, L-dopa may be their best choice.

In specific clinical situations, drugs with lower potency may be useful. Anticholinergic drugs may provide mild symptomatic treatment and may be beneficial to treat tremor. Unfortunately many patients experience cognitive change, which is quite limiting, and this restricts these drugs to the younger population. Amantadine may also provide mild symptomatic benefit in patients in the early stages of disease. It is relatively inexpensive, has a low incidence of side effects of swollen ankles and is generally well tolerated in younger patients. In older individuals it may be associated with confusion as well. It may be a very effective first-line therapy in younger patients.

Dopamine agonists are drugs that directly stimulate dopamine receptors. They do not have to be metabolized into active drugs and are either ergot (bromocriptine and pergolide) or nonergot in structure (ropinirole and pramipexole). Dopamine agonists may be used to treat patients with early Parkinson's disease. Two recent studies have provided evidence that initial therapy with either ropinirole²⁴ or pramipexole²⁵ may have potential advantages over L-dopa therapy. Patients treated with ropinirole developed fewer dyskinesias and wearing-off symptoms compared with patients treated with L-dopa. The patients treated with L-dopa had better improvement of their motor

function compared with the ropinirole group. Similar results have been shown with pramipexole. In a longer study of bromocriptine versus L-dopa, the frequency of disabling dyskinesias and other response fluctuations was similar for the 2 groups.²⁶ Clearly, dopamine agonists may be associated with the development of response fluctuations less frequently in the shorter studies, but they have less efficacy and more side effects including nausea, postural hypotension, hallucinations and drowsiness. The cost of treatment with dopamine agonists is also higher compared with L-dopa. Younger patients (aged < 65 years) may be offered dopamine agonists as a first-line treatment, because they are often able to tolerate these drugs more easily.

Different treatment strategies for the patient with early Parkinson's disease are outlined in Fig. 2. The clinician

must assess the needs of the patient and determine the best first choice of therapy. Continuous assessments are required to identify whether the treatment goals have been achieved and if side effects have developed. Canadian physicians are very fortunate to have so many therapeutic choices. If one agent or class is used and has limitations or is not effective, switching to another class of drug is recommended as long as a proper therapeutic trial has been attempted. As the condition progresses, other options will be required.

Advanced Parkinson's disease

There are a number of challenges that need to be addressed as patients' symptoms evolve over time. It has

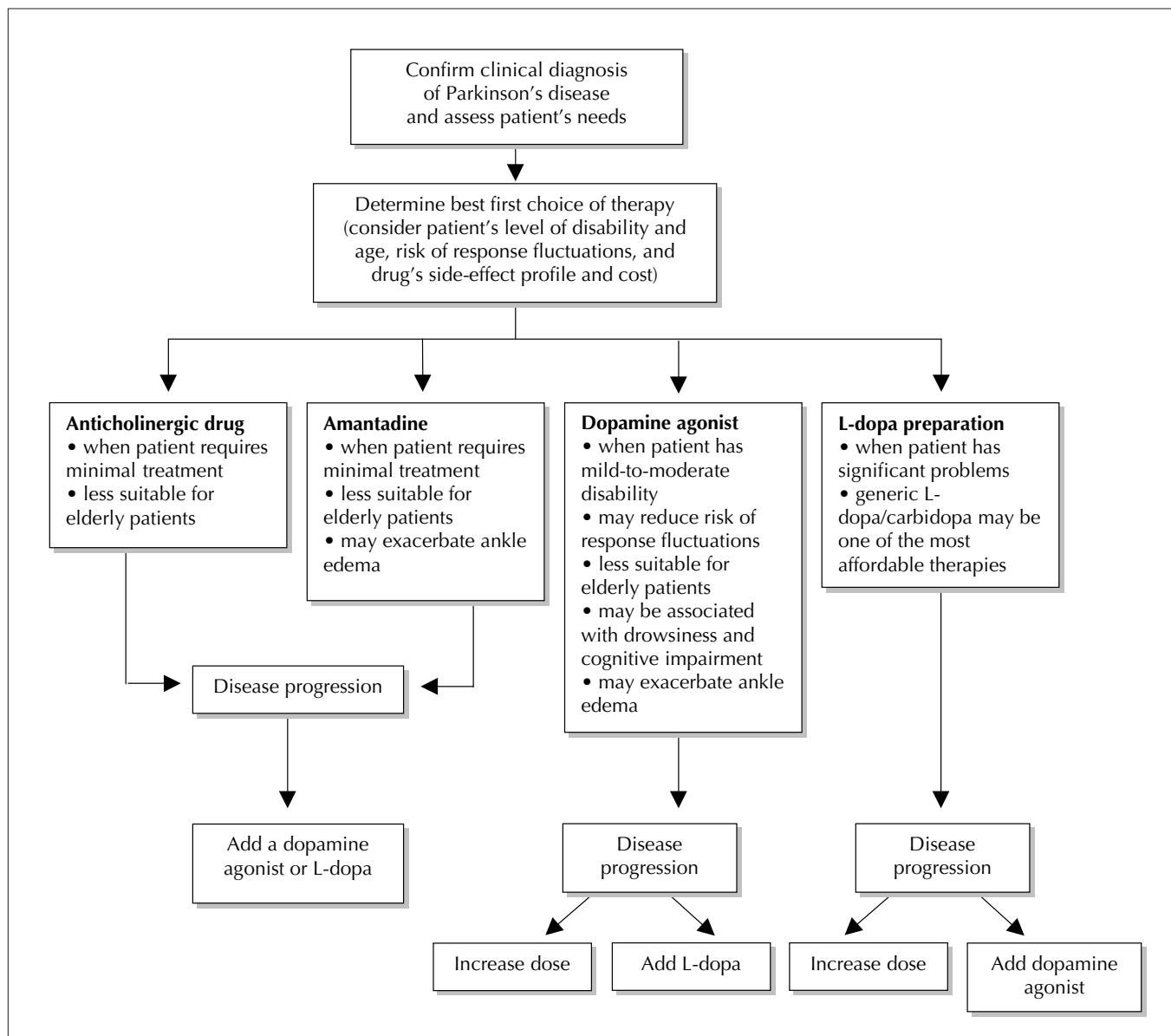


Fig. 2: Treatment algorithm for the management of the early stages of Parkinson's disease (see text for further details).

been our experience that some clinical problems do not respond to drug therapy, including reduced vocal volume, swallowing problems and balance control. Again the role of allied health professionals should be emphasized in the treatment of patients with advanced Parkinson's disease. Physiotherapy may be very helpful to improve muscle tone and strength, which will allow better motor function. Occupational therapy assessment is useful to determine whether devices such as rollator walkers, bedside poles and bathroom aids improve safety and function. Speech therapists may assist with swallowing problems to avoid aspiration, and communication skills may be improved with exercises and devices to improve vocal volume. Each set of clinical problems may have specific solutions once a pattern is recognized.

In patients with advanced disease, combination therapy is often used. The importance of understanding the potential advantages, interactions and side effects cannot be underestimated, as well as having the clinical experience of knowing which combination is most useful for different response patterns.

Wearing off

The most common initial problem as Parkinson's disease symptoms advance is end-of-dose deterioration or wearing-off phenomenon. This is when the symptoms related to Parkinson's disease that respond to treatment become more manifest before the next dose is administered. Therapeutic options include increasing L-dopa dose frequency, conversion of patients from standard formulation L-dopa preparation to Sinemet CR and the addition of entacapone, dopamine agonists, amantadine and selegiline (Box 1).

Do the new dopamine agonists provide better treatment than the older drugs for wearing off? Studies as yet are limited, but preliminary data with ropinirole and pramipexole show similar efficacy compared with bromocriptine (but were not powered to show differences). Pramipexole was superior to bromocriptine when considering the speed of onset of benefit and showed improvement in wearing off in advanced disease.²⁷

In a patient with wearing off, are there advantages to using entacapone compared with a dopamine agonist? Entacapone has a more rapid onset of benefit and often does not require titration to achieve therapeutic benefit. On the other hand, careful L-dopa titration is required and the process may induce dyskinesias and other L-dopa-related side effects. If a patient has had previous problems with severe dyskinesias, a physician should be cautious in using entacapone. If a patient has hallucinations, the physician should avoid prescribing agonists and should consider prescribing the catechol *O*-methyltransferase (COMT) inhibitor. Overall, physicians should prescribe the least amount of medication that allows the patient to do the things important to him or her.

Box 1: Treatment options for "wearing off" in patients with advanced Parkinson's disease

- Increase dose frequency of L-dopa
- Change standard formulation L-dopa to Sinemet CR
- Add entacapone
- Add dopamine agonist
- Add amantadine
- Add selegiline

On-off fluctuations

These are episodes that relate to exacerbation of the patient's Parkinson's disease-related symptoms that do not correlate with specific dose times after L-dopa administration. This usually occurs in patients with more advanced disease. On-off periods may be treated by similar strategies as for wearing off but have not been as well studied.

Nighttime deterioration

Nighttime deterioration occurs in patients with moderate-to-severe disease. This can manifest as frequent urination, difficulty rolling over in bed or muscular discomfort. Because many patients with parkinsonism suffer from fatigue, it is important to stress the need for adequate sleep at night. Often the use of mild sedative agents is helpful to maintain a proper sleep pattern. Treatment includes the addition of a dose of L-dopa in the middle of the night, conversion to Sinemet CR, the addition of entacapone or the use of a dopamine agonist.

Early morning deterioration

Many patients experience their most severe symptoms of Parkinson's disease upon waking in the morning and may also have painful foot dystonia. Many patients rely on a rapid onset of response after the first L-dopa dose. The response can be facilitated by crushing the standard formulation tablet and administering it with a carbonated beverage on an empty stomach.

Dyskinesias

Dyskinesias refer to involuntary movements that are related to the effects of the anti-Parkinsonian therapy. Initially, patients may prefer to experience mild dyskinesias, because they are associated with times of improved function compared with when their treatment is not working. Extreme dyskinesias do not allow the patient to rest, and gait may be impaired because of the flailing movements. Dyskinesias can be more prominent later in the day and they may represent a buildup of L-dopa (Box 2).

Recently, amantadine has been shown to be effective in

Box 2: Treatment options for dyskinesias in patients with advanced Parkinson's disease

- Add amantadine
- Add dopamine agonist and reduce dosage of L-dopa
- Eliminate selegiline
- Eliminate entacapone
- Change controlled-release L-dopa/carbidopa to standard formulation L-dopa

the treatment of dyskinesias.²⁸ The response is usually quite rapid and may occur in the first few days after treatment is initiated. If a patient is already on a dopamine agonist, an increased dose with a concomitant reduction of L-dopa dosage may permit appropriate control of dyskinesias and Parkinson's disease symptoms. For a patient not on an agonist, the introduction of a dopamine agonist may be beneficial if it is tolerated. Withdrawal or reduction of selegiline or withdrawal of entacapone may improve dyskinesias. If a patient is on controlled-release L-dopa/carbidopa, then conversion to the standard formulation may improve dyskinesias because titration is often easier with the standard preparation. Often, combinations of treatment changes may be required to correct the balance between adequate symptom control and reduction of dyskinesias.

Psychiatric manifestations

Patients with Parkinson's disease may become depressed more often than the general population. There is usually a good clinical response to antidepressant medication, but controlled trials to determine the optimal treatment strategy have not been carried out. Many psychiatrists currently use selective serotonin reuptake inhibitors because of their better side-effect profile than tricyclic antidepressants.

Drug-induced psychosis may be a major management problem and may lead to a family's inability to provide care at home. Patients with Parkinson's disease may develop visual hallucinations, paranoia and other psychotic symptoms. These symptoms may resolve with the reduction or elimination of some of the anti-parkinsonian therapy (Box 3). Amantadine, selegiline, anticholinergics and dopamine agonists are more often associated with psychosis. Treatment with small doses of atypical neuroleptics including quetiapine or clozapine may be the best option. Other atypical neuroleptics including risperidone and olanzapine have produced exacerbation of Parkinson's disease symptoms in some patients.

Sudden onset of sleep

The Canadian Movement Disorder Group has recently reported that excessive daytime sleepiness occurred in 51%

of 638 patients with Parkinson's disease surveyed in Canadian clinics.²⁹ Of these patients, only 3.8% experienced at least one episode of sudden onset of sleep while driving, and in 0.7% it occurred without warning. Health Canada has instructed the makers of pramipexole and ropinirole to warn physicians that patients should not drive while taking these medications.³⁰ The recent Canadian Movement Disorder Group study did not identify any differences in the risk of drowsiness between dopamine agonists to support this preferential concern about driving. Provincial ministries of transport have responded differently to the concern about driving, and in some jurisdictions driving is not allowed while taking these drugs. This has resulted in further loss of independence for patients with Parkinson's disease, and efforts are underway to have Health Canada re-examine this issue.

Surgical treatment

Stereotactic surgery is another option for patients with advanced Parkinson's disease. The optimal patient for surgical treatment is someone whose disease is not adequately controlled by medication, with early onset Parkinson's disease (aged < 50 years), good response to drugs, no evidence of other parkinsonian conditions and has had every drug treatment tried by a neurologist experienced in dealing with Parkinson's disease, has no cognitive impairment and no other major medical problems. A number of different surgical options are currently available.³¹ Most surgical centres focus on deep brain stimulation (DBS) of the subthalamic nuclei, globus pallidum or thalamus depending on the clinical scenario. Stimulation of the subthalamic nuclei or globus pallidum has been associated with improvements in bradykinesia, rigidity, drug-induced dyskinesias and off time, that is, when the medication is not effective in helping control patients' symptoms.³² Although the exact mechanism of action of DBS is unknown, there are potential benefits of adjustable settings of stimulator frequency and intensity, no lesion is created and there is potential to have bilateral improvement. Ablative lesions of these anatomical

Box 3: Treatment of psychosis in patients with advanced Parkinson's disease

Reduce or eliminate:

- Amantadine
- Selegiline
- Anticholinergics
- Dopamine agonists

Consider adding:

- Quetiapine
- Clozapine

areas are possible but are associated with higher risks. Despite the resurgence of these techniques, only a small proportion of patients are good candidates and surgery should only be considered as a last option. Transplantation surgery is still experimental.

Conclusion

Patients with Parkinson's disease have a constellation of clinical symptoms that evolve over the course of the condition. Patient management involves the accurate clinical diagnosis of the disease, multidisciplinary management of clinical problems and the use of a number of therapeutic options. Until disease-modifying drugs become available, we must focus on reducing the burden of Parkinson's disease by treating the symptoms and helping our patients cope with their disability by improving their quality of life.

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