Parkinson's Disease: An update on Pathophysiology, Epidemiology, Diagnosis and Management Part 5: Management Strategies

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ABSTRACT

Parkinson's disease has a wide variety of motor and non-motor symptoms. Treatment aims to control the patient's symptoms by replenishing the dopaminergic system with levodopa or dopamine agonists. Monoamine oxidase B inhibitors are also effective first-line drugs. Keeping symptoms under continual control early in the course of the disease may have beneficial effects as Parkinson's disease progresses. Therapy is tailored to each patient's response to the drugs and their ability to tolerate them. Limited responses of motor and many non- motor symptoms may require the addition of other treatments. The adverse effects of drugs used in the treatment of Parkinson's disease are usually reversible. As the disease progresses and problems accumulate, deep brain stimulation (DBS) surgery may be a reasonable therapeutic option for some individuals, although many people with PD do not qualify for DBS for a variety of reasons. In addition nonpharmacological alternatives are helpful , including diet, exercise and occupational therapy. However, the majority of people with PD can lead full and active lives with good symptom control for many years.

Key words: Parkinson's Disease, Pathophysiology, Epidemiology, Diagnosis, Management

Introduction

It is crucial for individuals with PD to understand that while the underlying condition progresses steadily, the clinical course differs greatly with each person over several years. A competent and caring healthcare professional, can assist the person with PD and his or her care partner with careful management of PD symptoms to establish a treatment plan consisting of suitable drugs, daily exercise, a balanced diet, social involvement and cognitive exercises, and other therapies.

Parkinson's disease treatment is intended to maximize the quality of life of the patient. Just one of the many services available is addiction treatment. To better deal with the diverse needs of patients and their families, the necessary role of other allied health professionals must be stressed. There will also be a significant effect on the participation of nurses, social workers and occupational, physiotherapy and speech therapy facilities. Various medical treatments, as well as other options from a multidisciplinary, would be needed to assist patients coping with their illness at various levels of impairment. The ultimate aim of medical management is to allow the patient to work as near as possible to normal without suffering therapy side effects. The signs are not a concern in many cases of early illness and medication is unnecessary. Table 1 lists the types of medications that are used.

Treatment should be personalized to the individual's needs, as always. Patients should be encouraged to make informed treatment decisions and strive to include the caregivers as much as the patient requires.

Management strategies

When Parkinson's disease is diagnosed, whether to initiate any type of drug therapy and which medications to use are the most important questions to determine. This will rely in part, on the degree of functioning and extent of impairment of the patient. Planning for long-term development and impairment often includes early treatment of Parkinson's disease. How will the potential complications of a chronic, degenerative condition that will have to be treated over a period of several years be avoided or delayed?

The main method of treating symptoms of Parkinson's disease is treatment with antiparkinsonian medications. The right therapeutic choices may lead the patient to additional years of productive work and may even decrease the period of later dependent living. However, among the available choices, no single medication is suitable for initial therapy for all patients.

The choice of treatments, in addition to clinical considerations, is conditioned by the financial resources of the individual patient. The older demographic differs markedly in terms of access to prescription payments. In most larger populations, services that can be used nationally and locally for the management and education of patients with PD are readily accessible. Because a decade of medical management may be necessary, the primary care physician should pay special attention to the patient's personality, concerns, desires, and aspirations about PD therapy. Ideally, any therapy decisions may include those patients early on. Others will prefer to avoid medical attention longer than others will, and some will require gentle encouragement to try any drug. There is no evidence that indicates that withholding therapy actually eliminates potential side effects.

There is no universal consensus as to how and when to begin antiparkinsonian-drug treatment. No two individuals with Parkinson's have the same symptoms, so it's a case of trial and error at first. But no drug treatment for Parkinson's is really successful until the correct formula is identified for the symptoms.

In Parkinson's disease, dopaminergic drugs are the foundation of symptomatic care for motor symptoms. Levodopa was the first symptomatic therapy for Parkinson's disease, discovered in the 1960s, followed by the availability of dopamine agonists and inhibitors of monoamine oxidase B. The decision as to which care to initiate has, until recently, been not fully discussed. There is no single drug currently prescribed for initiation of treatment, but consideration should be given to factors such as symptom intensity, embarrassment, willingness to perform tasks, cost and patient preference. The patient may prefer not to begin therapy if the symptoms are very mild (1, 2).

Since levodopa-induced irregular movements (dyskinesia) are more likely to occur in patients with early onset disease, dopamine agonists are often introduced as initial treatment, but this early benefit of dopamine agonists over levodopa declines with time (about 10 years) (1). There is also some questionable proof of neuroprotection with the 1 mg daily dose of monoamine oxidase B inhibitor rasagiline; (3) but it is expensive and may not be covered by insurance.

Levodopa is frequently initiated first because of the increased risk of neuropsychiatric adverse effects from dopamine agonists in late-onset Parkinson's disease (1). Levodopa is much better at managing Parkinson's motor symptoms than dopamine agonists and monoamine oxidase B inhibitors, but after long-term usage or high-dose therapy, dyskinesia and motor fluctuations occur (4). With the addition of adjunctive procedures, the patient will possibly require multiple prescription changes over time (5,6). Most patients taking dopamine agonists will also need levodopa after two to five years (7).

Since Parkinson-plus syndromes (e.g. multiple system atrophy and progressive supranu-clear paralysis) respond to levodopa at an early stage, this drug should be tested for at least several months at doses of up to 1000 mg/d before non-responsiveness is concluded (8). After a trial with levodopa, the condition should also be re-evaluated. In about 80% of patients with idiopathic Parkinson's disease, levodopa responsiveness occurs (8). While bradykinesia and rigidity respond well to levodopa, tremor is not seen to have this consistent response (9).

In patients with early-onset Parkinson disease and extreme tremor, anticholinergic medications, such as trihexyphenidyl, can be used, but not as a first option due to reduced effectiveness and potential for neuropsychiatric adverse effects (2). Recent data suggest that injections of botulinum toxin can effectively treat Parkinson's disease tremors (10).

In 5 percent of Parkinson's disease patients and up to 20 percent of those taking dopamine agonists, behavioral addictions and impulse control disorders occur (11, 12). Risk factors for impulse control disorders include younger age (perhaps linked to the prescribing activity of dopamine agonists in this group), personality seeking novelty, family history of addiction, dopamine agonist use, and previous history of impulse control disorders (11).

Dopamine dysregulation syndrome is a form of addictive behavior that occurs in up to 4% of patients and is characterized by the compulsive overuse of dopaminergic drugs, usually short-acting (e.g., levodopa and apomorphine), which affect physical, social and occupational functioning (12). Punding involves repeated, often meaningless, stereotyped actions, such as sorting or disassembly, which occurs in up to 15% of Parkinson's disease patients (13). Dopamine dysregulation syndrome and punding can occur with the use of short-acting dopaminergic agents, including levodopa (1). Impulse control disord

ers can occur at any time after initiating dopamine agonists.

To prevent acute akinesia or neuroleptic malignant syndrome, antiparkinsonian pharmaceutical products should not be suddenly removed. Owing to the risk of dopamine agonist withdrawal syndrome, dopamine agonists should not be stopped quickly (occurs in 15% of patients taking dopamine agonists; the risk is higher in people with impulse control disorders) (14-16).

Drugs that should be avoided

Drugs that block dopamine receptors in patients with Parkinson's disease can lead to Parkinson's disease or greatly exacerbate motor symptoms which can lead to malignant neuroleptic syndrome. These include neuroleptics such as haloperidol, thioridazine, chlorpromazine, promethazine, fluphenazine, risperidone and olanzapine; antiemetics such as metoclopramide and prochlorperidone; tetrabenazine; and antihypertensives such as methyldopa (17,18). For those receiving monoamine oxidase B inhibitors, meperidine should be avoided (19).

Drugs to avoid

These are some (but not all) of the drugs to avoid in Parkinson's:

- chlorpromazine (Largactil)
- fluphenazine (Modecate)
- fluphenazine with nortriptyline (Motival)
- perphenazine (Fentazin/Triptafen)
- trifluoperazine (Stelazine)
- flupenthixol (Fluanxol/Depixol)
- haloperidol (Serenace/Haldol)
- metoclopramide (Maxalon)
- prochlorperazine (Stemetil)
- Decongestants or cold remedies

Managing motor and nonmotor symptoms in advanced disease

Most patients respond well to levodopa; however, motor fluctuations and dyskinesias will grow in 40 percent-50 percent of patients within five years of chronic levodopa treatment and in 70 percent-80 percent after 10 years of treatment (1, 20,21). Motor fluctuations are spontaneous changes in motor response to dopaminergic therapy that may be erratic, whereas dyskinesias are involuntary and intrusive movements resulting from levodopa, primarily choreiform (22). In patients receiving less than 400–500 mg per day of levodopa, dyskinesias are less likely to develop (23). In patients with early-onset disease and possibly in women (6,20,23,24), there is a higher cumulative frequency of dyskinesias, wearing off and on-off changes in symptoms. Dyskinesias may suggest better medication response, and most patients tend to be "on" rather than "off" with dyskinesia. (24)

In one study, 20 percent of Parkinson's disease patients had problematic motor fluctuations and 4 percent had five-year dyskinesias, which were serious enough to warrant a change in care (25). In order to minimize 'off' period, catechol O-methyltransferase (COMT) inhibitors, such as entacapone, administered with each levodopa-carbidopa tablet; monoamine oxidase B inhibitors, such as rasagiline or selegiline; and dopamine agonists, such as pramipexole, ropinirole, rotigotine patch and bromocriptine (2), may be offered. Owing to the dangers of pulmonary and cardiac valve fibrosis, ergot derivatives such as bromocriptin should be used with caution. To minimize motor variability, modified-release levodopa preparations, such as controlled-release preparations, can be used but should not be used as a first option. The use of combined formulations of levodopa-carbidopa with COMT inhibitors has been shown to be associated with earlier onset and increased dyskinesia frequency (26). Dyskinesias can be known to be minimized by amantadine, an antiviral with antiglutamatergic effects; it is effective in 60%-70% of patients (27). Axial signs appear to develop later in the disorder, including postural dysfunction and gait, and can be less receptive to dopaminergic therapies. There is evidence that cholinesterase inhibitors and/or methylphenidate are being investigated (28).

Table 1: Drug 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 Ethoprpazine	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 o dopamine in cells that contain dopa-decarboxylase	Nausea, hypotension, hallucinations and psychosis, dystonic and chroreiform dyskinesias	L-dopa/carbidopa, L-dopa/benseracide, Sinemet CR	100-2000 mg/d as condition advances. Sinemet CR has about 25% reduced biovailability	From tid to every 2 h
Dopamine agonists	Directly stimulate dopamine receptors	Nausea, hypotension, hallucinations and psychosis, 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