

PARKINSON'S DISEASE - A REVIEW

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ABSTRACT

Parkinson's disease is not only among the most common neurodegenerative disorders, it is also one of the most famed neurological illnesses with several celebrity figures suffering from Parkinson's disease. Over the past few decades there has been steady increase in the understanding of disease pathophysiology and clinical course, with advances in management choices including new drug therapies, surgical treatment options and growing hopes in neurotransplantation and gene therapy. The rapid change in this arena makes it necessary for clinicians and students of neurology to come abreast with these advances. This becomes more informative if we also examine what we know from past. This article provides a concise yet meticulous review of Parkinson's disease through a thorough literature review exploring all major aspects including epidemiology, etiology and pathophysiology, signs and symptoms, diagnostic evaluation, management including pharmacotherapy, and new modalities of treatment such as deep brain stimulation and neurotransplantation. Ongoing research is also outlined.

Parkinson's disease (PD) is probably the most famous movement disorder presently known to man. From Muhammad Ali and Michael J. Fox to Pope John Paul II, there are numerous celebrities who have brought this disorder to light. This is the second most common neurodegenerative disorder after Alzheimer's disease.¹ There is a significant financial and social burden of PD especially with the aging population.² It has been described as one of the most disabling chronic neurologic illnesses, with a significant loss of quality of life.³

James Parkinson provided the first detailed description of the disease in his 1817 monograph *An Essay on the Shaking Palsy*.⁴ Parkinsonism is a term used for clinical conditions characterized by akinesia and rigidity that do not meet clinical or pathologic criteria for idiopathic PD.⁵

EPIDEMIOLOGY

The most consistent risk factor for developing PD is increasing age; the prevalence increases from 1% at the age of 65 to 4-5% by the age of 85.^{6,7} An estimated 1 million Americans alone are affected by PD.⁸ The lifetime risk for PD is estimated to be 2.0% and 1.3% for men and

women, respectively; and between 3.7 and 4.4% for Parkinsonism.⁵ PD may be more common in nations with primarily white populations; however, the evidence is far from clear.⁹ A review from India suggested a low prevalence of PD compared with the rest of the world, except in the Parsi community.¹⁰ No population based data are available from Pakistan.

ETIOLOGY AND PATHOPHYSIOLOGY

The etiology of idiopathic PD remains unknown, although environmental and genetic factors (or a combination of the two) is considered to play a role in the development of the disease. PD has been associated with exposure to a number of environmental agents, including pesticides, herbicides, metals, and well-water consumption, but the results of many of these studies have not been fully substantiated.^{5,11} 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is the most famous toxin associated with the Parkinsonian syndrome.⁹ Recent advances in molecular genetics have revealed important genetic influences underlying the development of PD.¹²

The mainstay of pathophysiology is progressive loss of

neurons in the substantia nigra (SN) with the presence of ubiquitinated protein deposits in the cytoplasm of neurons (Lewy bodies) and thread-like proteinaceous inclusions within neurites (Lewy neurites).¹ Dopaminergic cell loss in SN directly leads to dopaminergic deficiency in the substantia nigra pars compacta (SN pc).^{4,13} The pathophysiologic progression is thought to start in the dorsal motor nucleus of the vagus nerve and intermediate reticular region of the medulla, then progressing to SN, and then involving the forebrain and ultimately the neocortex as the disease advances.¹³

This scheme, although warranting further study, underscores the widespread multisystem nature of PD and appearance of new motor (gait disturbances, disequilibrium, falls, freezing, camptocormia, swallowing, and speech difficulties) and non-motor (autonomic dysfunction, sleep disorders, pain, depression, dementia) symptoms that are only partially responsive or non-responsive to dopaminergic treatment.¹³

On a cellular level, mitochondrial function deficiency, increased oxidative stress, apoptosis, excitotoxicity, and inflammation are part of the processes that ultimately result in neurodegeneration.¹³ Impaired mitochondrial function has been detected in a variety of tissues from PD patients, including substantia nigra, platelets, and muscle.⁹

On a molecular level, three genes have been causally linked to PD; PARK1, PARK2 and PARK7. The PARK1 gene (4q21.3) encodes the presynaptic protein-synuclein; PARK2 (6q25.2-27) is associated with parkin protein, and leads to autosomal recessive juvenile Parkinsonism (AR-JP); whereas the PARK7 gene (1p36) results in mutation in DJ-1. Several other loci including PARK3, PARK4, PARK5, PARK6, PARK8, PARK9 and PARK10 have been thought to be associated with this disorder, although a definitive relationship has not been established.^{7,12}

CLINICAL FEATURES

Parkinson's disease is characterized by resting tremor, bradykinesia, rigidity, and postural instability. Most patients have a majority of these cardinal symptoms at some point during their illness, although wide variations occur. Initial symptoms are usually asymmetric.¹⁴ Mean age at onset is 55 to 60 years.¹⁵ Patients typically present with asymmetric resting tremor, or slowness of activities, such as difficulty in opening jars, rising from a chair, and performing other activities of daily living. Some patients present with gait difficulty as their major problem.

Neuropsychiatric disturbances - including mood and anxiety disorders, fatigue and apathy, psychosis, cognitive

impairment, sleep disorders and addictions - can be part of the process of PD itself, or may result from complex interactions between the progressive and widespread pathologic changes of the disease, emotional reactions to Parkinsonism, and treatment-related side-effects. More than 60% of patients with Parkinson's disease report one or more psychiatric symptoms at some point in the course of their illness. These symptoms are often a significant source of disability and constitute some of the most difficult treatment challenges in advanced Parkinson's disease.¹⁶ About 50% of patients with Parkinson's disease without dementia on standardized cognitive tests have mild cognitive impairment. Dementia occurs later in the disease process in up to 30% of people with PD and has clinical and pathological similarities with dementia with Lewy bodies.¹⁶ Dementia associated with PD is accompanied by a reduced quality of life for both patients and caregivers and by rapid functional and motor decline.¹⁷

Common signs on clinical examination include decreased facial expression (masked facies), decreased eye blinking (reptilian stare), bradykinesia (slow movements), resting tremor, and rigidity. The classic tremor is 4-6 Hz at rest, although it may be absent in one quarter of the cases of PD.¹⁸ Rigidity can be cogwheel (catch-and-release) or lead-pipe (continuously rigid).^{14,19} Other signs include flexed posture, shuffling gait, retropulsion, freezing of gait, decreased olfaction, and micrographia.^{14,19,20} Myerson's sign is the inability to resist blinking when the glabella (area above the nose and between eyebrows) is tapped with finger; it can be seen early in PD.¹⁵

There are a few other neurodegenerative disorders that have Parkinsonian features. Differentiating these disorders from Parkinson's disease can be difficult and depends on the presence of other additional characteristic clinical findings. Hence, these diseases are often referred to as Parkinsonism-plus syndromes. These include progressive supranuclear palsy, the Shy-Drager syndrome, striatonigral degeneration, and olivopontocerebellar atrophy.¹⁹ Drug-induced Parkinsonism, vascular Parkinsonism, corticobasal degeneration and dementia with Lewy bodies are other major differential diagnoses. Dementia and psychiatric symptoms at onset should raise the suspicion of Parkinsonism-plus syndromes. Presence of pyramidal and cerebellar signs, falls at presentation or early in the disease course, poor response to levodopa, symmetry of motor signs, rapid progression, lack of tremor, and early dysautonomia (urinary urge incontinence, fecal incontinence, urinary retention requiring catheterization, persistent erectile failure, and symptomatic orthostatic hypotension) are signs that are probably useful in identifying patients with forms of Parkinsonism other than PD in patients with mild disease.²¹

DIAGNOSIS

No laboratory blood test for PD is currently available.²² The diagnosis remains mostly a clinical one.^{4,19} Neuroimaging studies are used to exclude other causes of Parkinsonism. Good to excellent response to levodopa or a dopamine agonist is considered a good marker of PD.¹⁹ Genetic studies are not routinely performed and are still research tools; they should be considered in cases with a relevant family history. The gold standard for PD remains neuropathological examination.¹⁸ Underdiagnosis is common.¹⁸

Drug challenge tests

Levodopa and apomorphine challenge tests are useful in distinguishing PD from other Parkinsonian syndromes. A positive response favors PD; however, these tests have high false-negative (at least 30%) and high false-positive (20 to 30%) rates.

Olfaction testing

This may be useful in differentiating progressive supranuclear palsy and corticobasal degeneration from PD. A significant loss of smell is suggestive of PD rather than other Parkinsonian syndromes.²¹

Neuroimaging

MRI is useful in distinguishing PD from multisystem atrophy (MSA). The distinguishing characteristic is putaminal hypointensity on T2-weighted images or putaminal hyperintensity on proton density-weighted images. Fast spin echo (FSE) protocol images may show putaminal abnormalities as well. These are usually much more common in MSA than PD.²¹ Routine neuroimaging of the brain is rarely helpful in PD.¹⁸

MANAGEMENT

The management of PD has seen several advances in the past two decades. Not only has pharmacological treatment improved, but several other management options are either available in clinical practice or are in the experimental stage. While managing patients with PD several considerations are taken into account, including degree of severity, associated conditions such as dementia and depression, co-morbid conditions, and social situation.

The Unified Parkinson's Disease Rating Scale (UPDRS) is a standardized assessment tool that facilitates accurate documentation of disease progression and treatment response.²³ This four-part scale measures mental effects,

limitations in activities of daily living, motor impairment, and treatment of disease complications. The instrument is available at <http://www.mdvu.org/pdf/updrs.pdf>. In addition to assessing the severity of PD, screening for depression and dementia are also recommended. Some of the screening tools are listed in Table 1.

Table 1 Screening tools for depression and dementia in patients with PD

Instrument	Use	Comments
Beck Depression Inventory (BDI)	Depression	self completion questionnaire (21 items, range 0-63)
Hamilton Depression Rating Scale (HDRS-17)	Depression	requires trained administrator (17 items, range 0-52)
Montgomery Asberg Depression Rating Scale (MADRS)	Depression	Requires trained administrator (10 items, range 0-60).
Cambridge Cognitive Examination (CAMCog)	Dementia	lengthy and relatively complex
Mini-Mental State examination (MMSE)	Dementia	sensitive but less specific

PHARMACOLOGICAL TREATMENT

Although a number of drugs are currently available for prescription, none addresses the underlying problem associated with the progressive loss of dopaminergic neurons.²⁴ The first drug to choose in an individual with PD is still something of an art. Each patient should be individualized and therapy selected accordingly. The following is a brief overview of the currently used medications and their advantages, disadvantages, and potential problems. A summary of commonly used medications is provided in Tables 2 and 3.

Levodopa/carbidopa

Since its introduction by Birkmayer and Hornykiewicz in 1961, levodopa has remained the most effective drug for PD and remains the primary treatment for symptomatic patients.^{2,25,26} Carbidopa prevents peripheral conversion of levodopa to dopamine by blocking dopa-decarboxylase; thus the combination increases cerebral levodopa bioavailability and reduces the peripheral adverse effects of dopamine (e.g., nausea, hypotension). Levodopa is particularly effective at controlling bradykinesia and rigidity, whereas speech disturbance, impaired postural reflex, and gait instability are less likely to respond. The clinical efficacy often declines after long-term therapy and

Table 2 Commonly used medications in patients with Parkinson's disease

Agent	Category	Indication	Route/Preparation	Starting dosage	Daily dosage (mg)	Common side effects	Caution/Comments
Carbidopa/Levodopa	L-DOPA	Most potent for most cardinal and secondary symptoms of PD. Most neurologists do not use as a first-line agent, particularly in young patient due to loss of efficacy and motor complications in 5 years	Oral only 25/250 mg strength routinely available in Pakistan	1/2 tablet three times a day	1/2 to 1 tablet 3 to 6 times a day 300 - 1500 mg of levodopa/day	Nausea, anorexia, vomiting, dizziness, drowsiness, dyskinesias, hallucinations, psychosis, behavioral changes, postural hypotension	Efficacy declines with long term use; motor fluctuations and dyskinesias develop
Ropinirole	Dopamine agonist	Monotherapy in early PD, or adjuvant therapy in advanced PD	Oral 0.25, 0.5, 1.0, 2.0, 5.0 mg tablets	0.25 mg twice a day	0.5 - 24 in 3 divided doses	Nausea, dizziness, orthostatic hypotension, somnolence, dyskinesias, vivid dreams and hallucinations, behavioral changes, confusion, fatigue	Fewer motor complications compared to levodopa but more hallucinations, somnolence, and edema
Pramipexole	Dopamine agonist	Monotherapy in early PD, or adjuvant therapy in advanced PD	Oral 0.125, 0.25, 1.0, 1.5 mg tablets	0.125 mg three times a day	0.1 - 1.5 in 3 divided doses	Nausea, dizziness, orthostatic hypotension, somnolence, dyskinesias, vivid dreams and hallucinations, behavioral changes, confusion, fatigue	Fewer motor complications compared to levodopa but more hallucinations, somnolence, and edema
Bromocriptine	Dopamine agonist	Monotherapy in early PD, or adjuvant therapy in advanced PD	Oral 2.5 mg tablets	1.25 mg at bed time	10 - 30 in 3 divided doses	Headache, nausea, anorexia, dyspepsia, dizziness, orthostatic hypotension, somnolence, dyskinesias, vivid dreams and hallucinations, behavioral changes, confusion, fatigue	Limited use in presence of newer dopamine agonists
Selegiline	MAO-B inhibitor	For symptomatic control of Parkinson's disease and as adjuvant therapy for patients with Parkinson's disease and motor fluctuations	Oral 5 mg tablets	10 mg as a single dose in morning or divided at breakfast and lunch	10	Insomnia, night mares and exacerbation of all potential dopaminergic adverse affects	Contraindicated with tricyclic antidepressants, SSRIs, and meperidine
Rasagiline	MAO-B inhibitor	Monotherapy in early PD, or adjuvant therapy in advanced PD	Oral 1 mg tablets	One tablet daily	1	Postural hypotension, anorexia, vomiting, weight loss, balance difficulties	Caution with MAO inhibitors
Entacapone	COMT inhibitor	Managing motor fluctuations ("wearing-off" effect) in patients taking levodopa	Oral 200 mg tablets	1/2 to 1 tablet with each tablet of Carbidopa/Levodopa	1200 - 1600	Diarrhea, nausea, exacerbates levodopa adverse effects, bright orange urine	
Carbidopa/Levodopa/Entacapone	Combination	To decrease the total use of levodopa	Oral 25/100/200 mg tablets	1 tablet three times a day	Up to 6 to 8 tablets per day	As described in Carbidopa/Levodopa and Entacapone sections	

Agent	Category	Indication	Route/Preparation	Starting dosage	Daily dosage (mg)	Common side effects	Caution/Comments
Amantadine	NMDA inhibitor	Monotherapy in early or mild PD; more effective for tremor than bradykinesia or rigidity; adjuvant agent for use with dopamine agonists or levodopa; anti-dyskinesia agent	Oral 100 mg tablets	100 mg once a day	300 - 400 in 2 divided doses	Dry mouth, urinary retention, constipation, confusion, hallucinations, depression, ankle edema, livedo reticularis, insomnia or somnolence	
Procyclidine	Anticholinergic	Monotherapy or in conjunction with dopamine agonists in mild, tremor predominant PD in young	Oral 5 mg tablets	2.5 mg twice a day	Max. 30 mg daily in 3 divided doses	Confusion, forgetfulness, blurred vision, constipation, dry mouth, urinary retention, hallucinations, psychosis	Cautious use in patients over 65 years of age, those with glaucoma and cardiac disorders
Trihexphenidyl	Anticholinergic	Monotherapy or in conjunction with dopamine agonists in mild, tremor predominant PD in young	Oral 2 mg tablets	1 mg once a day	4 - 8 mg in 2 to 3 divided doses	Confusion, forgetfulness, blurred vision, constipation, dry mouth, urinary retention, hallucinations, psychosis	Cautious use in patients over 65 years of age, those with glaucoma and cardiac disorders
Apomorphine	Dopamine agonist	Rescue for severe 'off' periods; refractory motor fluctuations	Subcutaneous injections 10 mg/ml 5mg/ml	Titration required between 1 to 3 mg per dose	3 - 30 mg If > 10 injections are required per day, then consider continuous infusion	Nausea, vomiting, profound hypotension, dyskinesias, hallucinations, injection site reaction	Antiemetics (domperidone) should be used before injection to avoid nausea/vomiting

disabling side-effects appear, most notably motor fluctuations such as the wearing-off or on-off phenomena and dyskinesias.^{25,26}

Dopamine agonists

These include bromocriptine, pergolide, pramipexole, ropinirole, and cabergoline.¹⁴ Cabergoline, ropinirole, and pramipexole treatment of PD results in fewer motor complications (wearing off, dyskinesias, on-off motor fluctuations) than levodopa treatment.² However, they are associated with more frequent adverse effects including hallucinations, somnolence and edema. The American Academy of Neurology recommends that the choice between levodopa and dopamine agonists depends on the relative impact of improving motor disability (better with levodopa) compared to the lessening of motor complications (better with dopamine agonists) for each individual patient with PD. Pergolide and cabergoline (ergot-derived dopamine receptor agonists) were recently found to be associated with significantly increased risk for valvular heart disease and were recalled from the market.^{27,28}

Monoamine oxidase B (MAO-B) inhibitors

This group includes the compounds selegiline and rasagiline. The Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) trial demonstrated that selegiline reduced the risk of developing disability requiring levodopa therapy by 50 percent.²⁹ Further follow-up of the patient cohort revealed a symptomatic benefit of selegiline, with a 17.2% absolute reduction in the risk of requiring levodopa in the selegiline arm, compared with placebo. However, clinical evidence for neuroprotective benefit with selegiline is still debated. Rasagiline has been found to be well tolerated and effective in the treatment of early PD, and as adjunctive treatment in motor fluctuations. Whether rasagiline is associated with clinically significant neuroprotection is still under study.³⁰

Anticholinergic agents

These agents are commonly used as initial therapy, especially in cases where tremor is predominant, but there is evidence that anticholinergic agents are not better than levodopa for tremor.² They are associated with a lower

Table 3 Commonly used adjuvant medications in patients with Parkinson's disease

Indication	Agent	Route/Preparation	Starting dosage	Usual target daily dosage (mg)	Common side effects	Caution/Comments
Depression Sialorrhoea	Amitriptyline	Oral 25 mg tablets	12.5 to 25 mg at bed time	75 - 100	Sedation, dry mouth, weight gain, confusion, orthostatic hypotension	Anticholinergic/cognitive side effects in elderly; cautious use in patients over 65 years of age
Psychosis	Clozapine	Oral 25, 100 mg tablets	12.5 mg once or twice daily	300 - 450	Drowsiness, sedation, dry mouth, dizziness, vertigo, visual disturbances, hypotension, constipation, nausea	May cause agranulocytosis, seizures, myocarditis, increased mortality in elderly
Psychosis	Quetiapine	Oral 25, 50, 100, 200 mg tablets	50 mg at bed time	300 - 400	Somnolence, dizziness, headache, dry mouth, agitation, asthenia	Caution in elderly patient for increased mortality risk
Dementia	Rivastigmine	Oral/Transdermal Patch 1.5, 3, 4.5, 6 mg capsules 9, 18 mg patches	1.5 mg twice a day	9 - 12	Nausea, vomiting, anorexia, diarrhea, dizziness	
Dementia	Donepezil	Oral 5, 10 mg tablets	5 mg once a day	5 - 10	Headache, nausea, diarrhea, insomnia, fatigue, vomiting, muscle cramps	
Postural hypotension	Fludrocortisone	Oral 0.1 mg tablets	0.05 to 0.1 mg once a day	0.1 - 0.2	Hypertension, edema, congestive heart failure, cardiac enlargement, potassium loss, hypokalemic alkalosis	Periodic checking of electrolytes; monitor blood pressure
Postural hypotension	Midodrine	Oral 2.5, 5, 10 mg tablets	2.5 to 5 mg in morning	10 mg 3 times a day in waking hours	Supine hypertension, paresthesias, dysuria, piloerection, pruritis	Monitor for supine hypertension; cautious use in patients with cardiac history; do not give after 6 pm
Sleep disturbances REM sleep behavior disorder	Clonazepam	Oral 0.5, 2 mg tablets	0.5 mg at bed time	2 - 4	Somnolence, dizziness, fatigue, depression	
Urinary urgency	Tolterodine	Oral 1, 2 mg tablets 2, 4 mg extended release capsules	1 to 2 mg twice daily	2 - 4	Dry mouth, headache, constipation	Interactions with antifungals, macrolides, cyclosporine, vinblastine
Urinary urgency	Oxybutynin	Oral 5 mg tablets 5, 10, 15 mg extended release tablets	5 mg two to three times daily	15 - 20	Dry mouth, constipation, nausea, dizziness, somnolence, headache, blurred vision, urinary hesitation	
Constipation	Lactulose	Oral 3.35 gm/5ml syrup	15 ml twice daily	30 - 60 ml (20 - 40 gm)	Flatulence, diarrhea, abdominal cramps, hypokalemia, hypernatremia	
Levodopa induced nausea	Domperidone	Oral 10 mg tablets 1 mg/ml suspension	10 - 20 mg three times daily	40 - 80 mg	Galactorrhoea, gynecomastia, dry mouth, headaches, abdominal cramping	

effectiveness and a higher incidence of gastrointestinal and neuropsychiatric adverse effects, which limit their use in older patients. Anticholinergics typically are used in patients younger than 70 years with disabling resting tremors.¹⁴

Catechol o-methyl transferase (COMT) inhibitors

These included entacapone, and tolcapone. COMT inhibitors decrease the degradation of levodopa and extend its half-life, thus relieving the end-of-dose wearing-off effect and reducing “off” time. Compared with placebo, adjuvant COMT inhibitors reduced “off” time and levodopa dose and modestly improved motor symptoms and disability in PD.³¹ The use of tolcapone has been associated with potentially fatal hepatotoxicity in rare cases and is not routinely used now.¹⁴

Amantadine

Amantadine is an N-methyl-D-aspartate receptor inhibitor. It was originally used as an antiviral agent. It has a modest effect on all features of the disease and has a low adverse effect profile.² It has been shown to improve akinesia, rigidity, and tremor in patients with PD, although rigorous studies are lacking.³²

Motor fluctuations with levodopa and their management

Motor fluctuations include wearing off, dyskinesias, random freezing, nocturnal akinesia, early morning akinesia, “off” period freezing, early morning dystonia, dose-related “off” period dystonia and dose-related “on” period dystonia.² Risk factors for motor complications include younger age at onset of PD, disease severity, need for higher levodopa dosage and longer disease duration.³³ Motor fluctuations and dyskinesias can be resistant to medical therapy. Entacapone and rasagiline should be offered to reduce off time.³³ Other drugs such as pramipexole, ropinirole, tolcapone, apomorphine, selegiline and amantadine may be considered to reduce off time.³³ The available evidence does not establish superiority of one medication over another in reducing off time.³³ Sustained-release preparations add no benefit for motor complications compared with immediate release preparations, nor is there a difference in rate of motor complications.² Deep brain stimulation of the subthalamic nucleus may be considered to improve motor function and reduce off time, dyskinesias, and medication usage.³³ Preoperative response to levodopa predicts better outcome after deep brain stimulation.³³

OTHER PHARMACOLOGIC AGENTS

Apomorphine

This is a short-acting dopamine D1 and D2 receptor agonist and was the first dopamine receptor agonist used to treat Parkinson's disease.³⁴ Apomorphine has a rapid onset of action qualitatively comparable to that of levodopa.³⁵ It is indicated for the management of sudden, unexpected and refractory levodopa-induced 'off' states in fluctuating PD.³⁴ Although several routes have been tried, subcutaneous administration is so far the best and most frequently applied.³⁵ Subcutaneous apomorphine can be used either as intermittent rescue injections or continuous infusions. Adverse events consist predominantly of cutaneous reactions and neuropsychiatric effects. The incidence of adverse events is higher in patients receiving continuous infusion than in those receiving intermittent pulse administration.³⁴

Coenzyme Q10

A recent study of Coenzyme Q10 (CoQ10) supported its possible neuroprotective role in neurodegenerative diseases, including the MPTP model of Parkinsonism.³⁶ On the other hand, three prior studies have shown limited utility of CoQ10 in neuroprotection (as compared with levodopa).³⁷ The definitive role of CoQ10 in PD is yet unanswered.

MANAGEMENT OF CONCOMITANT NEUROPSYCHIATRIC ISSUES

Depression, psychosis, and dementia are commonly associated with PD as described earlier. It is imperative to screen for these problems and treat as indicated.

Amitriptyline is effective in treating depression associated with PD.³⁸ Anti-cholinergic side effects, especially problems with tricyclics, are an important consideration in the PD population due to potential worsening of cognition, and orthostatic hypotension increasing the risk of falls. Clozapine improves psychosis and results in improved motor function in some cases. Quetiapine also improves psychosis in PD. However, olanzapine probably does not improve psychosis and worsens motor function.³⁸ In a randomized, multicenter, double-blind, placebo-controlled trial, rivastigmine produced moderate but significant improvements in global ratings of dementia, cognition (including measures of executive function and attention), and behavioral symptoms, among patients with dementia associated with PD.¹⁷ The magnitude of the benefit is modest and tremor may be exacerbated.³⁸ For patients with PD dementia, donepezil is also modestly effective in improving cognitive function.³⁸

PHARMACOLOGIC TREATMENT OF OTHER NON-MOTOR SYMPTOMS

Constipation

Patients should be advised to increase fluid and fiber intake; increase physical activity; discontinue anticholinergics; and use stool softeners, lactulose, mild laxatives, or enemas as needed.³⁹

Dysphagia

In symptomatic patients, swallowing evaluation should be performed; attempts should be made to increase "on" time (the period when symptoms are decreased) and patients should be encouraged to eat during this time; patients should eat soft foods. Gastrostomy should be considered in severe dysphagia.³⁹

Orthostatic hypotension

Antihypertensive medications should be discontinued; the head of the patient's bed should be elevated, and patients should rise slowly from a prone position; fludrocortisone or midodrine should be considered if above measures do not help.³⁹

Sleep disturbance

In patients with daytime somnolence and sleep attacks, dopamine agonists should be discontinued. In patients with night time awakenings because of bradykinesia, a bedtime dose of long-acting carbidopa/levodopa, adjuvant entacapone or a dopamine agonist should be considered. For rapid eye movement (REM) sleep behavior disorders, anti-Parkinsonian medications should be decreased or discontinued, and clonazepam should be considered.³⁹

Urinary urgency

Patients should be advised to reduce evening fluid intake; tolterodine or oxybutynin should be tried for symptomatic benefit and a urological evaluation should be sought if needed.³⁹

NEUROPROTECTIVE AND ALTERNATIVE THERAPY

Two trials (one randomized and one non-randomized) have shown that vitamin E does not delay the need for levodopa therapy. The role of riluzole and Coenzyme Q in neuroprotection is debatable and the studies were underpowered to exclude a possible beneficial effect.³⁷ Levodopa is possibly protective for at least 9 months and thus may be used as initial treatment. There is insufficient evidence to definitely decide the role of acupuncture,

chiropractic, massage, or osteopathic therapy in PD.

Various other modalities have been tried, including multidisciplinary rehabilitation, active music therapy, treadmill training, and balance training, which are effective in improving functional outcomes, but the effects are small and not sustained.³⁷

EMERGING PHARMACOLOGICAL THERAPY

Two emerging treatment approaches under investigation are adenosine A2A receptor antagonists such as istradefylline and glutamate AMPA receptor antagonists such as talampanel.²⁴ Another drug currently undergoing clinical trials is a triple monoamine reuptake inhibitor that has therapeutic potential in both Parkinson's and Alzheimer's disease (NS-2330).²⁴ Several other agents under clinical scrutiny as neuroprotectants include molecules that combine one or more of the following properties: monoamine oxidase inhibition; mitochondrial enhancement; anti-apoptotic activity; anti-inflammatory activity; protein aggregation inhibition, or neurotrophic activity.¹³

ROLE OF SURGERY IN PARKINSON'S DISEASE

Surgical treatment is becoming increasingly common in PD, mainly due to advances in neuroimaging and neurosurgical techniques.¹⁴ Procedures include unilateral pallidotomy or deep brain stimulation (DBS) of the subthalamic nucleus (STN).¹⁴ DBS essentially entails the administration of high-frequency continuous electrical stimulation to the subthalamic nucleus through a surgically implanted device. In 1995, researchers from France first reported effectiveness of high-frequency, deep-brain stimulation targeting the STN. Since then, numerous other groups have replicated the findings.³ Randomized trials of deep brain stimulation for PD by Günther et al (156 patients) and Krack et al (49 patients) demonstrated the superior efficacy of neurostimulation over best medical management in patients with advanced PD and levodopa-related motor complications.^{3,40} Another randomized control trial in patients under 75 years of age with severe motor complications of PD showed that neurostimulation of the STN was more effective than medical management alone at 6 months.¹⁴ The impact on quality of life and neurostimulation is a debatable issue.³ Complications of surgery or medication are frequent and may decrease the quality of life, despite improvement in motor signs.³ It must be realized that therapy will be acceptable to patients only if symptomatic benefits are greater than the inherent surgical risks and if it reduces the burden of disease more effectively than optimal drug therapy.³ Furthermore, this line of treatment should only

be considered at specialized centers with surgeons who are experienced in performing these procedures.¹⁴

STEM CELLS IN PARKINSON'S DISEASE

This ostensibly miracle therapy still has a long way to go. It essentially requires pluripotent embryonic stem cells which are obtained from the inner cell mass of the blastocyst stage of embryonic development.⁴¹ A variety of different treatments or "cocktails" have been devised to coax these cells into developing into a neuronal lineage and then into authentic dopamine neurons. These are then used for cell replacement therapy by transplantation into the area of the brain where DA nigrostriatal neurons have degenerated. The main road blocks in this novel field are that the trials thus far conducted all focused on delivering these neurons to the striatum, but there is still doubt about the site of introduction. Another major challenge is getting the transplanted cells to maintain their specific phenotype in large numbers and for a significantly long period of time.⁴¹

NEUROTRANSPLANTATION

Human trials of neural tissue transplantation used adult adrenomedullary tissue and human fetal mesencephalic tissue. Adrenomedullary transplantation showed little efficacy and unacceptable morbidity and mortality.⁴¹ The trials with human fetal mesencephalic tissue had more promising results, but failed to show a significant clinical benefit.⁴¹ Current goals in this field are to create authentic dopaminergic cell lines that can be used to replace the missing neurons in the nigrostriatal system, and to get those cells to persist.⁴¹

GENE THERAPY AND FUTURE LINE OF RESEARCH

Gene therapy is the 'hot' current topic that includes both potentially neuroprotective and neurorestorative functions. One of these is subthalamic glutamic acid decarboxylase gene therapy and the use of glial cell line-derived neurotrophic factor (GDNF) which is delivered intracerebroventricularly, in the form of direct delivery via infusions into the basal ganglia and the use of viral vectors.²⁴ Recently published results from the phase 1 trial of hAADC gene therapy safety showed that the gene therapy approach has been well tolerated and shows PET evidence of sustained gene expression. Initial findings demonstrated the safety of this treatment.⁴² Future strategies may also target synaptic vesicle proteins, nonsynaptic gap junction communication mechanisms, or

signal transduction systems that modulate the phosphorylation state of glutamatergic receptors.¹³

PROGNOSIS OF PARKINSON'S DISEASE

Older age at onset and rigidity/hypokinesia at presentation predict a more rapid rate of motor progression.²¹ The presence of associated co-morbidities, features of postural instability and gait difficulty, and male sex are other factors predicting a rapid rate of progression.²¹ Tremor as the initial presentation is a good prognostic factor for slower progression and a longer response to levodopa therapy. Older age at onset and hypokinesia/rigidity also predict earlier development of cognitive decline and dementia. Additionally, older age at onset, dementia, and decreased dopamine responsiveness are factors that predict an increased risk for nursing home placement and shorter survival after diagnosis.²¹

CONCLUSION

Despite advances in our understanding of PD, and development of new treatment strategies, this disease remains one of the most disabling disorders in the older population. Early diagnosis, appropriate medication selection, right dosage, monitoring and management of side effects, adequate and early use of symptomatic management, timely consideration of surgical treatment, and patient education and participation in management are likely to improve patient quality of life and outcomes.

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