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National guidelines for diagnosis and management of Parkinson's disease in Pakistan

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NATIONAL GUIDELINES FOR DIAGNOSIS AND MANAGEMENT OF PARKINSON'S DISEASE IN PAKISTAN

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INTRODUCTION TO PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease. Prevalence in people older than age 60 is approximately 1.4%.[1, 2] PD is characterized by many motor and non-motor symptoms. It presents with a range of motor symptoms usually consisting of asymmetric bradykinesia, resting tremor, and rigidity; postural instability may develop later in the course of the disease.[3, 4] However 'pre-motor' PD-a range of non-motor symptoms, particularly sleep disorders, mood disorders, impaired sense of smell, and constipation may occur up to 20 years before the onset of motor symptoms.[5] The clinical paradigm has shifted from PD being considered a pure motor or movement disorder to being recognized as a systemic synucleinopathy with many motor and non-motor symptoms and signs. The etiology of PD is largely unknown, but a combination of genetic and environmental factors is postulated. Several genes have been associated with inherited and early onset form of PD (LRK1, PINK1, Parkin, and DJ-1) but these represent only a small subset (10-15%) of all PD cases.[6] It is now known that PD can present with changes in mood, sleep, behavior, cognition and autonomic function this can initiate referrals to psychiatric, general medicine, geriatric, orthopedic and even rheumatology clinics, before neurological referral is considered. Etiology is multifactorial and is thought to be related to multiple mechanisms. Factors associated with development or Parkinsonism include exposure to oxidant toxins (e.g. pesticides, MPTP), head trauma, manganese exposure, head trauma.

General Approach to Parkinson's disease
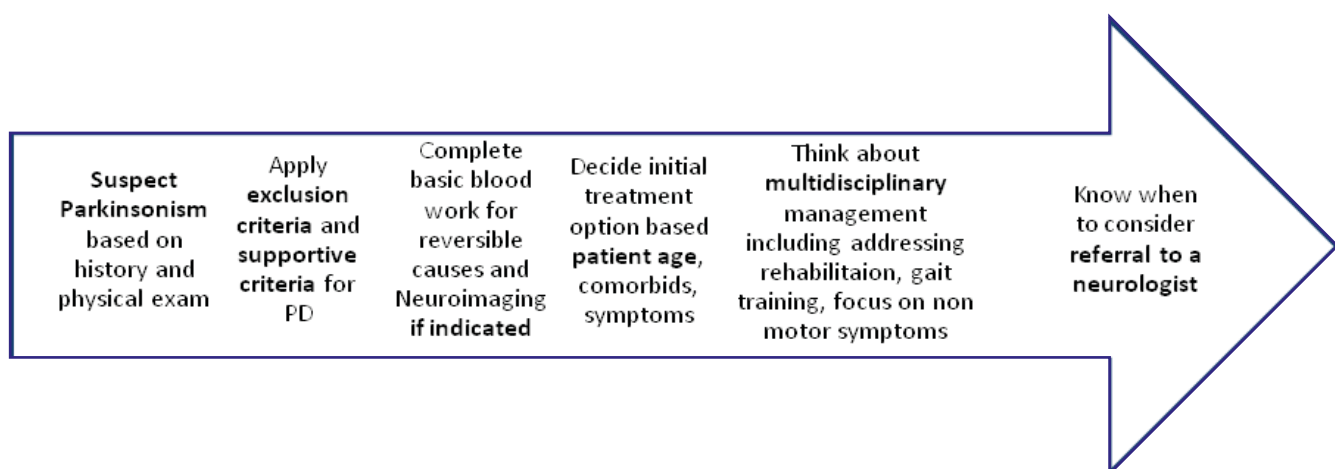
Diagnosis of Parkinson's disease

The diagnosis of PD remains primarily clinical. In 1988, Gibb and Lees developed the Queen Square Brain Bank (QSBB) criteria for PD, based on careful clinical observation combined with clinicopathological correlation. In subsequent studies it has been demonstrated to have up to 90 % accuracy in diagnosing PD when diagnosed by an experienced neurologist. This is a three step recommended strategy for diagnosis of Parkinson's disease.

UK Queen Square Brain Bank Criteria for the diagnosis of Parkinson's disease[7]

Step 1: Diagnosis of a Parkinsonian Syndrome

Bradykinesia (slow to initiate voluntary movement with progressively reduced speed and amplitude of repetitive actions) and at least one of the following:
*   Muscular rigidity
*   Postural instability unrelated to primary visual, cerebellar, vestibular or proprioceptive dysfunction
*   Resting tremor

Step 2: Exclusion Criteria for Parkinson's Disease

History of:
*   Repeated strokes with stepwise progression
*   Repeated head injury
*   Antipsychotics or dopamine-depleting drugs
*   Definite encephalitis and/or oculogyric crisis on no drug treatment
*   More than one affected relative (Note: this exclusion criteria is usually ignored)
*   Sustained Remission
*   Negative response to large doses of levodopa (if malabsorption excluded)
*   Strictly unilateral features after 3 years
*   Other neurological features: supranuclear gaze palsy, cerebellar signs, early severe autonomic involvement, Babinski's sign, early severe dementia with disturbance of language, memory or praxis
*   Exposure to Neurotoxin
*   Presence of cerebral tumour or communicating hydrocephalus on neuroimaging

Step 3: Supportive Criteria for Parkinson's Disease

Three or more of the following are required for the diagnosis of definite Parkinson's disease
*   Unilateral onset
*   Rest tremor present
*   Progressive disorder
*   Persistent asymmetry primarily affecting the side of initial onset
*   Excellent response to levodopa (70%–100%)
*   Severe levodopa-induced chorea
*   Levodopa response for more than 5 years
*   Clinical course of over 10 years

Work up of Parkinsonism at Initial Presentation

In patients with a clear clinical diagnosis and no atypical signs the physician may decide not to order blood tests or neuroimaging studies. There is no definitive diagnostic test for PD. These tests are performed to diagnose other conditions that may present like Parkinson's disease.

Complete History and Physical Examination	• Look for cardinal signs and symptoms of parkinsonism • Address factors in history and on exam suggestive of PD mimics
Routine Blood work	• Complete Blood count • Calcium • ESR • TSH • Vitamin B12 • Ceruloplasmin,
Neuroimagimg	• MRI brain with diffusion weighted, T2 FLAIR, and susceptibility weighted images • This may be suggestive of structural causes of parinsonism • Classic Findings in Parkinsons Plus syndromes

[9-11]
Parkinson's disease Mimics

Once structural, infectious, toxic and metabolic causes of Parkinsonism have been excluded, the evaluating physician must consider features of the patient's history and physical examination that may suggest an alternative cause for the symptoms. A diagnosis of idiopathic PD should be assumed only after ruling out PD mimics such as other tremor disorders, drug-induced Parkinsonism, vascular parkinsonism, normal pressure hydrocephalus and parkinsonism-plus conditions. The following table outlines features that may help in the differential diagnosis of these conditions:[3]

Parkinson's disease more likely	Alternative diagnosis more likely
Slow onset and progression of symptoms over months and years For example a 55 year old man presenting with slowly progressive difficulty using left hand with a mild tremor at rest over the past year	Sudden onset or rapid progression over days and weeks should suggest an alternative diagnosis such as a stroke, brain tumour or TB meningitis
Unilateral disease or significant asymmetry on signs and symptoms in the beginning of the disease	Symmetrical onset more commonly is associated with other Parkinsoniansyndromes such as Diffuse Lewy Body disease, Multisystem Atrophy, Progressive Supranuclear Palsy etc.
Tremor: Tremor usually involves extremities and, less commonly the jaw. Head tremor is almost never present in idiopathic PD. 25% of Parkinson's patients may never manifest a tremor. The classic tremor in Parkinson's disease is a slow resting (low frequency) pill-rolling tremor best seen when the hands are at rest or while the patient is walking.It decreases with activity and can be suppressed temporarily by the patient. Re-emergent tremor: Tremor tends to diminish at least temporarily once the patient is asked to stretch out the arms and may return as this becomes the new rest position. Onset of tremor is generally unilateral and over time may involve the other side	**Tremor:** Enhanced physiologic tremor: Tremor related to anxiety is present in outstretched hands and throughout the range of motion. Benign essential tremor is more prominent when the patient stretches out his hands as it is predominantly a postural tremor. Benign essential tremor often involves the head causing a side-to-side or up/down tremor (a 'no-no' or 'yes-yes' tremor).). It can affect the voice, is worsened with activity and is often familial. Parkinson's plus syndromes are less likely to have a tremor at presentation.
Responsive to Levodopa	Lack of robust response to Levodopa
Autonomic symptoms include urinary urgency, orthostasis	Early onset of multiple autonomic symptoms suggest MSA
Bulbar involvement is possible	Predominant early bulbar signs suggest a Parkinson's Plus syndrome like PSP
Falls occur late after significant rigidity or bradykinesia develop	Frequent falls early in the course of disease suggests a Parkinson's Plus syndrome like PSP
Non motor symptoms may include constipation, anosmia, insomnia and depression.	
Lack of eye movement restriction except there may be some impairment of conjugate upgaze and convergence	Vertical gaze palsy in which initial abnormality is impairment of downgaze with intact oculocephalic maneuver suggests PSP
Lack of early respiratory muscle compromise	Stridor/strangulated dysarthria suggests MSA
	Chronic history of neuroleptic use or antiemetic use suggests a medication induced parkinsonism

Table 1
Neuroimaging in Parkinson's disease and Parkinson's Plus Syndromes

Idiopathic Parkinson's Disease	• Loss of normal Substantia Nigra signal • Loss of red nucleus Signal on MRI
Multiple System Atrophy	•. Cerebellar Atrophy • T2 hyperintensities in pontocerebellar fibers (Hot cross bun sign) • T2 hypointensities in the striatum,
Progressive Supranuclear palsy	•Midbrain Atrophy •Humming bird sign •Dilated third ventricle

In a patient with classic features of Parkinson's disease, and absence of red flags for atypical Parkinsonism, neuroimaging is not indicated initially. If the patient subsequently develops any atypical features, then brain MRI without contrast can be considered [10, 12] Treatment of Motor Symptoms in Parkinson's disease PD is the only common neurodegenerative condition in which effective long-term treatment is readily available. Special care needs to be exercised in treating PD as both under treatment and over treatment can worsen a patient's condition and may even accelerate the progression to disability. The key is to treat the patient appropriately and not to under or over treat. This implies a level of treatment that relieves symptoms to the point that the patient has a fairly good quality of life. The physician needs to explain to the patient early on that PD is an incurable but treatable disease that will require a lifelong patient-physician partnership. The objectives of optimal treatment should be clearly explained. The objectives should be to treatment to a point that the patient is adequately functional and has a good quality of life. The first step in managing PD is to determine whether treatment is needed or not. It is important for the physician to partner with the patient and the family to treat PD. The treatment usually results in many years of a productive and functional life. In many patients the disease does progress and the symptoms become refractory to the treatments. Patients with social or functional impairment should be initiated on treatment and almost all patients that present to a physician require some form of treatment. The most obvious motor symptom for many patients is tremor, which is socially distressing; however the tremor often does not impair function if it is not severe. Rigidity, bradykinesia and in later stages postural instability are frequently greater sources of functional impairment. [30] The first step in managing a diagnosed case of PD is to determine whether treatment is needed or not. It is impor-

tant for the physician to partner with the patient and the family to treat PD. It is important that the patient understands that the treatment will allow for many years of very adequate function but that the disease is progressive and incurable. Any patient with social or functional impairment should be initiated on treatment. Almost all patients that present to a physician require some form of treatment. The most obvious motor symptom for many patients is tremor, which is socially distressing; however the tremor often does not impair function if it is not severe. Rigidity, bradykinesia and in later stages postural instability are frequently greater sources of functional impairment. [13]

Overview of Pharmacologic Therapy for Motor Symptoms in Parkinson's disease [9, 13-17]

Pharmacologic treatment options include: Carbidopa/levodopa; sooner or later virtually all patients with PD will require carbidopa/levodopa. Dopamine agonists (although not as effective ascarbidopa/ levodopa, carry an advantage of delaying motor fluctuations and dyskinesias, especially in younger patients) [35]. Monoamine oxidase type B inhibitors (symptomatic improvement is modest with these); these are rasagiline and selegiline)[36]. Anticholinergics (eg procyclidine and trihexyphenidyl). These predominantly improve the tremor, drooling and urinary frequency. These are associated with many adverse effects, which may be particularly severe in the elderly and include urinary retention, constipation, blurred vision, dry mouth, confusion, and orthostatic hypotension)[34,37]. Amantadine [38] may reduce dyskinesias very effectively and can also help tremor and fatigue. COMT inhibitors (entacapone, tolcapone)[39]; prolong the half-life of carbidopa/levodopa and make it last longer and make it more effective.

Carbidopa/ levodop

A variety of pharmacologic and non-pharmacologic treatments are effective in treating PD. The cheapest and the most effective medication is still carbidopa/levodopa. Common adverse effects include nausea and light headedness. In the past there was concern about potential neurotoxicity and acceleration of underlying disease associated with use of carbidopa/levodopa but this concern has been laid to rest. Recent studies reveal earlier use of carbidopa/levodopa does not accelerate progression of PD. Peak-dose dyskinesia (involuntary-dance like movements) may develop after several years of using carbidopa/levodopa in younger patients and patients on high doses. This is one reason why many neurologists would prefer to avoid carbidopa/levodopa as first line treatment in the younger (<60 years age) patient and initiate treatment with a dopamine agonist and rasagiline instead. In individuals already on carbidopa/levodopa, shortening the interdose interval and reducing individual doses may reduce the severity and even postpone development of motor fluctuations and complications [40]. In Pakistan the available formulation of levodopa contains 250 mg levodopa in combination with 25 mg of carbidopa. This may not be the optimal formulation to be given in the earlier stages of PD. Using a 25 carbidopa/100 levodopa formulation (available as imported medicine) or quarter or half of the 25/250 pill may be better.

Dopamine Agonists

Dihydroergocryptine, pergolide, pramipexole, ropinirole, piribedil, rotigotine, bromocriptine, cabergoline and lisuride are the dopamine agonists used in PD. Ropinirole is the most widely available and frequently used dopamine agonist in Pakistan. There is no particular difference in efficacy between different dopamine agonists, so physicians should familiarize themselves with the dosage titration and potential adverse effect of one of them. Ergot-based dopamine agonists, such as bromocriptine, are still used in Pakistan but should be avoided due to the associated high frequency of cardiac valvular, peritoneal and pleural fibrosis. Common adverse effects of dopamine agonists include: Sedation (may be severe and cause sleep attacks that may be sudden and severe enough to cause car accidents). Confusion, disorientation, hallucinations, delusions, psychosis and hallucinations. Postural hypotension and nausea. Impulse control disorder; this can consist of pathological gambling, hypersexuality, compulsive eating, compulsive shopping, compulsive hobbying.

Response to Treatment as Parkinson's disease Progresses

As PD progresses the response to treatment varies. Early Parkinson's disease; The early stage of PD is also called the "honeymoon period" when symptoms respond well to a variety of treatments and there is a sustained response to single doses of medications. [41] Late Parkinson's disease; As PD progresses, the response to dopamine therapy becomes less sustained, probably as a consequence of the loss of dopaminergic neurons. Motor fluctuations develop and the addition of MAO-B inhibitors or COMT-inhibitors may then be considered. These agents increase the potency of levodopa and prolong its effect by inhibiting the metabolic breakdown of levodopa and increasing its bio-availability. If given in combination with Carbidopa/levodopa they help to decrease off-time and prolong the on-time. MAO-B inhibitors include selegiline and rasagiline. This class of drug produces modest symptomatic benefit but has not been shown to delay motor complications. A rare adverse effect of selegiline but not rasagiline is precipitation of a hypertensive crisis if consumed with tyramine containing foods. COMT-inhibitors includeentacapone and tolcapone. COMT-inhibitors produce moderate improvement in motor symptoms. Entacapone in combination with levodopa shows minimal delay in onset of motor complications (dyskinesia). Tolcapone comes with a black box warning for fulminant liver failure, which may be fatal.

Treatment of Parkinson's disease based on Patient's Age
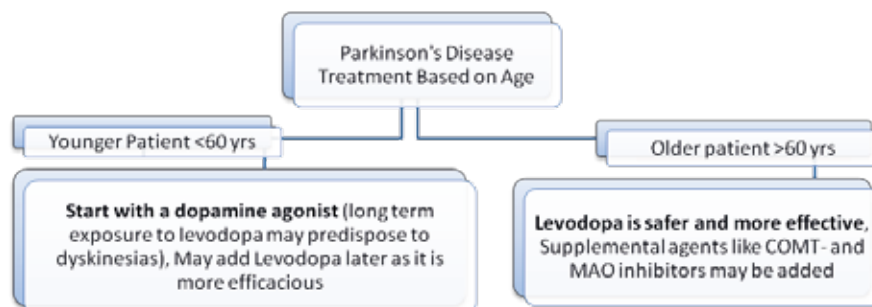
In patients older than 60 years of age who present with symptoms, consider starting with carbidopa/levodopa as it is more effective and generally better tolerated. In younger patients (<60 years) it may be better to start with one of the dopamine agonists in order to delay the dyskinesias that may occur with Carbidopa/levodopa therapy, particularly in the young PD patients. Eventually even the younger patients may require Carbidopa/levodopa as the disease progresses and a more potent medication is needed.

Table 1; Characteristics of commonly used medications for motor symptoms in PD [19]

Drug Class	Indication	Impact on Motor symptoms	Important Adverse Effects
Levodopa	First line therapy in patients over 60 years of age	Excellent	Motor fluctuations Dyskinesia
Dopamine Agonists	First line therapy in younger patients or add on to carbidopa/levodopa	Moderate	Sedation/sleep attacks Impulse control disorder Pedal edema, Weight gain
MAO-B Inhibitors	First line for mild disease with depression. Add on therapy for motor fluctuationsto carbidopa/levodopa	Limited	Serotonin syndrome and hypertensive crises may rarely occur Narrow therapeutic window
COMT inhibitors	Add on therapy for motor fluctuations	Improves wearing off of Carbidopa/levodopa	Diarrhea
Anticholinergics	Limited use. Only improves PD tremor	Limited	Confusion, Dry eyes/mouth Urinary retention, Constipation
Amantadine	Reduces dyskinesias and can improve wearing off symptoms	Limited	Confusion Lividoreticularis Pedal edema

Table 2 [3]
Relative Efficacy Profile

Factors affecting treatment choices	Levodopa	Dopamine Agonists	MAO-B Inhibitors	COMT Inhibitors
Efficacy on motor symptoms	High	Moderate	Low	Moderate
Ease of Use	Low	Moderate	Moderate	Low- Moderate
Risk of inducing motor complications	High	Low	Low	Low

Table 3 Relative Cost of Different Medications (as listed in Pharma guide 2014, electronic version)

Carbidopa/ levodopa 25/250 mg	Name of company	Price in PKR /tablet	Rasagiline 1 mg	Name of company	Price in PKR /tablet	Ropinirole 1 mg	Name of company	Price in PKR/tablet
Aptidopa	aptcure	8	Alzilo	Searle	19.20	Propinol	Shrooq	9.50
Dopasel	kurative	8	Rasagin	HiranisPharma	11.40	Reol	Genome	16,66
Meddopa	medera	8				Requip	GSK	34.28
Neudopa	Platinum	8	Amantadine 100 mg	Name of company	Price in PKR /tablet	Ronirol	Hilton	21.19
Sinedopa	Valor/Al-Hameed	9	Amantin	Gene-Tech	11.35	Ropinol	Amarant	24,33
Sinemet	OBS	14.61	PK-Merz	Brookes	15.60	XMG	Atco	12
			Viofral	Biocare	13.25			

Table 4
Titration Template for Commonly Used Medications for Motor Symptoms in Parkinson's disease [19, 20]

Medication	Start of titration	Weekly up-titration	Maintenance dose	Daily dose
Carbidopa/levodopa	50 mg AM	50 mg Q3day	3-4 x 100 mg	300-800 mg
Pramipexole	3x0.088 mg	2nd week 3x0.18mg		
		3rd week 3x0.35mg		
		Then weekly 3x0.18 mg	3x0.35-0.7 mg	1.05-3.3 mg
Pramipexole ER	0.25 mg AM	2nd week 0.52 mg	1x 1.05-2.1 mg	1.05-3.15 mg
		3rd week 1.05 mg		
		4th week 2.1 mg		
		5th week 3.15 mg		
Ropinirole	1 mg AM	Weekly 1mg	3x 3-8 mg	6-24 mg
Ropinirole ER	2 mg AM	2 mg	6-24 mg	6-24 mg
Rotigotine Patch	2mg/24h	2mg/24 hr	4-8 mg/24h	8-16 mg/24h
Piribedil	50 mg HS	50 mg every 2 weeks	2-3 x 50 mg	150-250 mg
Selegiline			5-10 mg	5-10 mg
Rasagiline			1 mg	1 mg
Entacapone	50 mg AM	50 mg every 3 days	3-4 x 100 mg	600 mg
Tolcapone	100 mg AM		2-3 x 100 mg	600 mg
			at 6-12 hour intervals	
Amantadine	100 mg AM	100 mg q3days	1-3 x 100 mg	100-400 mg

Deep Brain Stimulation in Parkinson's disease [21]

Deep brain stimulation of the sub thalamic nucleus or globus pallidus internum is used in the treatment of motor symptoms of PD. There are multiple theories to suggest the mechanism of action including a micro-lesioning effect, resetting of aberrant pathways and circuits and modulating excito-toxicity.

Deep brain stimulation of the subthalamic nucleus or globus pallidum may be considered in the following situations.

- Medication refractory disabling tremor.
- Carbidopa/Levodopa responsive disease.
- Motor fluctuations (on-off fluctuating motor symptoms that require high doses of medications that need to be given very frequently.
- Disabling dyskinesias.
- Patient does not have dementia or severe depression.

Axial and autonomic symptoms and freezing of the gait usually does not get better with this surgery. The surgery should only be done by high trained and experienced Parkinson's disease surgeons and after the surgery the medications and the stimulator needs to be adjusted by experienced Parkinson's disease neurologists. It requires life-long management by these teams and if not done and managed properly can often make the condition of the patient worse after the surgery.

Treatment of Non-Motor Symptoms in Parkinson's Disease

Non-motor symptoms are a major contributor to impaired quality of life of patients suffering from PD. [5] However, these symptoms are often neglected during evaluation and treatment. Non-motor symptoms are often easily treatable, but lack of attention to them may make treatment of motor symptoms more difficult.[12] Non-motor symptoms include behavioral symptoms like depression, anxiety and psychosis, sleep disorders, dementia, dysautonomia (dysphagia, drooling, constipation, urinary urgency and frequency, orthostatic hypotension) and sensory symptoms (pain, Restless Legs Syndrome, numbness, joint stiffness in the limbs affected by the symptoms, etc). Non-motor symptoms can precede motor symptoms by years.

Sleep Disorders:

These include rapid eye movement (REM) sleep behavi or disorder (acting out dreams), insomnia, restless legs syndrome (RLS), and poor sleep maintenance. Usually the history provides the diagnostic clues needed to address sleep issues. Insomnia can be related to lack of dopamine or underlying anxiety/ depression. Nocturia may disturb the normal sleep pattern and may be due to an over active bladder or an underlying sub-clinical urinary tract infection.. Dopaminergic drug-wearing-off may contribute to poor sleep and this may require a bedtime dose of a long acting dopaminergic agent. Restless legs syndrome is commonly associated with Parkinson's disease and can be readily diagnosed and treated. RLS presents with restlessness, pain, cramps or vague discomfort in the legs upon rest, particularly after laying down to sleep at night. The symptoms improve upon movement, such as moving the legs or getting up and walking, but symptoms often return once the patient is recumbent again. RLS is associated with involuntary leg movements as well, which can occur during wakefulness or sleep. RLS symptoms should trigger a search for underlying iron deficiency, which should then be treated with iron replacement and Vitamin C which may facilitate its absorption. If iron deficiency is not present, RLS responds well to dopaminergic agonists such as ropinirole, typically administered 2 hours before bedtime. Gabapentin, pregabalin and tramadol also are effective REM sleep behavior disorder includes a variety of presentations wherein patients may seem to be acting out dreams. Questioning the family members may reveal the patient has been talking in their sleep or even thrashing around and acting out physical fights while asleep (which may result in injuries). Always screen for REM sleep behavior disorder as it is a treatable condition.[22-25] It is usually responsive to a low dose of clonazepam.

Depression And Anxiety:

Mood disorders are common in Parkinson's disease and are frequently under-recognized and under-treated. PD patients with depression may be difficult to motivate to engage in regular exercise and in rehabilitation programs. They also are more likely to be noncompliant with treatment. Serotonin specific reuptake inhibitors (SSRI's) often are effective in usual doses and can greatly improve the quality of life of the patients. Episodic shortness of breath and sweating are often seen with advancing Parkinson's disease and may or may not respond to dopaminergic medication. These resemble panic attacks.[17,18]. Anxiety can be a non-motor component of PD and although it perhaps most often appears as a wearing off phenomenon, it also can present as a more pervasive sense of anxiety in some patients. It can often be treated by giving the dopaminergic medications more frequently at lower doses.

Dementia:

PD dementia may develop in people after several years

and correlates with the presence of subcortical and cortical Lewy bodies. Environmental modifications are the best tolerated interventions. Try to minimize changes to routine, provide familiar things and memory cues to minimize agitation.

Discontinue potential aggravators:

Anticholinergics, amantadine, tricyclic antidepressants, tolterodine and oxybutynin, benzodiazepines. If treatment becomes necessary, the addition of a cholinesterase inhibitor, such as rivastigmine, donepezil or galantamine may be considered. Memantine also may be tried.[26, 27]

Psychosis:

Symptoms of psychosis, such as hallucinations, delusions, and illusions, are complications of therapy and also may arise from the progression of the disease process. When they occur, it is important to first correct any metabolic abnormalities or fluid imbalance and to treat any infection. It is important to minimize polypharmacy. Decreasing or stopping non-levodopa medications and optimizing levodopa can improve psychosis. Antipsychotics may be needed, but those that are potent dopamine depleting drugs can worsen Parkinsonism, especially the typical antipsychotics. Quetiapine is a sedating antipsychotic that does not appear to worsen the motor symptoms of Parkinson's disease. However as with other atypical antipsychotics, there may be a small risk of cardiac complications and therefore its use requires considering the risks and benefits for each individual patient.

Urinary Urgency, Frequency and Nocturia:

These are common autonomic symptoms in PD. Recognizing and treating sub-clinical urinary tract infection is very important. Initial treatment may involve reduced intake of fluids after 6 pm and no caffeinated drinks after 12 noon. If that is not sufficient, then anticholinergic medications may help. Anticholinergics that do not cross the blood brain barrier are better, since these do not worsen cognition. Tolterodine (2 mg twice daily) can be considered for these symptoms. Botulinum toxin type A injected in the detrusor muscle can also help but is a very expensive form of treatment that should be given only by trained physicians.[22,23]. For patients who cannot tolerate medications, diapers and bedside urinals should be available for patients.

Dysphagia:

Multiple factors contribute to dysphagia in PD. Optimization of motor control with dopamine replacement therapy may be helpful. Speech therapy is important along with assessment of swallowing and advice regarding the prevention of aspiration. Enteral feeding options (short-term nasogastric tube or percutaneous endoscopic gastrostomy) may be needed in advanced cases. [24]. Eating pureed and soft foods with the head slightly bent may be better and extra care with thin fluids like water and tough foods like meat that are more likely to cause dysphagia is important. Pills can be also be crushed and administered with yogurt to facilitate swallowing.

Orthostatic hypotension:

This is very important to recognize, prevent and treat as it can cause dizziness, fainting spells and falls. This is aggravated by volume depletion, diuretics, antihypertensive drugs, tricyclic antidepressants, nitrates and alpha-blockers used to treat prostatic hypertrophy. Dopaminergic drugs also may induce orthostatic hypotension. It improves with increased salt intake. Elevating the head-end of the bed at night $^{(30-40°)}$ may be helpful, as may wearing of waist-high elastic-pressure stockings and/or abdominal binders (if weather allows). Changing positions slowly and exercises of the legs (leg crossing, toe raising, and thigh contraction) before sitting up and standing can help. If all of these are unsuccessful, medications, such as midodrine or fludrocortisone, may be necessary. [25,26]. Domperidone can block the peripheral effect of the dopaminergic medications and can help as well.

Constipation:

Constipation is a manifestation of general bradykinesia and autonomic dysfunction in Parkinson's disease. This is a common problem aggravated by poor oral intake of water/fiber. Bowel dysfunction has two components decreased bowel movement frequency and difficulty with the act of defecation. Decreased bowel movement frequency results from slow colon transit and the difficulty with the act of defecation is due to impaired coordination and relaxation of the anorectal muscles. Slow transit constipation often responds to increasing water intake, fiber (ispaghula husk) and regular use of Milk of Magnesia or lactulose. Defecatory dysfunction usually does not respond to these interventions.

Drooling:

Drooling is another common and distressing symptom. Drooling is typically due to impairment of the swallowing mechanism rather than overproduction of saliva and may improve with chewing gum or sucking on honey or ice. Drooling may require use of anticholinergic agents or botulinum toxin injections into the salivary glands [19].

However anticholinergics should generally be avoided in the elderly patients and those with cognitive impairment as they can result in confusion, hallucinations, blurring of vision, constipation and urinary retention.

Pain and Dystonia:

Patients with PD suffer from pain related to multiple pathogenic mechanisms, including central and peripherally mediated pain. Some of this may be related to immobilization from bradykinesia or dystonia. Exercise, physical therapy, pain management and botulinum toxin injections for dystonia may improve the quality of life of the patient.[28-30]

When to Refer to a Neurologist

Primary care providers can diagnose and treat Parkinsons however consider referring to a neurologist if diagnosis is not clear; difficulty in managing or complications with management; suboptimal response with management options

Importance of Multidisciplinary Care in the Management of Parkinson's disease

Effective management of PD not only includes management of motor and non-motor symptoms but also addressing multiple areas of rehabilitation and improving the quality of life of the individual as a whole. There is a significant role for speech therapy, swallow evaluations, physical therapy, exercise and gait training from the time of diagnosis. Counseling patients and discussing possible modifications to their life style and home set-up in anticipation of expected disease progressionsoare important. There is increasing data to suggest that exercise is neuroprotective for Parkinson's disease, may improve executive function and slow progression of motor symptoms. SPARX trial and other smaller studies show that exercise improves motor scores in patients with Parkinson's disease hence reducing falls and improves quality of life.[31-44] Levodopa therapy is related to increase homocystine due to its metabolism by COMT enzyme. This theoretically increases the risk of stroke in patients suffering from Parkinson's treated with levodopa. It might be reasonable to treat prophylactically with Vitamin B 12, folate, Vitamin B6.[45] Rehabilitation measures are focused towards improving mobility and preventing fall-related morbidity. The team caring for a PD patient should ideally be a combination of a physician, speech therapist, occupational therapist and physical therapist.[13, 46, 47]

Fall prevention in Parkinson's Disease.

Gait Training: Take larger steps and make larger truns

↓

Home modifications; - Imporve lighting. - Remove rugs and minimize clutter. - Avoid slippery surfaces

↓

Careful selection of gait aid: Usually walker better than cane

↓

Most Falls occur during Freezing: Use Laser pointers or visual cues to help re-initiate gait

↓

Always consider an early referral to Physical medicine

↓

Work closely with the family and care takers

[48, 49]
Resources and Support for Patients with Parkinson's disease
There are many global patient education and advocacy forums where patients may be referred for information and counseling.
Pakistan Parkinson's Society
American Parkinson's Disease Association www.apdaparkinson.org
National Parkinson Foundation. www.parkinson.org
The Michael J. Fox Foundation for Parkinson's Research www.michaeljfox.org
World Parkinson Congress. www.pdf.org/world_parkinson_congress