Parkinson's disease: a review

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1. ABSTRACT

Parkinson's Disease is the second most common progressive neurodegenerative disorder affecting older American adults and is predicted to increase in prevalence as the United States population ages. Resulting from a pathophysiologic loss or degeneration of dopaminergic neurons in the *substantia nigra* of the midbrain and the development of neuronal Lewy Bodies, idiopathic Parkinson's Disease is associated with risk factors including aging, family history, pesticide exposure and environmental chemicals (e.g., synthetic heroin use). Its ultimate cause(s) is (are) unknown. Characterized by both motor and non-motor symptoms, PD patients classically display rest tremor, rigidity, bradykinesia, and stooping posture. PD can also be associated with neurobehavioral disorders (depression, anxiety), cognitive impairment (dementia), and autonomic dysfunction (e.g., orthostasis and hyperhidrosis). Recent decades have witnessed a proliferation of medical pharmacologic therapies and innovative surgical interventions like deep brain stimulation (DBS). However, definitive disease-modifying therapy is still lacking. Experimental therapies are being developed and tested with limited results. Knowledge of strategies to promote optimal quality of life for PD patients is of paramount importance for caregivers, health providers and patients themselves.

2. INTRODUCTION AND EPIDEMIOLOGY

Parkinson's disease (PD) is an idiopathic disease of the nervous system characterized by both motor and non-motor system manifestations. It is a chronic progressive neurodegenerative disorder that occurs mostly in older persons but that can appear in much younger patients. It is the second most common neurodegenerative disease (1). Other neurodegenerative disorders can mimic idiopathic PD. These include Dementia with Lewy Bodies (DLB), Corticobasal Degeneration (CBD), Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP). The major focus of this review will be idiopathic PD and not these other parkinsonian-like syndromes.

Parkinson's Disease has been recognized since the early 1800's when the physician after whom the disease is named first described it. Sometimes called "paralysis agitans," PD is uncommon in young people, especially those under 40 (2). As many as one million Americans are affected by PD and nearly 60,000 new cases are diagnosed each year. Worldwide, an estimated 7 to 10 million people are thought to be affected. Men are 1.5 times more likely to have PD than women (3).

A population-based study of US Medicare beneficiaries found a mean prevalence of 1.6% for PD

among persons 65 years and above. Less blacks and Asian Americans are affected than whites. Higher rates of PD are existent in the Midwest/Great Lakes region and the northeastern US seaboard. Exposure to environmental toxins in these areas is suggested to be a possible etiologic factor (4, 5).

The prevalence of PD is expected to rise dramatically over the next 20 years as Americans age. Consequently, it will continue as an important health issue and strong economic drain due to its direct and indirect costs (1). The economic and human burden may prove to be substantial especially in developed nations where average lifespans are continuously increasing (6).

3. PATHOPHYSIOLOGY

The pathological definition of PD is loss or degeneration of the dopaminergic (dopamine-producing) neurons in the *substantia nigra* and development of Lewy Bodies (a pathologic hallmark) in dopaminergic neurons (7). Pathologic changes may precede obvious symptoms by two decades or more (8). This preferential loss of dopamine producing neurons results in marked impairment of motor control. Lewy Bodies, or abnormal intracellular aggregates, contain various proteins including alpha-synuclein and ubiquitin that impair optimal neuron functioning.

Recent publications suggest that environmental stress and aging itself may promote neuropathology. Specifically, exposure to environmental toxins (e.g., pesticides) (9), drugs of abuse, or the stress of the aging process promotes a chronic low-level inflammation in the brain ("Inflammaging"). This inflammatory process over time generates cellular senescence in brain neurons (6, 10).

From a pathologic perspective, the brain's substantia nigra pars compacta and the pontine locus ceruleus are affected by typical abnormalities of PD patients including depigmentation, neuronal loss and gliosis. By the time PD symptoms occur, about 60-70 percent of the neurons in the substantia nigra pars compacta are gone (11, 12).

Genetic nutations that code proteins of the central nervous system play a role in neuronal death. Specifically, alpha-synuclein becomes abnormal and self-aggregates. This aggregated, insoluble alpha-synuclein is a major constituent of Lewy Bodies, cellular inclusions that are the hallmark of PD (11). In addition, systems designed to break down abnormal proteins like the ubiquitin – proteasome system also become impaired. Other impaired processes that may play a role in PD are mitochondrial dysfunction or abnormal oxidative stress through reactive oxygen species causing neuronal degeneration (11).

Some researchers use the theories of Braak and colleagues (13) to explain PD pathophysiological progression. Called the "dual-hit" hypothesis, the theory suggests that an unknown, possibly viral, pathogen enters the brain through the olfactory route. Notably, PD patients often have prodromal olfactory deficits. Or the swallowing of nasal secretions introduces the pathogen to the gut and it enters the vagus nerve and the CNS. Pathologic support for this hypothesis derives from the identification of Lewy Bodies in the intestinal structures, vagus nerve, and brain structures (4).

4. RISK FACTORS/DIAGNOSIS

Age is the most potent risk for PD (1, 7) with an average age of onset of approximately 50 to 60 years. Two other risk factors have shown to be important: family history (a genetic link) and pesticide exposure. Additional risk factors have been identified though how they may differentially affect men vs. women is still unclear (14).

Many other risk factors have been suggested though epidemiologic evidence is not as robust. These include: Use of well water, milk consumption, excess body weight, exposure to hydrocarbon solvents, living in rural areas, farming or agricultural work, living in urban areas or industrialized areas with exposure to copper, manganese and lead, high dietary intake of iron, history of anemia and higher levels of education (11).

PD diagnosis is a clinical diagnostic decision that is based upon the presence or manifestations of rest tremor, rigidity, postural instability (gait disturbance) and bradykinesia. If a patient history reveals gradual symptom progression and then he/she responds well to drug therapy with levodopa, PD is likely the correct diagnosis (8, 15).

Differential diagnosis is challenging given the fact that the classic PD symptoms (e.g., rest tremor, rigidity etc.) can be present in other neurodegenerative disorders. Careful history taking and astute physical assessment coupled with initial medical therapy (e.g., the individual's response to pharmacotherapy) are necessary to distinguish idiopathic PD from Essential Tremor, DLB, CBD, MSA, PSP, or secondary Parkinsonism due to drugs, toxins and head trauma (8, 15).

Despite decades of research, the diagnosis and management of Parkinson's disease is hampered by suboptimal methods for detection and prognosis. In other words, validated biomarkers (tests or screening mechanisms) with high sensitivity and specificity for the disease are critically needed but are currently lacking. This deficit constitutes a major research roadblock since clinical trial design demands a target or biomarker to test neuroprotective therapies (16). In addition, no single marker is presently able to predict PD progression with good reliability and validity (12).

Features that increase the likelihood of Parkinson Disease diagnosis include those associated with bradykinesia, such as micrographia, a shuffling walk, and difficulties performing motor tasks such as turning in bed, rising from a chair and manipulating objects. Conversely, other symptoms decrease the likelihood of PD including falls early in the disease, symmetric tremor at the beginning, rapid disease progression, little response to dopamine therapy, etc. (8).

Neurologic imaging plays a small role in PD diagnosis and is not used routinely. Studies like magnetic resonance imaging (MRI), ultrasonography, positron emission tomography (PET) scan, etc., lack evidence in diagnosing PD. At best they may help distinguish PD from MSA or Essential Tremor but not idiopathic PD itself (8). Despite the best of contemporary medical and surgical therapies, PD steadily worsens over time in both motor and non-motors aspects. Mortality rates are higher in PD patients versus matched controls. The mean age at death is about the same (mid-70s) regardless of age of onset and quality disease management (17).

5. CLINICAL PRESENTATION

The clinical presentation of PD represents a nexus of four major components: motor symptoms, cognitive changes, behavioral/neuropsychiatry changes, and symptoms related to autonomic nervous system failures. Individual variation affects the area(s) that become(s) more prominent. Each aspect will be discussed.

The cardinal motor features of PD are tremor, bradykinesia, rigidity and postural instability. The latter symptom develops more with disease progression over time (2). A mnemonic is sometimes used to encapsulate the major motor symptoms: T-R-A-P. It stands for **T**remors (resting), **R**igidity (possibly cogwheel jerking), **A**kinesia (or Bradykinesia), and **P**osture (stooped shuffling gait) (18). Pathological and neuroimaging studies suggest that motor signs of PD only develop when 50-70% of *substantia nigra* neurons have degenerated (12). LBD, PSP, CBD, and MSA are clinical syndromes that have differing clinical presentations from classic PD. Key differences among the disorders are discussed in these references (2, 4, 8, 15, 19) and are beyond the scope of this article.

The "pill rolling" rest tremor of idiopathic PD is most noticeable when the body part is not engaged in purposeful movement. Usually unilateral initially, PD often progresses to bilateral rest tremor overtime. Rest tremor is the presenting symptom in over 70 percent of PD patients (2). Bradykinesia or slowness of movement is often described as tiredness or weakness by patients. It is manifested in lessened finger manual dexterity shuffling steps or difficulty getting out of a chair (2). Difficulty with opening packages or containers is commonly reported. Rigidity is seen in almost all PD patients. It can begin unilaterally but moves to the other side. When joint range of motion is examined, the PD patient often demonstrates a "cogwheel" rigidity that is similar to the ratchet pattern of a gear.

Later in the disease course, patients with PD will likely display postural instability with an increased risk of falling. Falling early in the course of PD suggests another disorder such as PSP. Another manifestation may be "festination" where patients take much quicker and shorter steps, assuming a running gait. Notably, postural instability responds least well to dopamine treatments.

Interestingly a prodrome of non-motor features may precede motor symptoms of PD by many years. These include: constipation, hyposmia (altered sense of smell), REM sleep disorder, orthostatic hypotension, depression, urge urinary incontinence, and erectile dysfunction (20). Since no biomarkers exist for PD, neuroprotective agents (if they were available) cannot be used to prevent further neurodegeneration.

5.1. Motor symptoms

PD is associated with resting tremor (initially unilateral), bradykinesia (slow movements), rigidity, shuffling gait, and postural instability. The onset is insidious where individuals may attribute the symptoms to aging processes. PD symptoms are progressive but rates of motor progression are highly variable (4). Also, subtypes of PD occur wherein tremor, rigidity, or postural instability dominate (2).

In addition to the "classic" motor symptoms previously described, other motor manifestations are observed. These include masked facial expression (hypomimia), decreased eye blink rate, blurred vision, impaired upward gaze, dystonia, stooped posture, difficulty turning in bed, kyphosis, scolosis, shuffling gait, "freezing" (inability to move) and speech impairment, such as hypophonia (increasingly soft voice), or palilalia (repetition of word or phrase) (2).

5.2.Non-motor symptoms

Non-motor symptoms of PD include cognitive changes, behavioral/neuropsychiatric changes autonomic nervous system failure, sensory and sleep disturbances (21) (See Table 1). Non-motor symptoms can represent some of the greatest challenges to quality of life and appropriate management in PD since they usually do not respond to dopamine therapy as well as motor symptoms (20). Notably, a number of non-motor features can precede the motor symptoms of PD by years, even decades. However, it is known that almost 90% of PD patients experience non-motor symptoms during the course of the disease (22).

In addition to the development of non-motor symptoms of PD as a component of the disease, therapy used in PD can exacerbate or cause the symptoms. For example, psychosis, orthostatic hypotension and, sleep attacks may relate to L-dopa dosing or side effects (20). Cognitive dysfunction and dementia are common in PD, but develop over time. The dementia of PD is subcortical with altered personality, psychomotor retardation, and memory problems.

Problems with decision-making, multi-tasking, memory retrieval and visuospatial perception are present. Dementia of PD occurs later in the disease. Early onset dementia is associated with the Parkinsonian Syndrome, DLB. A six-fold increased risk for developing dementia accompanies PD (23). Dementia is more common in PD patients with a strong family association of PD. However, up to 60 percent of PD patients develop dementia within 12 years of diagnosis (8).

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Table 1. Non-motor features in PD

Category	Disorders
Autonomic Dysfunction	• Sexual dysfunction (e.g., Erective Dysfunction; Vaginal Tightness) • Swallowing Disorder • Urinary Urge/Incontinence • Constipation • Gastropatresis • Fecal Incontinence • Orthostatic Hypotension • Sialorrhea (Excessive Salivation) • Temperature Control Dysregulation Rhinorrhea
Sensory Disorders	• Pain Syndromes (Aching) • Abnormal Sensations • Olfactory dysfunction (Anosmia)
Integumentary	• Seborrhea • Malignant Melanoma • Other Skin Cancers • Drug Rashes • Amantadine (Livedo Reticularis) • Skin Denervation • Hyperhidrosis • Flush
Visual	• Diplopia • Blurred Vision • Impaired Color Discrimination
Miscellaneous	• Fatigue • Weight Gain or Loss
Neurobehavioral	• Anxiety • Depression • Psychosis/Hallucinations • Cognitive Dysfunction • Dementia • Apathy • Bradyphrenia (Slowed Thinking)
Sleep Problems	• Daytime Sleepiness and Sleep Attacks • Insomnia • REM Sleep Disorder • Restless Leg Syndrome

Compiled from: 2,4,8, 17, 21,22,27,31,33,36,45

Psychosis and hallucinations can occur in PD patients. Visual hallucinations are the most common psychotic symptom. Up to 40 percent of drug-treated PD patients demonstrate some form of psychosis. This is a serious problem as all anti-parkinsonian medications have demonstrated induction of psychosis (2).

Mood disorders such as depression, anxiety, and apathy occur in PD patients. Mood disorders have been ranked among the most troublesome non-motor symptoms in both early and late PD patients (19, 24). Anxiety is the most frequent psychiatric mood disorder in PD and occurs in about 1/3 of patients (2). Apathy (loss of motivation) and abulia (loss of ability to think or act) can also occur. Both apathy and constant anxiety seriously erode quality of life in PD patients.

Sleep disturbance is another major non-motor symptom of PD, affecting up to almost 98% of PD patients (25). Most commonly, early morning awakening and frequent waking during the night are reported. Rest tremor may act to awaken the patient during light sleep (2). Conversely, daytime somnolence is also a noteworthy problem. PD patients may be sleepy or experience "sleep attacks" (unintended sleep episodes). Whether they are due to PD or PD therapy is uncertain. Safety risks related to driving and machine operation are obvious. Fatigue can be related to sleep issues or occur independently (2). Research suggests that sleep disorders seriously lower quality of life for affected PD patients (25).

Autonomic disturbance or aberration is manifested in multiple body systems in such conditions as orthostasis, constipation, dysphagia, urinary difficulties, sexual dysfunction, fecal incontinence, and sialorrhea (excessive salivation). The risk of dysfunction increases with higher age, greater disease severity, and higher doses of dopaminergic medication (22).

Notably, the urinary difficulties that can occur in PD include such issues as urgency, frequency, nocturia, and urge incontinence. The literature suggests that urinary storage problems are more prevalent than voiding difficulties. An important differential is time of onset. Urinary symptoms are more frequent and occur earlier in MSA versus PD. From a pathophysiological perspective, the loss of dopamine plays a critical role in pathogenesis since dopamine receptors play an inhibitory and facilitative role in higher brain centers. One outcome is impaired detrusor control (26).

Non-motor symptoms have to be monitored and managed. PD patients and caregivers have to be educated about orthostasis and need for slower movement from sitting to standing and no fast turns. For constipation, an increased fiber diet with plenty of water can help with regularity. If necessary, laxatives such as polyethylene glycol (PEG) may be needed (27, 28). Nutrition support or referral may be very helpful as well (29). Dysphagia and sialorrhea may respond to speech therapy at least initially. The literature also suggests that anticholinergics like glycopyrrolate (Robinul) and botulinum toxin injections into the salivary glands may ameliorate drooling (28).

Fecal incontinence may respond to approaches for normalizing stool consistency like use of soluble fiber or foods that thicken stool. Bedbound end-stage PD patients may benefit from external fecal collection devices to protect the skin and control odor (30). Urinary dysfunction should be monitored and the urinary tract "worked up" for other disorders. Since PD most affects aged men, other urinary tract problems (benign prostatic hypertrophy, prostate cancer) may be present along with PD. Anticholinergic medications and external collecting or protective devices (high quality incontinence pads) may help with promoting better quality of life. Medical therapy for an enlarged prostate (e.g., alpha blocker or 5-alpha reductase inhibitor) may be needed. Some literature suggests that nerve stimulation (sacral or posterior tibial nerve) may produce significant improvement in urologic symptoms (26). Both fecal and urinary dysfunctions are likely related to the peripheral autonomic nervous system changes created by PD (31).

Sexual dysfunction has also been a challenge to quality of life in PD patients. For men with PD, they may develop erectile dysfunction. Treatment with agents like sildenafil may help. Sexual dysfunction in female PD patients is not well studied and good therapy therefore lacking (27).

Changes in the integumentary system due to the dopamine deficit of PD include seborrhea, hyperhidrosis (excessive sweating especially at night), and increased risk for malignant melanoma, and non-melanoma skin cancers (22, 30). The risk for melanoma and non-melanoma skin cancers has been identified for decades in PD patients. However, disagreements existed about whether these skin neoplasms were related to L-Dopa (dopamine) therapy or the disease process itself. Most research teams suggest that the increased risk is associated with PD disease process rather than its therapy (32, 33, 34, 35, 36, 37, 38, 39, 40).

The skin may be affected by PD pathomechanisms but also by drug therapy. For example, amantadine, a drug used to treat dyskinesias, is associated with a rash called livedo reticularis. Looking like a purple network, the rash usually resolves with drug cessation (30, 41). In addition, transdermal patches (e.g., rotigotine) can be associated with skin reactions. In some instances, local reactions are so severe that the drug patch must be discontinued. Most are mild to moderate in nature (30, 42, 43, 44).

Another pathological impact of PD on skin physiology is autonomic denervation of the skin. Research conducted by Dabby *et al* (45) found via the use of skin biopsy that the autonomic peripheral nervous system was denervated in the skin of 20 out of 22 PD patients. In addition, they found this denervation was occurring in early stages of the disease. These findings may explain some of the previously noted skin and autonomic changes.

Parkinson's disease skin changes need to be monitored and treated. Seborrhea, excessive oiliness of skin and hair, may need use of special dandruff shampoos, and the skin should be checked by PD patient and their caregivers for new growths.

Parkinson's disease also alters skin health processes by affecting micro RNAs (ribonucleic acids). Micro RNAs are small endogenous, noncoding RNAs that regulate protein-coding genes. Micro RNAs are involved in angiogenesis and wound healing. How PD could possibly or theoretically alter wound healing ability as the disease progresses remains to be elucidated (30).

Urinary and fecal incontinence may damage peri-genital skin if protection is not used. Frequent assessment and use of continence aids should be considered. Excellent quality barrier ointments can protect against moisture-associated skin dermatitis or incontinence-associated dermatitis (30).

Two other non-motor symptoms are frequently reported: Olfactory dysfunction and sensory symptoms of pain. Olfactory dysfunction (hyposmia) is detected in more than 90% of PD patients. Most affected PD patients are usually unaware of the deficit. Olfactory testing helps with differential diagnosis of idiopathic PD versus other Parkinsonian Syndromes (22).

Painful sensory symptoms can be localized or general and have been described as burning, tingling or lancinating (2). Estimated to affect about 2/3 of PD patients, the pain is likely due to dystonia and disease-related joint and skeletal deformities that are common in PD. Some hypothesize that there is abnormal processing of nociceptive inputs in PD patients. Health-related quality of life can be enormously affected by the chronic pain (22).

6. MEDICAL THERAPIES

Medical therapies are the mainstay of treatment for PD. They include pharmacotherapy and non-pharmacological alternative approaches such as exercise, education, support groups speech therapy and nutrition. Therapeutic approaches depend on patient's age, disease stage, troubling symptoms, and the benefit/risk ratios of treatments (34). Since pharmacotherapy for PD has increased substantively in its array of options, non-pharmacological approaches will be discussed first.

Patients with new onset PD may be frightened at the future affected by a chronic progressive disease of the nervous system. Focused education on symptoms and introduction to the disease process over time can act to decrease fear and support adaptation (46). Education about how to cope with the disorder can promote improved self-care in the long-term (29).

Non-pharmacological alternative therapies include exercise, education, support groups, speech therapy and nutrition. While not slowing the inexorable course of PD, each offers benefit to some aspects of the disease and/r deal with its pathophysiologic impact. A clear message pervades the literature about their use: Begin their usage early in the disease course (46).

Regular exercise and physical therapy can really assist with some of the bodily effects of PD such as joint rigidity and flexed posture. Exercises that target improved flexibility, strength, and balance should be emphasized. Patients may gain a sense of control over some components of the disease.

Patient and family/caregiver education is important but critically needed in a chronic progressive neurologic disease. Key to success is balancing need to know versus readiness to absorb potentially disturbing data (46). Some programs have been developed which delineate topics necessary for specific neurologic conditions like PD (29).

Support groups are used very effectively for many chronic disease patients, and PD is no exception. Support groups can allow discussion of emotional and psychological concerns for patients and their caregivers. Care has to be used in support group development. Some newly diagnosed patients may have difficulty in seeing others who had progressed further in terms of deterioration. Chaplin, Hazan, & Wilson (29) suggest that support groups cannot be solely focused on problem management

Table 2. Pharmacological therapies for Parkinson's disease

Group	Names	Mechanisms of Action
Dopamine	Carbidopa/Levodopa (Sinemet)	A dopamine precursor; crosses the blood brain barrier (BBB) and is converted to dopamine in dopaminergic terminals by dopa-decarboxilase
Dopamine Agonists Non-Ergot	Pramipexole (Mirapex) Ropinorole (Requip)	Stimulates D2, D3, D4 Receptors; weak stimulation of 5-HT2 and Alpha 2 – adrenergic receptors
Dopamine Agonists Ergot	Bromocriptine (Parlodel) Pergolide	Stimulates D2 receptors Stimulates 5HT1 and 5HT2 and NA Receptors Blockades D1 Receptors
Injectable Dopamine Agonists	Apomorphine (Apokyn)	Stimulates D2-D5 receptors Antagonizes 5HT1 and 5HT2 receptors Antagonizes Alpha-1 and Alpha-2 adrenergic receptors
Monoamine Oxidase-B Inhibitors	Selegiline (Eldepryl) Rasagiline (Azilect)	Selective Irreversible inhibition of MAO-B. Inhibition of presynaptic dopamine receptors and dopamine uptake
Catechol O– Methyltransferase (COMT) Inhibitors	Entacapone (Comtan) Tolcapone (Tasmar)	Reversible inhibition of COMT
N-Methy-D-Aspartate (NMDA) Receptor Inhibitor	Amantadine	Increase synthesis and release of dopamine; blocks NMDA Glutamatergic receptors
Anticholinergics	Benztropine Trihexyphenidyl	Blockade of muscarinic cholinergic receptors and possible inhibition of cholinergic transmission in striatal interneurons

Compiled from: 8, 23, 57

(negative issues) but should also be positive and emphasize sense of control and social well-being.

Speech therapy may be very helpful in addressing dysfunctions of phonation associated with PD. Early testing by therapists and incorporation of techniques maximizing phonation effort and loudness may significantly improve hypophonia. Speech therapy may also assist with swallowing difficulties (46). An interesting recent intervention is LSVT BIG and LOUD therapy. It emphasizes having patients make LOUD vocalizations and high intensity/amplitude (big) movements to "retrain" and recalibrate neural circuits to "understand" that LOUD, large movements (rather than soft and small) are normal (47). The author's personal exposure to physical therapy/speech therapy interventions based on big and loud therapy as part of a special educational program suggests an intriguing and effective therapy. While talking and walking soft and small, PD patients struggled to speak and walk. When walking with exaggerated big movements and talking loudly, movements like walking and voice volume normalized. The contrast witnessed was startling.

Nutritional consultation proactively can positively impact the progression of PD-associated conditions. No specific diet is a "PD diet" or alters its course. However, dietary interventions can address specific bothersome issues such as constipation (include high fiber and good hydration) and slowed gastric emptying (avoidance of large high fat meals). Good nutrition counseling can help offset weight loss and lack of appetite (48).

While physical therapy and exercise and speech therapy have demonstrated some positive response to PD motor symptoms, no effects have been found for vitamin therapy, food additives, and chiropractic or massage therapy. Tai Chi is showing great promise with Parkinson's Disease patients. Fuzhong *et al* (49) conducted a randomized controlled clinical trial (RCCT) of 195 PD patients assigned to Tai Chi, resistance training, or stretching therapies for 60-minute sessions twice weekly.

They found that Tai Chi training significantly reduced balance impairments, reduced falls, and improved functional capacity versus the other interventions. No serious adverse events were observed. Some medical school faculty members have introduced Tai Chi programs for their PD patient populations (50). Innovative treatments using traditional and other approaches are even more pressing than the need to create new motor therapies (51).

Pharmacological approaches to PD revolve around dopamine deficit or in inappropriate dopamine/other neurotransmitter imbalances. The American Academy of Neurology recommends initiating drug therapy once patients develop functional disability (52). Seven types of drugs are used to treat motor symptoms in PD patients (See Table 2). They include: Carbidopa/levodopa (Sinemet), dopamine agonists (both ergot and non-ergot types), monoamine oxidase-B (MAO-B) inhibitors, injectable dopamine agonist (apomorphine, or Apokyn), N-methyl-D-Aspartate receptor inhibitors, and anti-cholinergics (8). For initial therapy, levodopa, non-ergot dopamine agonists (pramipexole, or Mirapex; ropinirole, or Requip) and MAO-B inhibitors (selegine, or Eldepryl; rasagiline or Azilect) are commonly used.

The compensation for dopamine deficit or neurotransmitter balances can maintain functional independence for most patients using oral drug therapy. In later PD, oral medications can be supplemented by drug delivery via alternative routes (e.g., intrajejunal gels, subcutaneous injections and transdermal patches) (42, 51). Whatever the route, patients and caregivers must know that drugs need to be given on time to optimize dopamine levels and symptom control (53).

Notably, research is being conducted on the pharmacogenomics or pharmacogenetics of anti-Parkinson's disease drug therapy. Investigations are being conducted on elucidating the gene/drug pairings relationships for better drug metabolism. Unfortunately much more research must be conducted before prescriptions can be written with pharmacogenetic recommendations in mind (54).

An important troubling aspect of anti-Parkinson's drug therapy is behavioral problems due to the medications. These can include psychosis, hallucinations, punding (an intense fascination with repetitive handling of objects) and impulse control problems (pathologic, gambling, compulsive eating or shopping and hyper-sexuality). Clozapine and quetiapine can help with the psychotic behaviors but can have serious side effects. Conversely, lowering of dopamine dosing increases PD symptomatology (17).

A relatively recent practice parameter of the American Academy of Neurology found no effective neuroprotective treatment for PD (55) despite the fact that new drug therapies have been introduced in recent years. Some interventions (vitamin therapy and massage) have also proved ineffective neuroprotectors. No definitive disease-modifying therapy to slow or stop the disease exists (19). For improving quality of life during ongoing progression, exercise and voice therapy show some good effects (4).

7. SURGICAL THERAPIES

Surgical therapies are usually reserved for PD patients who are experiencing decreased effects of medical dopamine therapy over time. Specifically, continued motor fluctuations and dyskinesias (uncontrolled choreic or dystonic movements) may indicate candidacy. Motor fluctuations are manifested as alterations between good control "on" periods and PD symptomatic "off" periods. Both dystonia and motor fluctuations can seriously erode quality of life for PD patients (56, 57).

Deep brain stimulation (DBS) is the most frequently performed surgical therapy for PD. Over time, dopamine receptors terminals' dopamine levels fluctuate. This change is exacerbated by the short half-life (90 minutes) of levodopa and the decreasing ability of the terminals to absorb dopamine. In DBS, an electrode is surgically implanted in the subthalamic nucleus (STN), globus thalamus (GP) or ventral intermediate nucleus, providing continuous high frequency electrical stimulation. Generally, DBS response is best for patients who have had good preoperative response to levodopa, and report shorter disease duration (less than 16 years). The literature suggests that up to 5% of people with PD will have good outcomes (4).

If effective, DBS can help reduce tremor and stiffness and bradykinesia, and also enable drug doses to be lowered. This lowering can reduce involuntary movements (dyskinesias) associated with Parkinson's drug therapy (53). Most importantly, DBS does not involve brain tissue destruction, is reversible, and can be adjusted for disease progression (58).

8. EXPERIMENTAL THERAPIES

While the bulk of contemporary PD therapy is medical (pharmacological) in nature, and surgical therapy (e.g., deep brain stimulation) provides therapy to some PD patients, other experimental therapies offer hope and a possible treatment option. These include stem-cell-based therapies (59), bright light therapy for PD-related sleep disorders (60) and gene-therapy (51). Each will be discussed briefly.

The idea to substitute destroyed dopamine neurons with new cells, through transplantation dates back to the 1970's. Clinical trials conducted in the United States and internationally (e.g., Sweden, Mexico, etc.) with cell transplantation have had mostly mixed to poor results. Analysis of many trials has suggested that poor outcomes may be related to patient choice. That is, researchers have waited for cell therapy until the patient has had PD for the long-term and with worse motor symptoms. Current and future studies are attempting to target younger, less severe patients earlier in disease course. A major concern with the use of stem cells is the risk of tumor growth, especially with younger PD patients since life expectancy should be relatively normal for PD patients (61).

Though not therapeutic to the level of disease control such as deep brain stimulation, bright light therapy is being used to treat one non-motor symptom-sleep disturbances. PD patients with sleep disorders are suggested to be experiencing desynchronized circadian rhythm due to dopamine depletion. Bright light therapy delivered by light boxes (maximum 10,000 lux) for 30 minutes per session usually delivered in the morning has demonstrated success in improving both sleep and mood. More research is needed to ascertain best approaches and full potentialities (60).

Gene therapy represents a potentially useful method to improve the motor symptoms of advancing PD. Gene therapies under study to date do not have an effect on the neurodegeneration process itself, nor on non-motor symptoms. Four phase I/II gene therapy clinical trials are being tested for the treatment of patients with PD. The most common vectors are the adeno-associated viruses (AAV2, AAV5) and the lentiviruses (LV). By direct stereotactic injection, the viruses aim to transduce therapeutic genes into striatal, nigral or subthalamic nucleus cells to help regain normal function or provide neuroprotection from further deterioration. During the last decade, genes linked to the familial forms of PD have been discovered. They may improve understanding of the possible molecular causes of sporadic PD neurodegeneration (62). Some disease modifying approaches have included use of glial cell line-derived neurotrophic factor (GDNF) stimulation via use of adenovirus, lentivirus, and adeno-associated virus-based vectors (62). Another approach is use of transgenes to down-regulate α-synuclein expression since it interferes with neuronal activity. Parkin is another target for viral vectors since Parkin appears to be a neuro-protective agent (63). Other potential gene therapy interventions include Complex 1, MicroRNA, and 4E-BP targets. Theoretically, innovative gene therapies of the future may offer a "cure" to PD patients with an identified genetic cause(s) (51).

9. CONCLUSION

Parkinson's Disease represents a major clinical challenge since it is one of the most common

neurodegenerative diseases, affects primarily a population of aging individuals, a group that is growing rapidly in the world, and lacks a therapeutic means to influence the inexorable loss of dopaminergic innervation. Parkinson's Disease itself does not cause death but is associated with increased morbidity and mortality. Knowledge of the disease manifestations, treatments, and progressive long-term course is essential for optimal care and enhanced quality of life for people with Parkinson's disease.

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