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Treatment Options for Parkinson's Disease

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TREATMENT OPTIONS FOR PARKINSON'S DISEASE

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INTRODUCTION

Parkinson's disease was first described and named Paralysis Agitans in 1817 by British physician James Parkinson (Lieberman 2004). Later on, it took on its current name after Dr. Parkinson. Parkinson's disease (PD) is a neurological disorder for which the cause is yet to be discovered. Like many other diseases, PD has numerous facets. Throughout all of its different stages, it presents with motor, as well as non-motor, symptoms (Simuni et al. 2009). Though estimates of people affected by PD are constantly being made, it is difficult to determine a precise and accurate number. This difficulty arises since symptoms are often mistaken for other diseases of the nervous system (jointly known as Parkinsonism) or are mistakenly attributed to the normal aging process. It is estimated that over 1 million people in North America are affected by this degenerative disorder. As life expectancy increases, incidence of the disease rises (Lang and Lozano 1998).

The mortality rate of PD patients is 2-5 times greater than age-matched controls; this alone indicates the significance of its impact. It is predicted that, by the year 2040, Parkinson's disease will surpass cancer as the second leading cause of death among the aged (Bennett et al. 1996).

NEUROPATHOLOGY

Parkinson's disease is characterized by slow movement, rigidity, and involuntary movement, which occur because of death to dopamine-producing neurons. Dopamine is the main neurotransmitter to be affected by the disease, although it is not the only one; serotonin, acetylcholine, and norepinephrine are other affected neurotransmitters. However, their contribution to clinical symptoms is unknown.

The striatonigral complex is the region of the brain that is the source for the majority of the brain's dopamine. It includes the putamen, caudate, and substantia nigra; the substantia nigra is the main source of dopamine in the region. There are 5 dopamine receptors (D1-D5) found in various brain regions that include the cortex, striatum, and limbic system (Macphee and Stewart 2007). Three of the receptors (D1, D2, and D3) are present in the basal ganglia. D1 and D2 receptors are known to promote voluntary movement; D3's function is unknown. The limbic system, which controls emotion, contains D3, D4, and D5 receptors; thus, the dopamine deficiency of PD leads to the cognitive and emotional impairments associated with PD (Rezak 2007).

The basal ganglia have a circuit that enables voluntary and involuntary movement (Macphee and Stewart 2007). Nigral cells have axons that extend into the putamen and caudate nucleus. The globus pallidus located near this complex regularly inhibits movement by releasing the neurotransmitter gamma amino butyric acid (GABA), an inhibitory neurotransmitter, to the thalamus, which prevents the motor cortex from being excited. The substantia nigra excites the caudate and putamen via the transmission of dopamine, which then informs the globus pallidus as to which forms of movement it should stop inhibiting. Thus, dopamine is necessary for motor output and decreased stimulation by dopamine causes decreased motor output (Kalat 2009).

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The distinguishing characteristic of Parkinson's disease was once thought to be the presence of Lewy bodies. However, not all forms of the disease have this pathological feature. For example, those that are classified as autosomal recessive cases do not have Lewy bodies. In autosomal dominant cases, however, Lewy bodies are seen (Macphee and Stewart 2007). Lewy bodies are spherically shaped protein masses and contain transparent cytoplasmic centers with halos surrounding them. The center consists of neurofilaments and other proteins accountable for proteolysis (protein breakdown) including parkin, ubiquitin, and alpha synuclein. In those patients who experience Lewy bodies, Lewy bodies appear in all affected areas of the brain (Dauer and Przedborski 2003). The mechanism of formation of Lewy bodies and their function in the pathology of the disease is not yet known (Lang and Lozano 1998).

Many areas of the brain are affected by the disease. The most significant damage occurs in the pars compacta, the posterior part of the substantia nigra (Macphee and Stewart 2007). This region is located in the midbrain, midway between the cerebral cortex and the spinal cord (Lieberman 2004). Most of the motor symptoms associated with the disease occur because of damage to this area. Motor symptoms begin to appear after the majority of the cells in this area are lost. Damage to the nucleus basalis, an area of the brain that produces an abundance of the neurotransmitter acetylcholine, is correlated with impaired memory and cognitive function in PD patients (Macphee and Stewart 2007).

The pars compacta has both anterior and posterior parts to it. The posterior part is pigmented with neuromelanin, whereas the anterior is considerably lighter, as it lacks this pigment. Normal aging is consistent with cell loss in the posterior region. PD, on the other hand, impairs the anterior region. This shows that Parkinson's disease is not an effect of advanced aging (Macphee and Stewart 2007).

Studies show that neurological symptoms of Parkinson's disease develop in an upward manner. The disease starts with damage to the brainstem and advances upward to the cerebral cortex. The disease can be divided into six stages, each associated with the onset of specific neurological symptoms (Macphee and Stewart 2007). In the first two stages, symptoms are not apparent (Davie 2008).

CAUSES

GENETIC CAUSES

Most incidences of PD occur sporadically, rather than from genetic causes (Wood-Kaczmar et al. 2006). Onset generally occurs at younger ages in genetic forms of the disease and pathological symptoms are different (Vila and Przedborski 2004). Genetic inheritance of PD occurs in both autosomal dominant and autosomal recessive forms (Wood-Kaczmar et al. 2006). Dominantly inherited Parkinson's was first discovered in the 1990s upon studying a familial case. Alpha-synuclein was the gene identified as causing PD (Cordato and Chan 2004). Several other genes involved in the onset of the disease have been located since that initial discovery (Vila and Przedborski 2004).

ALPHA SYNUCLEIN

A mutated *SNCA* gene, which encodes the alpha synuclein protein, has an altered sequence of nucleotides (Vila and Przedborski 2004) and therefore codes for a different protein product (Klug et al. 2006). Three types of mutations were found that link this gene to Parkinson's disease. These genetic mutations are only associated with

dominant inheritance (Wood-Kaczmar et al. 2006). Mutations in *SNCA* are thought to account for a small percentage of Parkinson's disease since it was found in a small number of studied hereditary cases (Lang, and Lozano 1998).

Alpha synuclein is made up of 140 amino acids and is present in several locations of the brain. It is found in the highest concentrations in the cortex, hippocampus (Wood-Kaczmar et al. 2006), hypothalamus, olfactory neurons, and substantia nigra. Neural and glial cells produce this protein, which is mainly found at pre-synapses. Alpha synuclein has the shape of an alpha helix and is found in vesicles that transport lipids.

Studies were done on mice by transferring a gene from another organism to replace the gene that encodes for alpha synuclein, in order to test its function in living organisms. Absence of alpha synuclein showed fewer proteins at synapses and fewer vesicles available for transport (Cordato and Chan 2004). Its function is not well understood, although it is thought to play a role in transmission of chemical messages, learning, and neuroplasticity (the ability for neurons to adapt to environmental stimuli) (Wood-Kaczmar et al. 2006).

Alpha synuclein can also be harmful. In high concentrations, these proteins cluster together to form polypeptides that are associated with various diseases. These unwanted protein accumulations are normally broken down by enzymes that specialize in getting rid of harmful material to the cell. Toxicity to neurons can happen if mutated *SNCA* produces alpha synuclein proteins that are more likely to clump together or are folded in such a way that makes it difficult for enzymes to break them down. These proteins are part of Lewy body formation and are thought to cause cell death by breaking down the proteins of neurons (Cordato and Chan 2004).

Leucine-Rich Repeat Kinase 2

A number of mutations in the gene that encodes for leucine-rich repeat kinase 2 (LLRK2) have been located in late-onset dominantly inherited PD. The most common one is substitution of the G2019S gene. This mutation generally accounts for a small percentage of genetically inherited PD. It contributes to a significantly greater percentage of PD in North African Arabs and Ashkenazic Jews. The role of this protein and its contribution to the disease is not yet understood (Wood-Kaczmar et al. 2006).

Parkin

Parkin is made up of 465 amino acids. It is one of many proteins that have a ring finger domain. Proteins that have this characteristic are able to act as ubiquitin ligases by breaking down harmful protein buildup, such as buildup of alpha synuclein. Mutations in the gene that encodes for parkin, *PARK2*, are due to recessive inheritance and are consistent with early-onset PD (Cordato and Chan 2004). Mutations of *PARK2* and alterations in parkin's post-translational state cause parkin's inability to target certain forms of alpha synuclein for breakdown, which can lead to build-up of alpha synuclein and toxicity to neurons (Vila and Przedborski 2004). In addition, mutations in other proteins do not permit parkin to carry out its job properly, resulting in toxic accumulation (Wood-Kaczmar et al. 2006). *PARK2* mutations cause death to cells of the substantia nigra and locus ceruleus (Cordato and Chan 2004).

Parkin functions as an ubiquitin enzyme marking its target cell for destruction. Lewy bodies form when a sequence of ubiquitin enzymes binds to a target protein and

is unable to break it down. In its mutated forms, parkin cannot bind to its target proteins; thus, Lewy bodies are not seen in this instance (Cordato and Chan 2004).

The two types of mutations (Wood-Kaczmar et al. 2006) in the *PARK2* gene (missense and nonsense mutations) cause very similar symptoms, such as early onset (usually occurring before age 30) (Cordato and Chan 2004; Vila and Przedborski 2004), degeneration at a slower pace, receptiveness to levodopa (a medication used to treat motor symptoms of PD) (Macphee and Stewart 2007), and susceptibility to side effects of levodopa early on (Cordato and Chan 2004). Mutations in the *PARK2* gene account for 50 percent of early-onset familial PD and for 77 percent of early-onset sporadic cases (Wood-Kaczmar et al. 2006).

PARK7

The gene *PARK7* codes for DJ-1, a protein with many functions. It is found scattered in many areas of the brain. Several recessive mutations link this protein to PD. Compared to mutations in *PARK2*, mutations in DJ-1 account for a small amount of early onset PD. Mutations occur in various areas of the gene, yet they cause the same symptoms (Vila and Przedborski 2004). The normal function of DJ-1 is to stabilize proteins, while protecting them from damage by free radicals. Studies on mice that lack DJ-1 have shown dysfunction of dopamine pathways, causing motor disability (Wood-Kaczmar et al. 2006).

Environmental Causes

The development of PD in a group of drug users was linked to the intake of a drug containing methyl-phenyl-tetrahydropyridine (MPTP). MPTP has been shown to cause degeneration specifically in the nigral cells, by decreasing complex 1 (the first enzyme of the respiratory chain leading to the production of ATP) activity of the mitochondria. The discovery that environmental toxins can lead to the onset of PD has led researchers to extend their studies to pesticides and herbicides to test their contribution to the disease (de Lau and Breteler 2006). Rotenone is an agent commonly used by gardeners to prevent unwanted plant growth. Repeated exposure to this chemical in low doses has also been shown to cause degeneration specific to nigral cells. Studies show that exposure to this pesticide is linked to the formation of Lewy bodies, a major component of the PD, whereas exposure to MPTP has not yielded such results (Jenner 2001). It has been hypothesized that exposure and accumulation of heavy metals, such as aluminum, amalgam, copper, iron, manganese, zinc, etc., in the substantia nigra may cause an increased risk of PD by causing oxidative damage (de Lau and Breteler 2006).

Symptoms

Motor Symptoms

A number of motor features, including bradykinesia (slow movement), a resting tremor, muscle rigidity, and postural instability, distinguish PD from Parkinsonism. There are several scales to assess the rate of decline in PD patients. Two widely used scales are the Hoehn and Yahr, and the Unified Parkinson's disease rating scale (UPDRS). The Hoehn and Yahr, a scale that ranges from 0 (no symptoms) to 5 (bedridden) evaluates how far the disease has progressed. The UPDRS, on the other hand, is used to determine speed of progression of the disease. This scale is currently being modified to include non-motor symptoms of PD (Jankovic 2007).

The most apparent symptom of the disease is bradykinesia, or decreased movement. Bradykinesia adds difficulty to daily activity management, leading to an inability to initiate, plan, multitask, and/or carry out tasks in a consecutive order. Slow movement affects fine motor function such as buttoning a garment and handling utensils. Spontaneous movement, such as blinking, facial expressions, and arm swaying while walking, is also impaired. These hindrances are due to reduced dopamine activity, which causes a decrease in motor output (Jankovic 2007). Slowness of movement is related to the patient's emotional state, not their motor abilities. Thus, when an external stimulus, such as a yell of "Fire" or a signal telling them to beware of an obstacle, informs them of the need for quick movement, they regain the ability to move quickly (Jankovic 2007).

According to studies (Gelb et al. 1999), the most common symptom of PD (Jankovic 2007), which occurs in 79-90 percent of patients, is a resting tremor. Hand tremors begin on one side of the body and spread to the other. It is noticeable on the lateral parts of the hand or leg. Tremors may also affect the chin, jaw, lips, and legs. Tremors are not apparent while sleeping or in the course of action (Jankovic 2007).

Another feature seen in PD is stiffness, which can occur in several areas, such as the ankles, hips, neck, shoulders, and wrist. Stiffness can be accompanied by pain. A study found that rigidity, along with tremor and imbalance, was associated with an increased risk of PD in individuals who initially showed no signs of Parkinsonism (Jankovic 2007).

Rigidity can also cause bending of the elbows, knees, neck, and/or trunk. It can also lead to striatal hand or foot, which occurs when the thumb or big toe is extended while the joint by the knuckles and other toes are bent. These abnormalities usually occur later on in the disease and are generally associated with early onset of the disease (Jankovic 2007).

Postural instability usually arises in later stages of the disease. This symptom is the source for many falls that often cause hip fractures. One study indicated a wait of nine years for patients to experience their first fall. Interestingly, patients who fear falling show an increased incidence of falling. Unlike other symptoms, postural imbalance is generally untreatable by therapy (Jankovic 2007).

NON-MOTOR SYMPTOMS

Non-motor aspects of PD are currently receiving increased attention, since they affect the quality of life of patients significantly (Macphee and Stewart 2007). Non-motor features consist of autonomic dysfunction, sleep disorders, and impaired cognitive function (Jankovic 2007).

Autonomic dysfunction includes sweating, constipation, erectile dysfunction, orthostatic hypotension (a sudden decrease in blood pressure when the patient stands up) (Jankovic 2007), and reduced olfaction (Chaudhuri et al. 2006). Constipation is a common symptom that can serve as a precursor to PD. A study done over a period of 24 years showed that men who originally had constipation were three times more likely to develop PD, following a 10 year interval. Both elevated and decreased sex drive were reported by patients. Ninety percent of PD patients develop problems with their sense of smell. A number of studies concluded that decreased sense of smell is an early sign of motor symptoms in PD. Many relatives of patients who reported reduced

olfaction but did not report any other symptoms of PD were later diagnosed with PD (Chaudhuri et al. 2006).

Sleep disruption was once thought to be a side effect of treatment for Parkinson's. Several doctors now believe that it is a component of the disease. About one third of PD patients have rapid eye movement sleep behavior disorder where a dream accompanies dramatic motor movement. Insomnia occurs in over 50 percent of patients (Jankovic 2007). Sleepiness during daytime hours is common and may result from sleep disruption at night or as an outcome of treatment (Macphee and Stewart 2007). Degeneration of neurons in the brain's sleep regulation centers in the thalamocortical pathway and brainstem contribute to sleep disorders (Chaudhuri et al. 2006).

Studies have found decreased cognitive ability in nearly 85 percent of PD patients, while close to half of them developed dementia. Dementia in PD patients usually accompanies neuropsychiatric disorders. A study comprising 537 PD patients showed that close to 50 percent experienced anxiety, apathy, depression, and hallucinations. Other studies reveal that many patients display various forms of impulsive behavior, such as cravings, hypersexuality, obsession with shopping, pathological gambling, etc. These behaviors develop as a result of taking levodopa (Jankovic 2007), a medication used to treat PD (Macphee and Stewart 2007).

PREVENTION

Several case-control and population-based studies from numerous countries showed a significantly decreased risk for PD among cigarette smokers. The mechanism of cigarette smoking decreasing the risk of PD is not well understood. It is possible that nicotine in cigarettes stimulates dopamine release.

Several studies also found consumption of coffee to be consistent with a reduced risk for PD. The effective component in coffee is perhaps caffeine, because other studies showed a decreased risk for PD from taking in other sources of caffeine. According to studies, caffeine has a greater protective effect on men than woman (de Lau and Breteler 2006).

A third factor that may reduce risk of PD is alcohol consumption. Some studies found a decreased risk with alcohol consumption. Others, though, found no association (de Lau and Breteler 2006).

DIAGNOSIS

The main symptoms of PD at the time of diagnosis include rigidity, bradykinesia, and a resting tremor (Davie 2008). Postural instability is usually not present during diagnosis since it typically manifests itself later on in the disease (Jankovic 2007). Symptomatic features are generally not present on both sides of the body. Handwriting change and decreased facial expressions can be detected. Decreased olfaction can be reported since it is usually an early symptom of PD. Post-mortem studies showed that diagnosis of PD by a neurologist reflected a 25 percent misdiagnosis rate. Patients who were diagnosed in a clinic that specialized in movement disorders indicated less diagnostic inaccuracy. It is thus important to see an expert in the field to ensure proper diagnosis (Davie 2008).

There are several Parkinsonism disorders that can easily be mixed up with PD. Diagnosis of PD normally takes place in a clinical setting. Sometimes brain images using magnetic resonance imaging (MRI) and computed tomography (CT) are

necessary to rule out other Parkinsonism diseases. Using single emission computerized tomography (SPECT), other conditions can be ruled out (Davie 2008).

TREATMENT OF MOTOR SYMPTOMS

LEVODOPA

Each patient requires treatment dedicated to his or her specific symptoms and needs (Rezak 2007). Since the 1960s, levodopa has been the main drug used in treatment of PD (Schapira et al. 2006). Levodopa greatly reduces symptoms of rigidity and bradykinesia, but has a lesser effect on tremors (Macphee and Stewart 2007). Levodopa is currently the most effective drug on the market. However, since levodopa's effectiveness lasts for about ten years (Rezak 2007), it is held back from patients or given at low doses until it is absolutely necessary.

In order to reduce its side effects, levodopa may be combined with other drugs. Levodopa, a dopamine precursor, is usually combined with a decarboxylase inhibitor (Macphee and Stewart 2007), such as carbidopa or benserazide. These inhibitors occupy receptors on the enzyme dopa decarboxylase, thus preventing levodopa's conversion to dopamine before it reaches the brain. Decarboxylase inhibitors help alleviate side effects that accompany levodopa such as excessive sweating, low blood pressure, and nausea. Another drug that may be combined with levodopa and carbidopa is entacapone. This drug inhibits catechol-o-methyl-transferase, an enzyme that breaks down neurotransmitters, causing increased uptake of levodopa in the intestines.

Even when combined with other drugs, there are possible side effects that accompany levodopa (Rezak 2007). After five years of taking levodopa, 50 percent of patients may develop (Lieberman 2004) dyskinesia, motor fluctuations, hallucinations, sleepiness, nausea, and/or low blood pressure (Rao et al. 2006). Levodopa induced motor fluctuations can range between wearing off of dosage and unsystematic severe on and off motor functioning. Levodopa's half-life of 60-90 minutes causes a spurt of dopamine receptor activation. The occurrence of continuous abrupt spurts of dopamine receptor activation at the same time as the constant death of dopamine-producing cells causes abnormal receptor activation known as the "on-off" phenomenon. Initially, levodopa is prescribed very sparingly in order to protect patients from its adverse side effects (Rezak 2007).

DOPAMINE AGONISTS

Dopamine agonists activate dopamine receptors by mimicking the actions of dopamine (Lieberman 2004). They include bromocriptine, cabergoline, lisuride, pergolide, pramipexole, ropinerole, and rotigotine (Macphee and Stewart 2007). Dopamine agonists, which have been previously prescribed together with levodopa, are currently being given alone as an early PD treatment, thereby delaying the administration of levodopa. Pramipexole, ropinerole (Rezak 2007), and rotigotine are currently the most prescribed dopamine agonists (Davie 2008). Studies comparing the effects of pramipexole and ropinerole against levodopa have shown a decreased rate of progression of PD with levodopa use. The dopamine agonists, however, showed less motor complications (Rao et al. 2006). With advancement of the disease, dopamine receptor agonists are commonly taken with levodopa/carbidopa to reduce levodopa's accompanied motor complications (Lieberman 2004). Possible side effects of

pramipexole and ropinerole can include low blood pressure, dyskinesia, abnormal sleep patterns, impulsive behavior, and cognitive/psychiatric impairments. Unlike the other dopamine agonists, rotigotine is administered through a transdermal patch and is absorbed over a 24-hour period, thereby continuously stimulating dopamine receptors. Pergolide, bromocriptine (Rezak 2007), cabergoline, and lisuride are not prescribed that often since they cause cardiac valve degeneration (Davie 2008).

MONOAMINE OXIDASE-B INHIBITORS (MAO-B)

The enzyme monoamine oxidase-B (MAO-B) is responsible for degrading most of the dopamine in the basal ganglia. Selegiline and rasagiline are two drugs that inhibit this enzyme causing increased levels of available dopamine (Rezak 2007). Like dopamine agonists, selegiline can either be used alone to treat symptoms while delaying levodopa therapy or be joined with levodopa to reduce motor fluctuations (Macphee and Stewart 2007). Insomnia and nausea are potential side effects of this drug (Rao et al. 2006). Rasagiline is a newer and more powerful MAO-B inhibitor than selegiline. Rasagiline is an effective monotherapy in early PD as well as a preventer of motor fluctuations when taken with levodopa later on in the disease's progression (Rezak 2007). Compared to a placebo, when taken with levodopa, rasagiline has shown to decrease motor fluctuations by one more hour per day (Macphee and Stewart 2007).

CATECHOL-O-METHYLTRANSFERASE INHIBITORS (COMT-I)

Catechol-O-methyltransferase is an enzyme present in several locations, including the intestines, liver, kidneys, neural cells and glial cells. The goal of tolcapone and entacapone, the two catechol-O-methyltransferase inhibitors (COMT-I), is to prevent motor fluctuations resulting from the wearing off of levodopa's effects between doses (Macphee and Stewart 2007). These drugs can improve symptoms and effectively reduce the dose of levodopa (Rao et al. 2006). COMT-I drugs inhibit metabolism of levodopa by COMT in the gastrointestinal tract, thus increasing the amount of levodopa reaching the substantia nigra and thereby enabling levodopa's conversion to dopamine. In addition to increasing the availability of levodopa to the brain, tolcapone and entacapone also prolong the duration of levodopa's metabolism. COMT inhibitors can be good treatments for early Parkinson's disease. They delay the onset of levodopa's motor complications by stabilizing the blood concentration of levodopa and effectively decreasing peak dosage, via the increase of levodopa's half-life (Rezak 2007).

COMT-I drugs can have negative effects as well. Diarrhea can occur as a side effect (Rao et al. 2006), necessitating discontinuation of the drug. The addition of COMT inhibitors to levodopa therapy causes increased dopaminergic stimulation, possibly resulting in dyskinesia. Such cases may call for decreased dosage. Since tolcapone has been shown to cause hepatotoxicity, the FDA requires patients' liver enzymes to be monitored (Rezak 2007); it is thus given only when entacapone proves to be ineffective (Macphee and Stewart 2007). Although it has a shorter half-life and is less effective, entacapone is still more frequently used (Rezak 2007).

AMANTADINE

Amantadine, initially an antiviral drug, was discovered to be useful in PD treatment (Lieberman 2004) by improving dopamine release from presynaptic

terminals (Rezak 2007) and acting as an anticholinergic agent, which prevents glutamate activation of N-methyl-D-aspartate (NMDA) receptors (Lieberman 2004). Overstimulation of NMDA receptors are linked to dopaminergic death in PD. Amantadine's impact on treating symptoms is greatest for tremor and it has its greatest effects in the early PD stages. It has also shown to reduce dyskinesia associated with levodopa (Rezak 2007). Side effects of this drug may include hallucinations, confusion, hypotension, nausea, and edema (Rao et al. 2006).

Table 1: FDA Approved Medications for Parkinson's Disease

Medication	*Adverse effects*	*Indications and comments*
Anticholinergics		
Benztropine (Cogentin), trihexyphenidyl (Artane)	Dry mouth, dry eyes, constipation, hypotension, cognitive impairment, urinary retention	Useful for symptomatic control of Parkinson's disease (benefits are mild to moderate); associated with more adverse effects than other drugs
Carbidopa/levodopa		
Immediate- and sustained-release carbidopa/levodopa (Sinemet)	Nausea, somnolence, dyskinesia, hypotension, hallucinations	Levodopa is the most effective medication and remains the primary treatment for symptomatic Parkinson's disease; no added benefit for motor complications with sustained-release versus immediate-release preparations
COMT inhibitors		
Entacapone (Comtan)	Diarrhea; exacerbates levodopa adverse effects; bright orange urine	Useful for managing motor fluctuations ("wearing-off" effect) in patients taking levodopa; levodopa dose may need to be reduced if dyskinesia appears
Tolcapone (Tasmar)	Diarrhea; exacerbates levodopa adverse effects; rare liver failure (liver function monitoring needed)	
Dopamine agonists		
Bromocriptine (Parlodel)	Nausea, headache, dizziness	Useful for early and advanced disease
Pergolide (Permax)	Somnolence; hallucinations; nausea; edema; fibrosis of cardiac valves, lung, and retroperitoneum; retroperitoneal and pulmonary fibrosis	Useful for the initial treatment of parkinsonism and as adjunct therapy in patients taking levodopa
Pramipexole (Mirapex), Ropinirole (Requip)	Nausea, sleep attacks, edema, hallucinations, hypotension	Useful for early disease and in patients with Parkinson's disease and motor fluctuations
MAO-B inhibitors		
Selegiline (Eldepryl)	Nausea, insomnia, drug interactions with other MAO inhibitors/tyramine	Useful for symptomatic control of Parkinson's disease (benefits are mild to moderate) and as adjuvant therapy for patients with Parkinson's disease and motor fluctuations
Rasagaline (Azilect)	Weight loss, hypotension, dry mouth, drug interactions with other MAO inhibitors/tyramine	
NMDA receptor inhibitor		
Amantadine (Symmetrel)	Nausea, hypotension, hallucinations, confusion, edema	Useful for treating akinesia, rigidity, tremor, dyskinesia

FDA = U.S. Food and Drug Administration; COMT = catechol O-methyltransferase, MAO-B = monoamine oxidase-B; NMDA = N-methyl-D-aspartate.

Source: Cordato and Chan 2004

ANTICHOLINERGICS

Anticholinergic drugs also treat tremor in PD. Trihexyphenidyl, benztropine, and procyclidine, are the most commonly used anticholinergic drugs. Due to their adverse effects, they should not be given to the elderly. Side effects of anticholinergic drugs can include blurred vision (Rezak 2007), dry mouth, hypotension, constipation and cognitive impairment (Rao et al. 2006).

SURGERY

Brain surgery used to be a common method for treating tremor and rigidity in Parkinson patients, although success rates varied and detrimental risk factors such as death were involved. However, with the advent of levodopa in the 1960s, which proved to be a safer and more effective option for treatment, the idea of surgery diminished. With advances in neuroimaging, surgery has regained popularity as a treatment for PD among those who do not respond to drug therapy anymore (Lieberman 2004).

With greater understanding of the neuropathology involved in PD, two ablative procedures are renewably performed (Arle and Alterman 1999) to help control symptoms of PD (Lieberman 2004). A thalamotomy involves destroying part of the ventrolateral thalamus, a brain region involved in transmitting signals that control movement. This procedure significantly reduces tremor but shows little improvement to symptoms of rigidity and bradykinesia. Death rates are less than 1 percent due to better targeting and lesion technique. Since thalamotomy does not significantly improve many symptoms of PD, it is less favored than pallidotomy (Arle and Alterman 1999).

In a pallidotomy, the globus pallidus, a brain area responsible for involuntary intermittent movements in PD patients, is targeted (Lieberman 2004). Pallidotomy has been shown to greatly reduce rigidity, bradykinesia, and tremor. Patients taking levodopa can also benefit from this procedure because it decreases the "off" period in their motor fluctuations. Better UPDRS scores were reported for up to 2 years following this procedure (Arle and Alterman 1999).

Deep brain stimulation has become more common now because of its effectiveness. The head of the patient is placed in a stereotaxic frame, a halo-like device. Surgeons can spot the thalamus, globus pallidus, or the subthalamic nucleus through MRI on the brain. The skull is pierced, using a drill, and a probe is placed deep inside the brain to reach the target tissue. The probe transmits a burst of electricity, which causes the brain region's electrical activity to normalize reversing PD symptoms. This is a safe surgery and results can be seen immediately (Lieberman 2004).

STEM CELL THERAPY

Currently there is no cure for PD. Embryonic stem cells and stem cells that come from fetal brains and adult bone marrow have been successfully transformed into functioning dopamine producing cells. However, there are several setbacks. Use of embryonic stem cells is controversial (Arias-Carrion and Yuan 2009) as many people believe that fetal tissue should not be used for research as a fetus is unable to consent (McLaren 2001). Many believe that adult stem cells have much to offer for future treatment of degenerative diseases such as PD. Previously, adult stem cells have been scarce, but recent progress enables their use in large quantities. Adult stem cells can be

implanted into the brain where it can differentiate into neural cells. With a better understanding of the immune system and successful transplantation, the use of stem cells is under serious consideration for treating the various dimensions of PD. It is hypothesized that stem cells should come from the very same patient who will derive benefit from it; however, not much is known about this type of implantation. The current goal under study is to test the use of autologous stem cell transplant in animals, and further the findings to clinical studies (Arias-Carrion and Yuan 2009).

CONCLUSION

Parkinson's disease is a multi-dimensional disease for which there is currently no cure. Much advancement has been made in the treatment of PD symptoms as opposed to curing it. Current research is giving increased attention to treatment of non-motor symptoms since it greatly affects the quality of life of patients. Additionally, increasing focus is being given to stem cell research as a potential cure for Parkinson's disease by using the patient's own stem cells to repair their damaged dopaminergic tissue.

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