Parkinson's disease is a condition whose main features are slowed movement, tremor, and gait or balance problems. More than 1 million people in the United States have Parkinson's disease. Although it more commonly develops in people in their 60s or older, it can occur as early as age 20.

Parkinson's disease is caused by a loss of nerve cells in a specific part of the brain called the substantia nigra. Cells in the substantia nigra communicate with other movement control centers in the brain by secreting dopamine and other neurotransmitters. When substantia nigra cells die, they stop secreting dopamine, and the other movement control centers become disregulated. This disturbance in the movement control centers of the brain cause the main symptoms of Parkinson's disease (slowness, tremor and gait or balance problems).

In most patients, what causes the loss of substantia nigra cells remains unknown. Environmental toxins that may cause parkinsonism include: manganese, carbon monoxide, organic solvents, and certain pesticides However, most people with Parkinson's disease have not been exposed to these toxins. In about 10% of patients, there is another family member with Parkinson’s disease and therefore genetic factors are suspected. Over the past decade, a number of genes have been shown to cause Parkinson's disease, but these gene abnormalities do not occur in most individuals with Parkinson's disease. Currently, researchers suspect that the cause of Parkinson's disease in most individuals reflects a combination of genetic factors and environmental exposure(s).

The first symptom and disease course varies considerably in people with Parkinson's disease. However, several general statements can be made. The most common initial symptom is tremor, but about 25% of patients will never experience significant tremor. Symptoms of tremor or slowness usually begin on one side of the body, often involving either an arm or leg. Over time (in some people, 5 years or more) the other limb on the same side, and then limbs on the opposite side are affected. Mobility (arising from a chair or walking) may be limited as the disease progresses. For most individuals on treatment, lifespan is not shorted by Parkinson's disease.

In addition to the well-known symptoms of tremor, slowness, and imbalance, other problems such as excess saliva, a soft voice, as well as hand or foot cramps may occur. Loss of the sense of smell is common. Depression, anxiety and a number of sleep disorders are quite common. Constipation, more frequent urination, incontinence, increased sweating, and impotence may develop. About 40% of people with Parkinson's disease will develop changes in memory and intellectual function.

A variety of treatments are available for many of the symptoms of Parkinson's disease. These include general health measures, physical and speech therapy as well as number of medications. For some patients with advanced symptoms of Parkinson's disease, surgical treatments are appropriate. The treatment for Parkinson's disease is individualized and is guided by number of factors including the general health and symptoms of an affected individual. A number of new treatments for Parkinson's disease are under development.

Recognizing Other Causes of Parkinsonism

Although the symptoms and signs of Parkinson's disease (PD) are fairly specific, a significant fraction of patients with parkinsonism do not have PD.
In an epidemiologic study of patients with parkinsonism, Schrag et al (2000) found that
- 65% had PD
- 18% had drug-induced parkinsonism
- 7% had vascular parkinsonism
- 6% had atypical but non-specific features
- 2.5% had progressive supranuclear palsy
- 2% had dementia with parkinsonism
- 1.7% had multiple system atrophy

Identifying patients with atypical parkinsonism is important since these patients respond less reliably to
dopaminergic agents, do not respond favorably to surgical treatments of PD, and develop additional
clinical problems.

Atypical parkinsonism should be considered particularly in patients with poor dopamine responsiveness,
early loss of balance, prominent dementia, rapid onset or progression, prominent autonomic dysfunction,
and little or no tremor

**Medication-induced Parkinsonism**

Although tremor and postural instability may be less prominent, this condition may be indistinguishable
from PD. Medications frequently associated with the development of parkinsonism include:
antipsychotics, metaclopramide, reserpine, tetrabenazine and some calcium-channel blockers (especially
cinnarizine and flunarizine). The parkinsonism usually resolves after some months (or longer) after
discontinuing the offending medication.

**Progressive Supranuclear Palsy (PSP)**

Characteristic of PSP is the early onset of imbalance, frequent falls, axial rigidity and eye movement
problems. The symptoms usually begin after age 50 and progress more rapidly than with Parkinson's
disease. The most characteristic eye movement abnormality is a vertical gaze paresis, but a slowing of
vertical saccadic movements may often be appreciated first (Vidailhet et al, 1994). Dementia develops
later in the disease. There is no specific treatment for PSP. Dopaminergic treatment should be tried but
often offers little benefit. Supportive measures such as speech therapy, physical therapy and
antidepressants may help.

**Corticobasal Degeneration (CBD)**

CBD is the least common of the atypical causes of parkinsonism and often affects patients quite
asymmetrically and progresses more rapidly than PD. The initial symptoms of CBD usually develop after
age 60 and include: asymmetric bradykinesia, rigidity, limb dystonia, and postural instability. Additional
features such as ideomotor apraxia, alien limb phenomenon, progressive aphasia or the development of
contractures are typical (Stover and Watts, 2001). There is no specific treatment for CBD. Supportive
treatment such as botulinum toxin for dystonia, antidepressants, and speech and physical therapy may
help. Levodopa and dopamine agonists seldom offer benefit.

**Multiple System Atrophy (MSA)**

MSA is a sporadic neurodegenerative disease of unknown cause. The mean age of onset is 54 and median
survival is 6 years (Ben-Shlomo et al, 1997). It presents with varying degrees of bradykinesia cerebellar
ataxia and or dysarthria, autonomic dysfunction, and pyramidal signs
The term "multiple system atrophy" encompasses the three presentations of the illness that have overlapping clinical and pathological findings: striatonigral degeneration (parkinsonian presentation), olivopontocerebellar atrophy (ataxic presentation), Shy-Drager syndrome (autonomic presentation).

While at initial presentation a patient may have a rather pure phenotype, as the condition progresses other symptoms and signs develop that reflect involvement of a different system. Patients with the parkinsonian presentation typically have an asymmetrical tremor, bradykinesia, rigidity and postural instability. Men often develop impotence; both men and woman often experience urinary urgency and incontinence.

Although 30% of patients obtain a definite but short-lived benefit from levodopa and dopamine agonists, the parkinsonism is typically poorly responsive to medications. Dyskinesias and dystonia emerge in half of treated patients.

**Vascular Parkinsonism**

Multiple small strokes, particularly if located adjacent to the internal capsule, can cause parkinsonism. Winikates and Jankovic (1999) found that patients with this disorder are more likely to present with gait difficulty than tremor and are more likely to have symptoms that are worse in the lower extremities than upper extremities. Some will also report an abrupt onset of symptoms. Signs on neurological exam may include bilateral slowing, impaired fine movements, increased tone, and a gait disturbance. Treatment for this condition is the same as for PD but the benefit is often less striking.

**Dementia with Lewy Bodies (DLB)**

This disorder is characterized by early dementia, hallucinations, fluctuations in cognitive, and parkinsonism. In a study comparing DLB with PD, the absence of rest tremor, the presence of myoclonus, the symmetry of the extrapyramidal symptoms, and the lack of response to levodopa were more common in DLB (Louis et al, 1997). The neuropsychological profile is characterized by deficits in attention, executive function and visuospatial function (Hansen et al, 1990). Clock drawing is often helpful in demonstrating the visuospatial deficit.

Treatment with cholinesterase inhibitors may reduce delusions, apathy, agitation and hallucinations (McKeith et al, 2000). A severe extrapyramidal reaction to antipsychotic medication is another feature of this disease. If behavioral problems do not respond to cholinesterase inhibitors, low-dose treatment with atypical antipsychotic medications (quetiapine or clozapine) may be considered (Swanberg, 2002). Although motor symptoms may respond to levodopa, treatment may be limited by hallucinations.

**References:**


**Parkinson’s Disease Medications**

At this time no treatment has been shown to slow or stop the progression of Parkinson's disease. Treatment is therefore symptomatic. There is no standard or "best" treatment for Parkinson's disease. A number of treatment approaches help patients with Parkinson's disease. These approaches include:

- general lifestyle modifications (rest and exercise)
- dietary considerations
- physical therapy
- speech therapy
- medication therapy
- surgical therapy

**Medications for Parkinson's disease**

A number of medications are available for treating the motor symptoms of Parkinson's disease. Because individuals with Parkinson's disease experience various motor symptoms of differing severity, the optimal medication (and whether to treat with medication) varies considerably between individuals. With time and progression of disease, the dose of medication(s) may need to be increased or new medications added.

No drug has been shown with confidence to slow the progression of Parkinson’s disease (i.e., exert a ‘protective’ effect). In some cases a protective effect has been suggested but the evidence for benefit is incomplete and debatable. Early symptomatic treatment has been advocated by some in the belief that it may support basal ganglia compensatory mechanisms and restore normal dopaminergic transmission (Schapira, 2009).

**Levodopa (carbidopa/levodopa; Sinemet®, Parcopa®)**

The introduction of levodopa (L-dopa) more than 40 years ago revolutionized the treatment of Parkinson's disease. Although Parkinson's disease is characterized by a loss of neurons that contain and release dopamine, oral or intravenous dopamine is not effective because like other charged amino acids, it does not pass the blood/brain barrier. However, levodopa (a precursor of dopamine) is transported to the brain and is then metabolized to dopamine.

For most individuals, treatment with levodopa reduces the symptoms of slowness, stiffness, and tremor. To **prevent blood amino acid decarboxylases from metabolizing most of an administered does of levodopa** before it reaches the brain, levodopa is always **combined with an inhibitor of this enzyme**. In the US, the dopa decarboxylase inhibitor is carbidopa, whereas in Europe benserazide is used.
Many patients need a minimum of 75 mg/d of carbidopa to avoid the nausea that occurs if levodopa is converted to dopamine systemically.

Although levodopa remains the single most effective treatment for Parkinson's disease, treatment over a number of years may lead to variability in an individual's response to treatment—so-called “motor fluctuations.” The fluctuating response to levodopa can be broadly divided into "on" and "off" periods. During an "on" period, a person can move with relative ease often with reduced tremor and stiffness. “Off” periods describe those times when a person has greater difficulty with movement. A common time for a person with Parkinson's disease to experience an "off period" is just prior to taking the next dose of levodopa, and this experience is called "wearing off." The “off periods” may also occur unpredictably without a consistent relation to the timing of medication. Another form of motor fluctuation is uncontrolled abnormal movements, called “dyskinesias.” These may take a variety of forms and may be localized or generalized. About 40% of patients treated with levodopa will develop motor fluctuations within six years of treatment.

Levodopa is rapidly absorbed from the small intestine. Most patients experience improvement in symptoms about 30 minutes after a dose, and the benefit lasts for about 3-5 hours. However, the duration of benefit may range from as long as a day to as short as an hour. Food (in particular, protein-rich food) delays absorption of levodopa by the gastrointestinal tract and delivery into the bloodstream and diminishes transport across the blood-brain barrier. Thus, patients should be instructed to take levodopa 30-45 minutes before meals or 2 hours after meals to maximize the benefit of an individual dose.

Over the past decade, there has been increasing concern that treatment with levodopa might hasten the rate of neurodegeneration. The Early versus later Levodopa Study was designed to address this concern. About 360 patients with early Parkinson's disease were assigned to receive carbidopa/levodopa at daily doses of 37.5/150, 75/300, 150/600 versus placebo over a period of 40 weeks and then undergo a withdrawal of treatment for 2 weeks. After the 2-week withdrawal, the severity of parkinsonism was greater in the placebo group than in those undergoing treatment. These data were interpreted as suggesting that levodopa either slows the progression of PD or has a prolonged effect on the symptoms of the disease (Fahn et al, 2004).

**Levodopa preparations**

Levodopa is available in a standard and a "controlled-release" (CR or SR) formulation. Controlled-release levodopa has a longer duration of action because the time taken for the gastrointestinal tract to absorb levodopa is increased. However, because the controlled-release formulation only allows 70% of the levodopa to be absorbed by the gastrointestinal tract, it is often necessary to increase the amount of levodopa taken when a person is switched from standard (or immediate-release) levodopa to controlled-release levodopa, in order to obtain the same benefit.

**Standard release preparations**
carbidopa/levodopa (Sinemet®) available in 10/100, 25/100, or 25/250 tablets
Parcopa® is an accelerated-release preparation available in 10/100, 25/100, or 25/250 tablets

**Controlled-release preparations** levodopa/carbiopa (Sinemet CR®) 25/100 or 50/200 tablets

**Catechol-O-methyl transferase (COMT) inhibitors**
Another class of enzyme inhibitors, called COMT inhibitors, also prevent the metabolic breakdown of levodopa. Their **main effect is to prolong the duration of action of levodopa**. COMT inhibitors do not contain levodopa, and they must therefore be taken with levodopa for benefit. They may be prescribed when an individual experiences "wearing off," particularly when dopamine agonists (see below) are not tolerated. If dyskinesias develop after starting a COMT inhibitor, the dose of levodopa may need to be reduced. A recent study has shown that entacapone, when used as an adjunct to levodopa in parkinsonian patients without motor fluctuations, does not improve performance on standard rating scales but does improve a variety of quality-of-life measures (Olanow et al, 2004).

**COMT inhibitors:**
Entacapone (Comtan®)—200 mg tablets are usually given with each dose of levodopa.
Tolcapone (Tasmar®)—100 mg and 200 mg tablets; generally given three times a day.

**Combined carbidopa, levodopa and entacapone (Stalevo®)**
This preparation combines all 3 medications in one pill, which may be more convenient but may not be as flexible as taking the medications individually. The name of the pill refers to the milligrams of levodopa in the pill, eg Stalevo® 75, Stalevo®100 or Stalevo® 200.

**Dopamine agonists**
Dopamine agonists differ from levodopa, since they **do not have to be modified by brain enzymes in order to activate dopamine receptors**. They may be used in place of levodopa or in combination with it. Although treatment with dopamine agonists causes motor fluctuations less frequently than levodopa, dopamine agonists are **more likely to cause a number of other side effects** (such as nausea, somnolence, postural hypotension, hallucinations, and lower extremity edema), particularly in patients over 70 and those with baseline cognitive deficits. Thus, in prescribing dopamine agonists, the treating physician must weigh the potential benefits and adverse effects.

There are two commonly prescribed oral dopamine agonists in the United States: pramipexole and ropinirole. Apomorphine, a subcutaneously administered dopamine agonist, was approved for use in the United States in 2004. The dopamine agonists differ in several respects, including: chemical structure, duration of action, and side effects. Pramipexole and ropinirole have half-lives 6-12 hours and are therefore taken 2-3 times daily.

Large clinical trials comparing pramipexole and ropinirole to levodopa showed that they can be used in early Parkinson's disease and reduce the severity of symptoms. Over the years, differences in the effects of the dopamine agonists have emerged. One side effect is daytime sleepiness and "sleep attacks." Although this may occur with all of the dopamine agonists (and levodopa), it was first appreciated in people treated with pramipexole.

**Apomorphine**
Apomorphine is indicated in patients who experience "off states" refractory to modifications of oral medications such as increasing the dose or frequency of dopaminergic medications or introducing a COMT inhibitor. It has a rapid onset of action, usually within 10-20 minutes but the duration of action is short, lasting for only about an hour. Apomorphine is only available from specialty pharmacies. Because nausea occurs in the vast majority of patients, pretreatment with trimethobenzamide (Tygan®) is required. Initial titration and observation for side effects (syncope, hypotension) must occur in the physician's office.
Behavioral side effects occur in 5-10 percent of patients taking dopamine agonists. The behaviors often reflect a disorder of “impulse control” in which the patient fails to resist the behavior even when it may be distressing or may impair function socially or occupationally. These behavioral changes are often compulsive and include gambling, shopping, and binge eating, as well as increased sexual behaviors. These behavioral changes typically resolve once the dose of the dopamine agonist is reduced or discontinued.

Monoamine oxidase B inhibitors

Selegiline

Selegiline is an inhibitor of the enzyme MAO-B (monoamine oxidase B). MAO-B breaks down dopamine. When it is inhibited, the action of dopamine is prolonged in the brain, and the symptoms of Parkinson's disease are improved. MAO-B inhibitors also have a mild antidepressant effect. Early studies of selegiline suggested that it may delay the progression of Parkinson's disease but this appears to have been confounded by a mild symptomatic effect. Currently there is no firm evidence that selegiline slows disease progression. It is effective as monotherapy for symptomatic relief or as an adjunctive agent.

Selegiline preparations include:
Eldepryl®, Atapryl®, Carbex®, and Zelapar

Rasagiline

Rasagiline is another MAO-B inhibitor that has been approved for monotherapy and adjunct therapy in Parkinson’s disease. It is taken once daily and is less likely to cause insomnia than selegiline. A recent study showed that treatment with 1 mg rasagiline provided benefits that were consistent with a possible disease-modifying (or neuroprotective) effect whereas treatment with 2 mg daily did not (Olanow et al, 2009)

Rasagiline (Azilect®) is available as 0.5 and 1 mg tablets, usually taken once daily

Other medications

A number of other antiparkinsonian medications can be used alone or in combination with levodopa or a dopamine agonist in patients with Parkinson's disease. These medications do not stimulate dopamine receptors but alter basal ganglia neurotransmission by affecting other receptors. The most commonly used medications are amantadine and anticholinergic medications.

Amantadine

Amantadine may be used alone or in combination with levodopa or dopamine agonists. It reduces symptoms of fatigue and tremor in certain patients with early Parkinson's disease, but benefit may be short-lived. More recently, amantadine has been found helpful for people with advanced Parkinson's disease who experience levodopa-induced dyskinesias.

Amantadine (Symmetrel®) as 100 mg capsules, tablets, or in liquid form that may be convenient for an individual who does not tolerate a full 100-mg dose or has dysphagia

Anticholinergic Agents
Anticholinergic medications may reduce tremor or rigidity but have little effect on bradykinesia and imbalance. They can be taken alone or in combination with levodopa. They are rarely used in elderly patients or those with cognitive problems, because increased confusion is a side effect. Specific anticholinergic medications include:

- Biperiden HCL (Akineton®): 2 mg tablets
- Benztropine mesylate (Cogentin®): 0.5 mg, 1 mg, 2 mg tablets
- Trihexyphenidyl (Artane®): 2 mg and 5 mg tablets as well as liquid form

References:


Surgical Treatment for Parkinson's Disease

For most patients with Parkinson's disease, levodopa and other medications are effective for maintaining a good quality of life. As the disorder progresses, some patients develop significant motor fluctuations. Often, wearing off and dyskinesias can be managed with changes in the medication regimen (see Medications for Parkinson's disease). When medication adjustments do not alleviate motor fluctuations or when side effects from medications cause significant problems, surgical treatment of Parkinson's disease may be considered. Two recent studies have shown advantages of deep brain stimulation over best medical therapy in appropriated selected patients with Parkinson’s disease (Deuschl et al 2009, and Follett et al 2010). Selection criteria for these studies included levodopa responsiveness and persistent disabling fluctuations. Patients were excluded for atypical syndromes, dementia, and continuing drug or alcohol abuse.

There are different types of surgery for Parkinson's disease. Thalamotomy and pallidotomy were the first surgical procedures developed and are brain lesioning procedures. To perform them, the surgeon uses a small heat probe to destroy a small region of brain tissue that is abnormally active in Parkinson's disease. No instruments or wires are left in the brain after the procedure, which produces a permanent effect on the brain. Pallidotomy is the standard ablative procedure.

Deep brain stimulation (DBS) surgery involves placing a thin metal electrode into either the globus pallidus or subthalamic nucleus. A programmable pulse generator is implanted subcutaneously beneath the clavicle. A subcutaneous extension wire connects the pulse generator to the brain electrode. The stimulator can be adjusted during a routine office visit by a physician or nurse. Unlike lesioning, DBS does not destroy brain tissue. Instead, it reversibly alters the function of the brain tissue in the region of the stimulating electrode. Although DBS is a major advance, it is a more complicated therapy that may demand considerable time and patience before its effects are optimized.
What are brain targets for DBS?

There are now two main targets in the brain that may be selected for treatment of Parkinson’s disease:
- the globus pallidus (GPi),
- the subthalamic nucleus (STN).

Stimulation of the globus pallidus or subthalamic nucleus, in contrast, may benefit not only tremor but also other parkinsonian symptoms such as rigidity, bradykinesia, dyskinesias, and gait problems. A recent study compared the outcomes of 300 patients who were randomized to deep brain stimulation of either the globus pallidus interna or subthalamic nucleus (Follett et al 2010). Two years after surgery, there was no clear advantage to either location. Patients undergoing subthalamic stimulation required a lower dose of dopaminergic agents than did those undergoing pallidal stimulation. One component of processing speed declined more after subthalamic stimulation group, and the level of depression worsened somewhat after subthalamic stimulation and improved after pallidal stimulation. Serious adverse effects occurred at similar rates.

How does DBS work?

In Parkinson's disease, loss of dopamine-producing cells leads to excessive and abnormally patterned activity in both the GPi and the STN. "Pacing" of these nuclei with a constant, steady-frequency electrical pulse corrects this excessive and abnormal activity. DBS does not act directly on dopamine producing cells and does not affect brain dopamine levels. Instead, it compensates for one of the major secondary effects of dopamine loss, the excessive and abnormally patterned electrical discharge in the GPi or the STN. The mechanism by which the constant-frequency stimulation pulse affects neuronal function has not been determined.

How is the surgery performed?

The procedure for implanting a brain electrode varies somewhat from one medical center to another. Typically these operations are performed with the patient awake, using only local anesthetic and occasional sedation. The basic surgical method is called stereotaxis, a method useful for approaching deep brain targets though a small skull opening. For stereotactic surgery, a rigid frame is attached to the patient's head just before surgery and an MRI is obtained with the frame in place. The images of the brain and frame are used to calculate the position of the desired brain target and guide instruments to that target with minimal trauma to the brain.

Then, the patient is taken to the operating room. At that point sedative medication is given and a patch of hair on top of the head is shaved. After local anesthesia of the scalp, an incision is made on top of the head behind the hairline and a small craniotomy (1.5 cm) is performed. At this point, all intravenous sedatives are turned off so that the patient becomes fully awake.

To maximize the precision of the surgery, some surgical teams employ a brain-mapping procedure in which fine microelectrodes are used to record brain cell activity in the region of the intended target to confirm that it is correct, or to make very fine adjustments of 1 or 2 mm in the intended brain target if the initial target is not exactly correct.

Once the target site has been confirmed by microelectrode recording, the permanent DBS electrode is inserted. After the DBS electrode is inserted and tested, the patient is sedated. The electrode is anchored to the skull with a plastic cap, and the scalp is closed with sutures. The patient then receives a general anesthetic for the placement of the pulse generator in the chest wall and positioning of a connecting wire.
between the brain electrode and the pulse generator unit. This part of the procedure takes about 40 minutes and is sometimes performed at a second operation.

**Would both sides of the brain be done at once or separately?**

DBS on one side of the brain mainly affects symptoms contralaterally. Many patients have symptoms bilaterally. DBS leads can be placed on one side or both sides on the same operating day. The decision to place one or two stimulators in one operating day is made according to a patient's symptoms and general health. For elderly patients, or patients concerned about a longer operation, it may be best to stage the procedures a few weeks or months apart.

**What are the benefits of DBS surgery?**

The major benefit of surgery for Parkinson's disease is that it improves the off-medication state so that it is more like the on-medication state. In addition, it may reduce levodopa-induced dyskinesias. The procedure is most beneficial for patients with Parkinson's disease who cycle between states of immobility ("off" state) and states of better mobility ("on" state). Surgical treatments "smooth out" these fluctuations so that there is better function during of the day. Symptoms that improve with levodopa (slowness, stiffness, tremor, gait disorder) may also improve with DBS. Symptoms that do not respond at all to levodopa usually do not improve significantly with DBS. Following DBS of the STN, there may be a reduction, but not elimination, of antiparkinsonian medications. At present, we believe that DBS only suppresses symptoms and does not alter the underlying progression of Parkinson's disease. In addition to improvements in motor function, recent studies show improvements in quality of life measures for subjects randomized to DBS compared to those randomized to best medical therapy (Deuschl et al 2006; Weaver et al 2009).

**What are the risks of DBS surgery?**

The most serious potential risk of the surgical procedures is a cerebral hemorrhage, producing a stroke. This risk varies from patient to patient, depending on the amount of brain atrophy and the general medical condition, but the average risk is about 2%. If stroke occurs, it usually occurs during or within a few hours of surgery. The effects of stroke can range from mild weakness that recovers in a few weeks or months to severe, permanent weakness, intellectual impairment, or death.

The second most serious risk is infection, which occurs in about 4% of patients. If an infection occurs, it is usually not life threatening, but it may require removal of the entire DBS system. In most cases, a new DBS system can be re-implanted when the infection is eradicated. Finally, in 10-20% of patients, hardware may break or erode through the skin with normal usage, requiring it to be replaced.

In the first few days after surgery, it is normal to have some temporary swelling of the brain tissue around the electrode. This may produce no symptoms, but it can produce mild disorientation, sleepiness, or personality change that lasts for up to 1-2 weeks.

Improvement after surgery correlates with preoperative levodopa responsiveness and younger age. Patients with dementia or atypical parkinsonism do not typically benefit from surgical treatments.

Following DBS surgery, the patient is given a hand-held battery-operated unit that can be used to determine if the device is on or off, to turn it on or off, and to check battery life. The device may also be programmed to allow patients to adjust stimulation parameters according to limits set by the programming physician. Normally, in DBS for Parkinson's disease, the device is left on all the time. The
newest generation of DBS devices offers a rechargeable system (using external charging pads for those subjects who require high power settings and stimulators with longer battery life.

Are "restorative therapies" available?

Many patients inquire about "restorative" therapies, a category of procedures that includes transplantation of fetal cells or stem cells, growth factors, or gene therapy. The goal of most of these procedures is to correct the basic chemical defect of Parkinson's disease by increasing the production of dopamine in the brain. Although theoretically very attractive, more experimental work must be done in order to make these therapies practical and effective. Phase 1 have been conducted for 3 different gene therapies and phase 2 studies have either been completed or planned to test these therapies against sham surgical control subjects. There have been no studies of stem cell treatments for PD thus far.

Summary

The surgical treatment options for patients with Parkinson's disease are expanding. DBS surgery offers important symptomatic relief in patients with moderate disability from Parkinson's disease who still retain some benefit from antiparkinsonian medications and who are cognitively intact. Patients who fluctuate between "on medication" and "off medication" states are usually good surgical candidates. The major risk is a 2% risk of stroke, due to bleeding in the brain. DBS requires regular neurological follow-up and periodic battery changes. It reduces, but does not eliminate, symptoms of Parkinson's disease. The time to consider DBS surgery is when quality of life is no longer acceptable on optimal medical therapy as administered by an experienced neurologist.

References:
Gene therapy for Parkinson’s disease

Parkinson's disease is characterized by loss of dopaminergic neurons in the substantia nigra. The loss of these neurons results in a change in the balance of excitatory and inhibitory pathways in the brain, and these pathways in turn affect movement control. Medication therapies, and in particular dopamine replacement therapies were developed in the late 1960s and remain the mainstay of therapy. More recently, surgical treatments (pallidotomy or deep brain stimulation of selected targets in the brain) have been developed to improve motor function by normalizing increased brain cell activity due the loss of dopamine releasing cells which occurs as a consequence of reduced dopamine release.

People with Parkinson's disease generally respond well to medication for a number of years. However with long-term treatment, the response to medication—especially to levodopa—may fluctuate. The most common “motor fluctuation” is called wearing off. Wearing off may develop years after beginning treatment with a dopamine agonist or levodopa. It occurs when the benefits of the prior dose are beginning to wane and is often appreciated as recurrence of tremor or slowness in the hour before the next dose of medication is taken. The other main motor fluctuation is involuntary twisting turning movements called dyskinesias which typically occur in the hour or so after taking dopaminergic therapies. Medications (insert link) and deep brain stimulation (insert link) are described in other modules. In this module, the potential advantages of gene therapy will be discussed.

Gene therapy has a number of potential advantages that may be useful in progressive medical conditions. Conceptually, it is a means of making cells produce a protein that they normally do not produce that might improve a particular condition. The technique inserts genes that provide specific genetic instructions that cells use to produce a desired protein. The treatments produce proteins that are involved in normal cellular processes and may therefore be less likely to cause side effects. Moreover, gene therapy can be targeted to a specific location where the treatment is needed, which also may limit possible side effects. Finally, gene therapy does not rely on the placement of devices that may fail due to mechanical or electrical reasons. A number of proteins have already been used for gene therapy for Parkinson's disease. The choice depends on the treatment strategy. For example one strategy is to improve the delivery of dopamine to the relevant brain regions in Parkinson's disease. Other strategies have tried to provide growth factor support to brain regions with the expectation that this might help damaged nerve cells to recover and thus slow Parkinson's disease progression or reverse it.

Gene therapy relies on transporting small pieces of genetic material, or DNA, into the targeted brain cells. Because human bodies have developed a number of enzymes that breakdown unprotected DNA, most gene therapies use some sort of “protective envelop”, called a vector, to carry the genetic material and deliver the gene to targeted cells. The most common vectors include adeno-associated virus type 2, lentivirus, adenovirus, and herpes simplex virus. Only viruses that have lost her ability to reproduce themselves and do not cause disease are selected as vectors for gene therapy. Adeno-associated virus type 2(AAV-2) has particular advantages. It carries genetic material only to neurons (not to the other supporting cells of the brain) and once within the brain it is particularly efficient in carrying the genetic material to the neurons affected in Parkinson's disease. Most gene therapy studies in Parkinson's disease have used AAV-2 as the vector. Lentiviruses have also been studied extensively. Because of their larger capacity, lentivirus is the vector when more than one gene is used.

Once a gene and vector have been selected, the treatment must be administered to the relevant area of the brain. The studies performed thus far have been directed to particular regions of the basal ganglia. The basal ganglia are number of interconnected deep brain regions that are involved in movement control. A major pathway connects the substantia nigra to the putamen (where dopamine is normally released) and then to the globus pallidus directly or by way of the subthalamic nucleus. To date, gene therapy for Parkinson’s disease has been administered by drilling a hole in each side of the skull and then injecting the selected dose of the viral vector (containing the gene) into the desired brain region (either putamen or subthalamic nucleus) using image-guided surgical techniques. These treatments are performed either in a standard operating room or in a specialized radiology suite. Recovery from
these procedures is usually quite rapid, with most patients being discharged home 1 or 2 days after gene therapy.

In the descriptions below, reference will be made to the clinical studies conducted thus far in humans. **Phase 1** studies refer to small studies, usually 10-15 patients at a single institution. These studies are designed to determine the safety and possible benefit of a particular treatment and no untreated comparison group is recruited. If a phase 1 study shows that a treatment is well tolerated and provides some evidence of benefit, a phase 2 study may be performed. **Phase 2 studies** are larger (typically 30-60 patients), are conducted at a number of medical institutions, and a control or placebo group is included for comparison to the group treated with the gene therapy. Humans in research studies often obtain substantial improvements that are unrelated to the specific treatment they receive. The improvement may be due to the expectation of benefit from treatment. This phenomenon is called the **placebo effect** and can be quite substantial in patients with Parkinson's disease. Therefore using a “control” or untreated group is considered crucial in determining whether a treatment offers true benefit, beyond the placebo effect. Because gene therapy involves surgical treatment, a simulated or “sham” surgical procedure is necessary in gene therapy studies. These sham surgical procedures usually involve drilling small holes in the skull but not injecting the brain with the gene therapy under study. In the studies, investigators who perform subsequent evaluations of the patients are also unaware of whether the patient underwent the gene therapy or the sham procedure. This is called a **double-blind** study since neither the subject nor the investigator who performs the routine visits knows the treatment status of the patient. Double-blind studies are considered fundamental in determining whether a treatment offers a true benefit. If a study treatment shows safety and benefit in a Phase 2 study, a **Phase 3** study may then be performed. This study is similar to a Phase 2 study but is larger study (usually involving hundreds of patients) and is designed to confirm the treatment effectiveness, monitor side effects, and collect information that will allow the treatment to be used safely. Information from a successful Phase 3 studies (along with other information about the study treatment) is then used by the United States Food and Drug Administration (FDA) to determine whether a new treatment is approved for routine treatment of a medical disorder.

Regarding therapeutic strategies, 3 approaches have been developed thus far. These are as follows:

(1) The first approach is to **increase dopamine production** in specific regions of the brain. One study using this approach approaches uses the gene for the enzyme **aromatic amino acid decarboxylase (AADC)**. This enzyme converts levodopa into dopamine, a neurotransmitter that is deficient in Parkinson's disease. Studies have shown that AADC is gradually lost in Parkinson's disease. The progressive loss of this enzyme is thought to contribute to the need to increase levodopa doses as time goes on. The rationale for this approach is that if a greater amount of AADC is present in the location where dopamine should be released, then a more reliable and perhaps a more robust response to levodopa will occur. Moreover, it is possible that a patient who no longer is obtaining a reliable benefit from levodopa therapy might regain responsiveness to this treatment after gene therapy with AADC. Inherent in this approach treatment is that the patient may alter the effect of his gene therapy by adjusting his daily dose of levodopa, since the effect of this therapy depends on continuing treatment with levodopa. A phase 1 study in which AADC was injected into the putamen has been completed at 2 different doses. In the 10 patients treated, clinical rating scales and diaries of motor function suggested benefit and specific imaging studies provided evidence of successful gene therapy.

**A variation on this strategy uses 3 genes that produce the enzymes** AADC, tyrosine hydroxylase (TH), and GTP-cyclohydrolase-1 (GCH-1). Together these 3 enzymes can generate dopamine independent of external levodopa. The advantage of this approach is that it may be possible for the patient to discontinue treatment with levodopa. Although this
approach seems very attractive, there are concerns that its benefits relies on producing precisely the right amount of dopamine. For example, too high a dose of gene therapy might result in complications due to excessive production of dopamine. The results of the study should be published in the near future.

(2) The second gene therapy strategy is to **adjust or modulate the excitatory and inhibitory pathways** of the brain. The rationale of this approach is that the nerve cells of the subthalamic nucleus are overactive and that release of an inhibitory neurotransmitter in this brain region might normalize these cells. The gene for the enzyme **glutamic acid decarboxylase (GAD)**, which produces the inhibitory neurotransmitter called GABA, has been examined in a phase 2 study in which 45 subjects were randomized to either bilateral treatment with GAD or a sham or simulated surgical procedure. While both patient groups showed improvement at 6 months, the improvement was greater in the subjects who underwent GAD treatment. Overall this study provided support for both the efficacy and safety of this approach.

(3) The third approach is using brain proteins, termed **growth factors** (because of their role in brain development), that might protect against progression of Parkinson's disease or possibly even reverse it by stimulating regrowth of injured nerve cells. A number of growth factors have been identified over the years. These include glial cell line-derived neurotrophic factor (GDNF) and Neurturin which is similar to GDNF and shares the ability to promote the survival of dopaminergic neurons. In models of Parkinson's disease, GDNF and Neurturin have been shown to promote the survival of dopaminergic neurons. Both a phase 1 and phase 2 study using Neurturin gene therapy targeted to the putamen have been performed. In the phase 2 study, 38 patients were randomized to Neurturin gene therapy or to sham surgery. Unfortunately, there was no significant difference in the main outcome measures at 12 months. While the lack of benefit in the main outcome measures was disappointing, a subgroup of patients followed for 18 months was slightly better in the Neurturin patient than the sham treatment group, suggesting that slightly longer period of observations might be necessary to see a benefit with this gene therapy. Because of this interesting result, a second phase 2 study is underway in which Neurturin gene therapy is also targeted to the substantia nigra.

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Gene(s)</th>
<th>Vector</th>
<th>Completed studies</th>
<th>Ongoing or Enrolling studies</th>
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<tr>
<td>Increase dopamine</td>
<td>AADC</td>
<td>AAV-2</td>
<td>Phase 1</td>
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<td></td>
<td>AADC, TH, &amp; GCH-1</td>
<td>Lentivirus</td>
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<td>Phase 1 &amp; 2 in progress</td>
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<td></td>
<td>Neurturin</td>
<td>AAV-2</td>
<td>Phase 1 &amp; 2</td>
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Other gene therapy strategies are being considered. One such study includes using human erythropoietin. This study in experimental animals showed protection against toxins that usually damage dopaminergic cells. Other therapies are using insights provided by improved understanding of genetic causes of Parkinson's disease. It is conceivable that, as our knowledge of specific genetic defects causing Parkinson's disease improves, specific gene therapies could be developed for each individual genetic defect.

**Conclusion:**

Limitations in the benefit of medical and the surgical treatments of Parkinson's disease have stimulated efforts to develop new therapies. Gene therapy has distinct theoretical advantages over conventional treatment for Parkinson's disease as it might preserve or restore dopaminergic neurons through the use of growth factors or alternatively increase the availability of enzymes required for dopamine synthesis. Over the past 10 years, 3 different strategies have emerged and have been implemented in carefully designed human treatment protocols. To date, these gene therapies appear to be safe and there is some evidence suggesting benefit. Ongoing and planned phase 2 studies will identify the most promising therapies that will require further evaluation in a phase 3 study. It is hoped that gene therapies will provide improved treatment options for people with Parkinson's disease in the near future.

**References:**


