

# A Review of the Shaking Palsy

*By: Dominique Comer, Pharm.D. candidate and Lynn Harrelson, R.Ph., FASCP*

*Lynn Harrelson discloses she has a relationship with the Parkinson Support Center of Kentuckiana. Dominique Comer has no financial relationships that could be perceived as real or apparent conflicts of interest.*

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## Objectives:

After completing this knowledge-based activity, the participant will be able to:

- Identify early and late symptoms of Parkinson's disease.
- Specify therapies currently available to decrease the progression of Parkinson's disease as well as treat movement symptoms.
- Describe important counseling points for patients with Parkinson's.
- Locate additional resources for Parkinson's disease.

## Overview of Parkinson's Disease

Parkinson's disease (PD) is a degenerative disorder of the central nervous system that affects movement. It is the second most common neurological disease in America, after Alzheimer's. The prevalence of this disease is more common in men than women and is approximately 0.5 to 1 percent among persons 65 to 69 years of age, rising to 1 to 3 percent among persons 80 years of age and older<sup>1</sup>.

Parkinson's is characterized by tremors, muscle rigidity and the slowing or freezing of movement. The nerve cells in the brain that produce dopamine (substantia nigra) begin to degenerate in a patient with Parkinson's. Over 80% of dopamine production in the substantia nigra is lost before symptoms of PD are seen. With the dopamine-acetylcholine ratio thrown into imbalance, movement disorders are manifested<sup>2,3</sup>.

## Cause

The cause of the dopamine cell death or impairment is not known. Some possibilities are<sup>4</sup>:

- Environmental and/or food toxins, e.g. fluorocarbons and combinations of pesticides
- Genetic predisposition
- Viral infections
- Aging, as dopamine cells are naturally being depleted over the course of life

There are several genes that are known to cause Parkinson's, but they account for a very small minority of cases. The most important is a gene called parkin. The parkin gene creates a protein, also called parkin, which helps to break down defective proteins inside neurons. When the parkin gene is altered or mutated, this function is impaired. It is hypothesized that the accumulation of defective

proteins contributes to death of neurons. Two mutated copies of parkin are needed to develop PD. This type of inheritance pattern is autosomal recessive, as one copy of the defective gene is inherited from each parent. Parkin mutations cause young-onset PD, with symptoms beginning usually in the fifth decade. Parkin mutations are the most common genetic cause of PD, but still account for less than one percent of all cases. Other known genes for PD include alpha-synuclein, DJ-1, PINK-1, and UCHL-1, but altogether these represent only a small number of PD cases<sup>5</sup>.

Parkinsonism, or the clinical state of PD, can be caused by medications that deplete dopamine<sup>5</sup>. The following are medications that are known to cause drug-induced parkinsonism:

Table 1. Drugs That Can Cause Parkinsonism<sup>2</sup>.

Antipsychotics	Haloperidol (Haldol) Chlorpromazine (Thorazine) Trifluoperazine (Stelazine) Amoxapine (Asendin) Risperidone (Risperdal) Olanzapine (Zyprexa) Ziprasidone (Geodon) Aripiprazole (Abilify) Reserpine Quetiapine (Seroquel)-less risk than those listed above Clozapine (Clozaril)-less risk than those listed above
Antinausea	Metoclopramide (Reglan) Prochlorperazine (Compazine) Promethazine (Phenergan)
Antiseizure	Valproate (Depacon)
Antirejection	Cyclosporine
Antidysrhythmic	Amiodarone

### Early symptoms

As the symptoms of early Parkinson's disease are slow and gradual, they may be difficult to notice. Early symptoms include an expressionless face, micrographia (small, cramped handwriting), shakiness, losing track of words or thoughts, and irritability. These early symptoms might last a long time before a patient realizes that anything is wrong. This is especially true because early

symptoms do not include tremors<sup>6,7</sup>.

### Late symptoms

The most prominent symptom of late stage Parkinson's is the appearance of tremors. Characteristic tremors involve a rhythmic back and forth motion of the thumb and forefinger (pill rolling). This may start on one side of the body, then can spread throughout the body and worsen. Tremors might become worse when the patient is relaxed or under stress, but often diminish with intentional movement or while the patient is sleeping<sup>6,7</sup>.

Rigidity or resistance to movement develops in many Parkinson's patients due to the simultaneous contraction of opposing muscles. With persistent contraction, muscles may ache and become stiff. Rigidity in the facial muscles can cause a patient's face to look emotionless. Other symptoms of Parkinson's disease that may present are bradykinesia, (the slowing, or loss, of spontaneous and automatic movement) and akinesia (the difficulty in initiating voluntary movements). These symptoms are unpredictable and range from non-existent to highly debilitating<sup>6,7</sup>.

Impaired balance and coordination can cause postural instability and an increased risk for falls in Parkinson's patients. Balance seems to worsen when the patient moves quickly or abruptly. Minor symptoms that only affect a smaller number of patients include depression, dizziness, difficulty swallowing, drooling and chewing, urinary

problems, constipation, skin problems and sleep problems. Memory loss and slow thinking can also occur; however, the ability to reason remains intact<sup>6,7</sup>.

### Current Drug Therapy

At present, there is no cure for Parkinson's disease. The therapies currently available decrease the progression of the disease as well as treat movement symptoms.

### Levodopa<sup>8,9</sup>

Levodopa (L-Dopa, L-3,4-dihydroxyphenylalanine) is the most effective drug treatment for Parkinson's disease and is the gold standard. This dopamine precursor is given orally. Dopamine itself cannot be orally administered as it cannot penetrate the blood-brain barrier. The most frequent side effect is nausea; this can be overcome by slowly titrating the dose up over time. Another frequent side effect is low blood pressure upon standing (orthostatic hypotension), which can cause dizziness. These effects usually lessen after several weeks of therapy. Levodopa therapy can have adverse effects on the central nervous system, including confusion, hallucinations and dyskinesias. This side effect profile is usually very problematic for PD patients as they usually have diminished strength for recovery.

Although it has helped relieve most Parkinson's symptoms, a decline in its effectiveness is usually seen after two to five years of use. Long-term levodopa usage leads eventually to periods of intermittent loss of

the drug's effectiveness, or "off" states, followed by "on" periods after a dose is taken and when smoother movement is again possible. Off periods are often a rapid loss of response (known as the "on-off" phenomenon), and often attributable to unpredictable drug response. "Off" phases can last as little as a few minutes to a few hours and the recurring cycles severely disable patients' lives.

Carbidopa, a decarboxylase inhibitor, is frequently added to levodopa (Sinemet) to allow for more levodopa to enter the brain by reducing the peripheral formation of dopamine from levodopa. This also allows smaller doses of levodopa to be given to the patient, decreasing the side effects of levodopa. Controlled-release formulations may aid in prolonging the effective interval of a levodopa dose.

### **Dopamine agonists**<sup>8,9</sup>

Dopamine agonists such as pramipexole (Mirapex) and ropirinole (Requip) last longer in the body than levodopa and are often used as add-on therapy when the on-and-off effects of levodopa appear. They are not nearly as effective in treating the symptoms of Parkinson's disease. Side effects of dopamine agonists include hallucinations, sleepiness, water retention and orthostatic hypotension. These medications may also increase the risk of compulsive behaviors such as hypersexuality, compulsive gambling and compulsive overeating.

### **Monoamine oxidase inhibitors (MAOIs)**<sup>8,9</sup>

MAOIs, including selegiline (Eldepryl) and rasagiline (Azilect), help prevent the breakdown of dopamine by blocking MAO-B in the brain. The onset of these medications may take weeks to be seen. Side effects are rare but may include confusion, headache, hallucinations and dizziness. These medications should not be used in combination with other antidepressants, ciprofloxacin, St. John's wort or certain narcotics, for fear of increasing the risk of serotonin syndrome.

### **Catechol O-methyltransferase (COMT) inhibitors**<sup>8,9</sup>

Tolcapone (Tasmar) and entacapone (Comtan) prolong the effect of carbidopa-levodopa combination therapy by blocking COMT, which breaks down levodopa. Tolcapone has been linked to liver damage and liver failure, thus it is normally used only in people who are not responding to other therapies. Entacapone does not cause liver damage and is available combined with carbidopa and levodopa (Stalevo). However, it may worsen other levodopa side effects, such as dyskinesias, nausea, confusion or hallucinations. It may also cause urine discoloration.

### **Anticholinergics**<sup>8,9</sup>

These drugs have been used for many years to help control the tremor associated with Parkinson's disease. A number of anticholinergic drugs, such as benzotropine (Cogentin) and trihexyphenidyl are available.

However, their modest benefits are often offset by side effects such as impaired memory, confusion, constipation, dry mouth and eyes, and impaired urination. Anticholinergics are not used very long due to this side effect profile. Benztropine is best taken at bedtime while trihexyphenidyl should be taken before or after meals, depending on the patient's response. This class of medications can be very problematic in the geriatric population and should be avoided in the elderly if possible.

### **Glutamate (NMDA) blocking drugs**<sup>8,9</sup>

Amantadine (Symmetrel) alone may provide short-term relief of mild, early-stage Parkinson's disease. It also can be added to carbidopa-levodopa therapy for people in the later stages of Parkinson's disease, especially if they have problems with dyskinesias induced by peak levels of levodopa. Skin examinations should be conducted periodically, as this medication may increase the risk for melanoma. Doses should be tritrated up from 100mg daily, with the final dosage based on renal function. Amantadine therapy must not be stopped abruptly, as this may cause a withdrawal syndrome. Symptoms of this compound include agitation, paranoia, stupor and hallucinations.

### **Alternative Therapies**

#### **Rescue therapy**

Apomorphine is given subcutaneously as rescue therapy to revert the patient from an excessively prolonged "off" period in matter of

minutes; the effect generally lasts for an hour. Apomorphine often causes nausea and therefore it is given with the antiemetic domperidone for pre-treatment<sup>10</sup>. An initial test dose must be given in the presence of a healthcare provider during an off period and blood pressure is monitored for at least 30 minutes post administration. Caution should be taken, as apomorphine may cause QT prolongation.

### **Surgery options**

PD patients that are ideal for surgery are those that have extensive “off” periods (over 25% of the day), severe “off” periods, painful dystonias or disabling dyskinesias. Deep brain stimulation is a non-pharmacological alternative that has been FDA approved for the treatment of Parkinson’s disease. An electrode is placed in a specific area of the brain (for PD, the most common area is the subthalamic nucleus), and a neurostimulator sends high-frequency electrical pulses to the area, suppressing PD symptoms. This treatment is used in advanced, levodopa-responsive patients whose symptoms are not adequately controlled with medication alone<sup>11,12</sup>.

### **Important counseling points**

#### **Exercise**

Regular exercise such as yoga, tai chi and dance can help improve the quality of life of those with Parkinson’s. By concentrating on movements that build on balance and gait, the severity of PD symptoms may be decreased<sup>13</sup>.

#### **Diet**

An important counseling point for the patient is to restrict protein intake. High concentrations of neural amino acids are formed by protein breakdown. These amino acids inhibit the transport of levodopa into the brain. This problem could be minimized by restricting daily protein intake to dinner or the evening meal, so that effectiveness can be maximized throughout the day. Some patients may not be able to do this as food helps with the nausea rather than taking an anti-nausea medication. The risks and benefits should be assessed, as there may be a lower biological response but fewer side effects.

#### **Sleep**

Lack of adequate rest or meaningful sleep weakens Parkinson’s disease patients’ ability to function, recover from weakness or disease. Any health deviation is more problematic for the PD patient and increases as they age.

#### **Other important points of care include:**

##### **1. Put the morning dose of medication and a glass of water on the nightstand.**

Many people with Parkinson's disease find that their ability to move around freely is worst in the morning. This might be because their last dose of medication, taken the previous evening, is already wearing off. By the time their morning dose has a chance to take effect, they have already been up and around for a while.

A good approach is to plan ahead. Suggest that patients set tomorrow morning's first dose on the nightstand along with a glass of water before retiring for the night. In the morning, encourage them to take the dose as the first thing they do. Another suggestion is to set the alarm clock for an hour before they plan to get out of bed, take their dose and continue to rest. By the time they get up to start their day, the morning dose has already gotten a head start.

##### **2. Pay attention to whether pills are taken with food.**

For medications that can be taken with or without food, explain to the patient the consequences of either decision. In general, when medication is taken on an empty stomach, more of it is absorbed into the bloodstream. On the other hand, if a medication makes the patient queasy, this can be minimized by taking it at mealtime.

##### **3. Avoid most anti-nausea medications.**

Most anti-nausea medications can worsen the symptoms of Parkinson's disease or interfere with the benefits of Parkinson medication. Some of the most common anti-nausea drugs, e.g. metoclopramide (Reglan), promethazine (Phenergan) and prochlorperazine (Compazine) block the body's chemical dopamine receptors. These are the very receptors that most Parkinson medications activate and essentially the two medications cancel each other out. One exception, ondansetron (Zofran), works on a different chemical receptor and avoids this problem.

#### **4. Be mindful of forgetfulness.**

People with Parkinson's disease may already be more prone to forgetfulness because of either their disease or their age. Certain medications used for Parkinson's disease, e.g. benztropine (Cogentin) and trihexyphenidyl (Artane), or urinary incontinence, e.g. tolterodine (Detrol) and oxybutynin (Ditropan), can worsen memory. Keep an eye out for these drug interactions.

#### **5. Know the difference between tremors and dyskinesias.**

Parkinson's disease often causes tremors, which are rhythmic oscillations of hands or other parts of the body. However, many Parkinson medications, when dosed high enough, can produce another kind of excessive, involuntary movements called dyskinesias. These might involve muscles of the face, neck, trunk, arms or legs, and have the appearance of wiggles and fidgets rather than of rhythmic oscillations.

Making sure that the patient and caregivers can distinguish between these different movement disorders is important because the presence of one might mean that the dose of medication should be increased, while the presence of the other might mean that the dose should be decreased.

#### **6. Maintain body weight.**

In patients with advanced Parkinson's disease, the mere act of chewing food can require so much work and effort that dietary intake plummets. If the

patient is presently overweight, this might be useful to a point, but continued weight loss can threaten health. In such circumstances, suggest that patients take advantage of food supplements that permit intake of important nutrients with a minimum of effort. Ice cream and milk shakes are packed with protein and calories and require a minimum of chewing. Supplementing one's usual diet with a can or two of pre-packaged products like Ensure or Sustacal adds missing ingredients that prevent weight loss. Carnation Instant Breakfast provides many of the same ingredients, but at lower cost.

#### **7. Manage Dry Mouth**

Dry mouth is common in people with Parkinson's and is often related to medications, especially anticholinergics or antidepressants.

If a patient is experiencing this side effect, have them discuss the problem with their doctor, as changing the dosage may be helpful. Some helpful tips for dealing with dry mouth include:

- Getting dietary advice. Some foods make dryness worse. Refer to a dietician when appropriate
- Taking frequent sips of water and avoid dehydration. Drinking two liters of fluid a day is recommended
- Applying lip balm to keep lips moist

- Visiting a dentist. They are able to remove some irritants that may be making the problem worse.
- Removing dentures at night
- Asking a dentist or doctor about the possibility of using artificial saliva
- Suggesting specialist dry mouth products such as Biotene, which are available over the counter
- Avoiding alcohol and smoking – both make dryness worse
- Avoiding mouthwashes that are not prescribed by a dentist or doctor. Many contain alcohol
- Do not turn to sweets and hard candies to increase saliva. This will only increase decay and other oral problems. To help avoid dry mouth, try using sugar free candy

There are a number of Parkinson's disease support groups and information websites. The National Parkinson Foundation ([www.parkinson.org](http://www.parkinson.org)) and the American Parkinson Disease Association ([www.apdaparkinson.org](http://www.apdaparkinson.org)) offer not only knowledge but links to local events and groups, as well as updates on the disease state.

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