

The Role of Pharmacists in Treating & Managing Parkinson's Disease

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Learning Objectives:

Pharmacists:

After completing this lesson, for each new drug described the pharmacist should be able to:

1. Identify the visual and clinical testing tools used to diagnose PD.
2. Identify the classes of medications used to treat PD.
3. Understand the pros and cons of each class of medications and when to use these medications.
4. Understand how comcomitant disease states and medications could lead to increased exacerbation of PD symptoms and identify methods to prevent this.
5. Understand ways that pharmacists can assist PD patients, their caregivers, and physicians to properly manage their condition.

Pharmacy Technicians:

After completing this lesson, for each new drug described the pharmacy technician should be able to:

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2. Identify the classes of medications used to treat PD.
3. Understand the pros and cons of each class of medications and when to use these medications.
4. Understand how comcomitant disease states and medications could lead to increased exacerbation of PD symptoms and identify methods to prevent this.
5. Understand ways that pharmacists can assist PD patients, their caregivers, and physicians to properly manage their condition.

Parkinson's disease (PD) is a group of conditions of motor symptom disorders that result in a reduction of dopamine producing cells in the brain. The exact cause of the disease is unknown, but genetic factors, environmental factors, and use of some illicit drugs are considered potential causes. An estimated 500,000 people in the United States suffer from PD with approximately 50,000 new cases identified each year. The average age of onset is 60 and the incidence is expected to increase as the baby boom population ages. The incidence rises as people reach their 70s and 80s. The total cost to the health care system is estimated to be \$6 billion including direct costs associated with treatment and indirect costs, including psycho-social care.

What is Parkinson's Disease?

Parkinson's disease (PD) is a group of conditions of motor symptom disorders that result in a reduction of dopamine producing cells in the brain. The exact cause of the disease is unknown, but genetic factors, environmental factors, and use of some illicit drugs are considered potential causes. Usually individuals are diagnosed based on presentation of symptoms common to the condition including tremors in the hands, arms, jaw and face; rigidity of the limbs; overall slowing of body movements; and impaired balance and coordination.

Symptoms generally begin suddenly but worsen over time. Often, older patients are not immediately diagnosed because many symptoms are associated with the effects of aging. A PD diagnosis is often overlooked in younger people because the disease is primarily associated with older people. When PD is suspected, diagnostic tools include genetic testing, testing of the olfactory and autonomic systems, and a variety of neurological functioning tests.

Scope of the Problem

An estimated 500,000 people in the United States suffer from PD with approximately 50,000 new cases identified each year. The average age of onset is 60 and the incidence is expected to increase as the baby boom population ages. The incidence rises as people reach their 70s and 80s. Parkinson's occurs more commonly in men than in women.

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Patients with PD experience serious deficits in activities of daily living and often require constant care through a professional caregiver or a family member or

friend. Patients with PD experience serious deficits in motor skills that make mobility extremely difficult.

Other symptoms of autonomic dysfunction also result from PD, including decreased libido, dry mouth, urinary retention and incontinence, orthostatic hypotension, and intolerance to heat and cold. These disorders often require specific medication therapy to treat. Treating PD and its concomitant disorders often lead to serious side effects if medication is not managed properly. These side effects might lead to discontinuation of therapy for PD or an exaggeration of PD symptoms. As frontline health care professionals, pharmacists have the ability to manage the complex medication regimens of PD patients and be aware of new, evolving treatments.

Current treatment of PD includes drug therapy, surgical procedures, and speech and physical therapy. No known cure exists, so the goal of treatment is reduction or management of symptoms. Drug therapy is usually initiated using one or more of the following categories:

- Levodopa/cardiodopa, a precursor product that is converted to dopamine. This product is sometimes used as single agent therapy or along with cardiodopa, an agent that delays the conversion of cardiodopa until it reaches the brain. These products have been the traditional treatments for Parkinson's disease.
- Dopamine agonists work to activate dopamine receptors in the brain. Newer medications in this category are often considered first line therapy for Parkinson's disease because of safety and side effect profiles in comparison to levodopa therapy, but may also be given in combination with levodopa depending on patient tolerance.
- Agents used to preserve dopamine levels in the brain, such as COMT inhibitors, an enzyme involved in the breakdown of neurotransmitters.
- Monoamine oxidase inhibitors (MAO-B) that work to block the breakdown of dopamine in the brain.
- Anticholinergics that help to regulate muscle movement to help control tremors and rigidity by restoring the balance between dopamine and acetylcholine by reducing the amount of acetylcholine. This class of medications has some serious side effects, particularly in seniors, and therefore use today is limited.

Diagnosing Parkinson's Disease

Parkinson's disease is typically diagnosed based on the development of symptoms but after 70-80% of dopamine receptors have been lost. New diagnostic techniques focus on early diagnosis to attempt to stop

the progression of the disease before substantial damage occurs. Symptoms that occur outside the substantia nigra, the portion of the brain most affected by advanced PD, often occur 10 or more years before the onset of motor symptoms. Such symptoms include rapid eye movements, vivid and violent dreams, and olfactory dysfunction. The nonmotor early symptoms include general aches, pains, fatigue, restlessness, paresthesias, and internal tremors. Depression often occurs prior to the emergence of PD. These early symptoms might be overlooked as PD because they are general and might be associated with other disease states, a psychiatric disorder, or extreme stress. PD cannot be determined to be the cause of these early symptoms and a blood test does not exist to confirm diagnosis.

Definitive diagnosis typically occurs through observation of a patient's motor symptoms over a period of time. Pharmacists can play a role in this observation by documenting a patient's family history of PD or noting any substantial changes in motor functioning. In some cases, symptoms mimicking PD occur because of medication therapy for other conditions. Therefore, pharmacists can work with physicians to determine whether the cause of the symptoms is PD or another condition.

Pharmacists and physicians should monitor patients for the hallmark symptoms of PD, including tremors, rigidity, bradykinesia, and postural instability. Tremors often occur in the hands or feet when a person is at rest, but in rare cases may occur in the jaw. Rigidity manifests through reduced range of motion or stiffness. One characteristic includes a patient's arms hanging by their sides rather than swinging freely. Cogwheel rigidity is a common symptom associated with PD and is demonstrated by pushing on a patient's arm resulting in jerky motion rather than smooth, fluid movement. Generalized bradykinesia manifests itself through difficulty initiating or continuing movement resulting in dysrhythmic awkward gait and mobility. All of the symptoms listed above result in a postural instability that can result in falls or difficulty walking, including a shuffling type gait, or a sudden freeze when walking. A patient's facial expression may be stolid and rigid, often known as masked. Pharmacists should be sensitive when approaching patients with potential PD because of the potential for embarrassment that could occur when pointing out irregularities in walking or posture.

When PD is suspected, a neurologist typically confirms the diagnosis using a variety of tests including a thorough neurological exam and full physical, including medical history and genetic risks. Then, CT scans or MRIs are used to establish the damage to the substantia nigra. CT scans and MRIs can more definitely rule out tumors, strokes, or other disorders that express

PD-like symptoms. Conditions often ruled out in the diagnosis include: progressive supranuclear palsy, a disorder that includes PD symptoms plus dementia and abnormal eye movements; Shy-Dager Syndrome, a rare disorder that causes neurogenic orthostatic hypotension; Wilson's Disease, a genetic disorder associated with PD-symptoms plus liver dysfunction and tremors.

PD is staged using the Hoehn and Yahr system, with evaluation criteria ranging from Stage 1 (little or no impairment function) to Stage 5 (confinement to a bed or wheelchair in the absence of assistance). Another system that is considered more complex, the Unified Parkinson Disease Rating Scale (UPDRS), measures mental functioning, behavior, and mood; activities of daily living; and motor function on a scale of 0 (no disability) to 199 (total disability). The UPDRS is generally reserved for clinical trials or monitoring progression. Pharmacists should understand patient's staging of PD to help monitor progression and the effectiveness of medication therapy.

Current medication treatment options for PD

Five classes of medication currently exist for the treatment of PD.

Cardiodopa/levodopa in combination marketed as the brand name Sinemet CR™ (Merck & Company) and also available in generic, is the standard therapy for PD. Levodopa is a precursor to dopamine that is metabolized quickly in the body and is unable to cross the blood brain barrier to reach the substantia nigra to replace dopamine in the nonfunctional receptors. Levodopa is also associated with severe gastrointestinal (GI) symptoms. Cardiodopa, a aromatic decarboxylase inhibitor, is administered in conjunction with levodopa to prevent peripheral metabolism of levodopa and results in a 70-80% reduction in the dosage of levodopa. Cardiodopa also helps alleviate the GI side effects associated with levodopa.

Levodopa and cardiodopa are generally given shortly after the diagnosis of PD with the goal of rapidly improving the motor symptoms, including tremor, bradykinesia, rigidity, postural instability, and depression. Levodopa does not generally act to improve mental changes, posture, dysphasia, and excessive salivation.

The cardiodopa/levodopa tablets as Sinemet CR or generic forms are available in the following dosages: 50-200 mg or 25/100 mg that releases the active ingredient over a 4-6 hour period. These dosages are titrated to provide patients with the maximum clinical benefit. The clinical response to levodopa is dose dependent, with higher doses generally resulting in a better response. A 2004 study in the New England Journal of Medicine examined the use of the cardiodopa/levodopa

combination in 361 patients with early PD. Patients were divided into 3 treatment groups and a placebo group. Patients in the treatment group were administered 37.5/150 mg, 75/300 mg, or 150/600 mg three times a day. Patients receiving the higher dosages showed greater improvement and patients in the treatment groups experienced better outcomes than those in the placebo group. However, patients should be given lower doses during initial treatment and then titrated slowly.

Short term side effects associated with use of cardiodopa/levodopa include nausea and vomiting, postural hypotension, sedation, and restlessness. Postural hypotension is exacerbated by the concomitant use of medications to reduce blood pressure. Pharmacists should carefully monitor PD patients who also have a diagnosis of hypertension. This information, when necessary, should be documented in the patient profile and pharmacists should assist patients in reporting this information to their neurologist. Long-term side effects of cardiodopa/levodopa include confusion, delusions, hallucinations, paranoia, compulsive behaviors such as hypersexuality and gambling, and psychosis.

Other concerns associated with the long-term use of levodopa include dyskinesias that occur after administration because of high levels of dopamine followed by the re-emergence of symptoms when the levodopa effect begins to dissipate. Signs of dyskinesia often develop as early as 6 months after beginning levodopa therapy. This can be frustrating for patients who are able to experience normal motions for a period and then suddenly become unable to move freely. This effect worsens with long-term use of levodopa and the duration of effectiveness of levodopa also decreases over time, thus increasing the number of “on and off periods” experienced by patients. The rate of dyskinesia is often as high as 40% for patients who use levodopa for 4-6 years. Patients diagnosed with PD at younger ages, between 20-40 years old, are more likely to develop dyskinesias than those diagnosed at 60 years old or above. The development of motor symptoms is often related to increasing dosages of levodopa and therefore is best managed by tapering the dosages to ensure that the patient receives maximum clinical effectiveness at the lowest dosage possible.

Cardiodopa/levodopa have been standard therapy for many years but the side effect profile, dosing difficulties, and the inability to sustain effectiveness over a long period of time have lead to the development of newer agents for treatment of PD. Today, rather than being first line therapy, cardiodopa/levodopa may be prescribed later in the course of therapy because physicians seek to maximize effectiveness when absolutely necessary. This course of action is especially relevant to younger PD

patients who will currently require a life-time of PD therapy.

The use of generic cardiodopa/levodopa should be carefully monitored because not all agents are therapeutically equivalent to each other and sudden changes could result in movement disorders. If patients take brand name Sinemet CR, then this should continue unless the patient is slowly titrated to a generic agent. Once a patient is stabilized on a generic agent, the patient should continue with this same agent unless slowly titrated to another generic version.

Anticholinergic agents. This class of therapy has fallen out of favor in recent years because of newer compounds available to more effectively treat PD. These agents are primarily used in younger PD patients and have been found to be more effective than levodopa for treating tremors, rigidity, and excessive salivation. The goal of anticholinergic therapy is to reduce the levels and action of acetylcholine, a neurotransmitter which is increased in the presence of low dopamine levels. The reduction of acetylcholine relieves symptoms.

Today, the most commonly used anticholinergic agents are trihexyphenidyl, benztropine, and diphenhydramine, all inexpensive generic agents.

Side effects from these agents can be severe for all patients with PD because they increase the risk of falls, which often occur because of the etiology of PD. These side effects tend to be more severe in older patients; therefore, use of these agents is recommended primarily for younger patients. Other adverse effects include dry mouth, constipation, urinary retention, and blurred vision. At higher dosages, cognitive impairment and hallucinations can occur.

Dopamine receptor agonists currently marketed include Parlodel® (bromocriptine, Novartis Pharmaceuticals, Inc.), Mirapex® (pramipexole dihydrochloride tablets, Boehringer Ingelheim Pharmaceuticals, Inc.), and ropinirole, available generically and as Requip® XL™ (GlaxoSmithKline). Neupro® (rotigotine transdermal patch, Schwarz Pharma LLC) was recalled by the Food and Drug Administration (FDA) effective April 2008 and is no longer available. This class of agents mimics the effects of dopamine in the brain.

These agents have been shown to be more consistent in stimulation of dopamine receptors compared to levodopa and are generally associated with less motor impairment. While levodopa continues to be the gold standard to improve motor skills and improve activities of daily living, Mirapex and ropinirole are often substituted as safer alternatives when beginning therapy because of a better side effect profile, particularly in younger PD patients and others who receive long-term treatment for PD.

Adverse effects common to the entire class of dopamine agonists include nausea, vomiting, orthostatic hypotension, hallucinations, confusion, daytime drowsiness, and sleep attacks. Bromocriptine is an older agent and is ergotamine based. Risks associated with its use include pulmonary fibrosis. In contrast, the newer agents, pramipexole, ropinirole, and rotigotine are non-ergotamine based and are generally considered to be safer than the older agents.

Like levodopa, the dosing recommendation is to begin low and titrate the dosage slowly upward until the patient experiences an appropriate clinical response with the minimal amount of side effects possible. At higher dosages or in combination with levodopa, patients experienced a greater rate of impulse control disorders (including compulsive shopping, gambling, binge eating, and hypersexuality). Younger patients are more susceptible to the impulse effects.

Other side effects specific to certain dopamine agonists include:

- Ropinirole and rotigotine are metabolized through the cytochrome P450 (CYP) system and therefore, must be dosed cautiously with other agents also metabolized by this system. Patients on maintenance medications metabolized through the CYP system should use other agents. Many antibiotics are metabolized through this system and therefore pharmacists should appropriately monitor patient's use of antibiotics and recommend alternatives when necessary.
- Pramipexole is renally excreted through the cationic transport system; therefore, medications should be monitored closely when used with agents such as cimetidine.
- Dosing of long-acting Requip XL should be carefully monitored once administered in the body as it is more difficult to stop side effects in comparison to the shorter acting agents.

COMT Inhibitors including Comtan® (entacapone, Novartis Pharmaceuticals, Inc.) and Tasmar® (tolcapone, Valeant Pharmaceuticals International) are administered in combination with levodopa to prevent the "wearing off" effect by inhibiting the enzyme catechol-O-methyltransferase that metabolizes levodopa. As a result, the effect of levodopa is extended. These agents are generally added to cardiodopa/levodopa therapy after the effectiveness has diminished. Side effects of these agents include vivid dreams, visual hallucinations, nausea, sleep disturbances, daytime drowsiness, headache, and dyskinesias. Some of the side effects could be associated with the use of levodopa and therefore patients should be carefully monitored to determine which agent is causing the side effect.

Stalevo® (cardiodopa/levodopa/entacapone, Novartis Pharmaceuticals, Inc.) is a combination product which can be used by patients who been stabilized on a combination of a Comtan plus cardiodopa/levodopa therapy. A similar combination product is not currently available with Tasmar and therefore patients who seek to achieve use of a single agent should begin therapy with Comtan to ensure that the transition to the combination is more clinically consistent.

MAO-B inhibitors including selegiline and Azilect® (rasagiline tablets, Teva Neuroscience, Inc.) increase the level of dopamine in the brain by inhibiting the catabolism of dopamine and also can be used to enhance the benefits of levodopa. Rasagiline is currently the only MAO-B agent approved as initial monotherapy for PD. This agent is effective in improving quality of life, improving movement, slowing functional decline, and helping to improve activities of daily living. Generally, dosages are recommended at about 1-2 mg/day with no clinical improvement at higher levels.

Side effects with rasagiline include flu-like symptoms, joint pain, depression, and upset stomach. Clinical prescribing instructions as well as many clinical pharmacy systems note that patients using rasagiline limit intake of foods containing levels of tyramine, including cheese. Antidepressants commonly known as MAO-A inhibitors have this effect because tyramine metabolism is affected by MAO-A system not MAO-B. However, as a cautionary measure this information was included in the labeling despite no clinical evidence of such reactions. Pharmacists should review messages regarding the MAO-A reactions from pharmacy benefit management companies or other pharmacy processing systems and document the rationale for dispensing medications.

Pharmacists must proceed with caution when dispensing MAO-Bs with meperidine, serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, non-selective MAO inhibitors, dextromethorphan, and St. John's Wort. Dispensing MAO-Bs with these agents could result in serotonin syndrome, a potentially life-threatening condition with a number of symptoms that mimic PD, including tremors, jerky movements, rigidity, and tremors. Other symptoms include generalized symptoms that are also commonly present in PD patients, including headache, chills, confusion, anxiety, rapid breathing, and high blood pressure. As a result, pharmacists should recommend other alternatives to MAO-B for patients who must continue to take agents that might cause serotonin syndrome.

Treatment for dementia associated with PD

FDA recently approved the Exelon® Patch

(rivastigimine transdermal system, Novartis Pharmaceuticals, Inc.) for the treatment of mild-to-moderate dementia in PD patients. This condition is known as Parkinson's disease dementia (PDD) and results from a loss of nerve cells in the brain responsible for memory and decision-making. Exelon is postulated to exert its therapeutic effect by enhancing cholinergic function through reversible inhibition of cholinesterase. Diagnosis of PDD is based on individuals who have dementia when other causes have been ruled out and who have had a diagnosis of PD for at least 2 years. (This product has also been approved for dementia associated with Alzheimer's disease.)

Exelon is a transdermal patch applied one time daily. Pharmacists should educate patients about the proper manner to apply the patch that is included in the packaging instructions. Patients should be given the lowest dose possible with a titration period of up to 4 weeks. GI side effects are the most commonly reported problems. Patients with a history of heart disease, lung conditions, asthma or other breathing problems, bladder problems, or seizures should use Exelon with caution. Pharmacists should be aware of these conditions, but should also note that the contraindications are common for most medications that treat dementia.

New Research in the Treatment of PD

Research continues in the area of PD. New therapies will focus on treating the underlying causes of PD in novel ways as well as finding genetic links to the disease to help prevent or cure PD.

FDA recently approved a clinical trial to treat a limited number of patients with spinal chord injuries with embryonic stem cells. Patients and advocacy groups associated with PD believe that this trial could lead to other research using stem cells to prevent or cure PD.

The Role Of The Pharmacist In Managing Patients With PD: Helpful Hints

Patients with PD often experience a plethora of other conditions and disease states, some resulting from the treatment for PD itself. Some medications may also exacerbate PD symptoms. As a frontline health care professional with access to the patient's complete medical record, the pharmacist can serve to coordinate care among physicians and communicate with the neurologist about actual and potential adverse effects associated with PD medications or other medications.

Pharmacists can work closely with physicians to determine whether a patient's existing conditions or medication regimens are the cause of PD symptoms or whether a diagnosis of PD can be made. Pharmacists must be sensitive when approaching patients with potential PD diagnosis to avoid embarrassment caused

when noting an awkward gait or other movements.

As therapy progresses, pharmacists also have the ability to observe a patient's gait and mannerisms that may change in response to PD therapy. Pharmacists should be familiar with the symptoms of PD and be able to determine whether a medication regimen is effective or whether alternative regimens are required. As a source of information and contact for PD patients and their caregivers, pharmacists can help a patient develop a medication schedule to ensure appropriate dosing of PD medications and to avoid interactions with other agents.

Summary

Several treatments exist for the management of PD. Most treatments focus on increasing dopamine levels in key portions of the brain with the goal of improving functionality and quality of life, improve activities of daily living, and increase life span. Most medications require a delicate balance of the correct dosage without undue side effects. Many medications require titration to determine the appropriate levels in a patient. This must be carefully monitored by physicians and pharmacists with progress appropriately noted. If a patient fails to respond to certain medications, medications in other classes should be considered.

Pharmacists and physicians must also be mindful of other concomitant disease states associated with PD, and that some medications could exacerbate PD symptoms or interact with PD treatments. A patient's overall treatment regimen should be carefully structured and monitored to avoid undue side effects.

PD is disease that requires direct observation of symptoms as well as clinical monitoring. Pharmacists can help patients, caregivers, and physicians to monitor the visual symptoms of PD to determine the effectiveness of therapy. Changes should be properly communicated to patients and others.

In the future, PD might be treated genetically based on the root cause of the disorder. Today, however, treatments focus on improving symptoms and functionality through medications. Much research is underway for other classes and types of medications effective in PD. Pharmacists should continuously update their knowledge about PD medications to ensure the best patient care for these patients.