Novel and Promising Treatments for Parkinson’s Disease

Kevin W. O’Neil MD, FACP, CMD
Internal Medicine and Geriatrics
Chief Medical Officer
Who Am I?

I am a boxing champion and began showing signs of Parkinson’s disease shortly after retiring from boxing in 1981. I was diagnosed with the disease in 1984 at the age of 42. Though my doctors are not entirely sure, they think my disease may be the result of repeated blows to the head during boxing matches.
I am most famous for my role as Marty McFly in the Back to the Future movies. I was diagnosed with young-onset Parkinson’s disease in 1991 at the age of 30. I went public with my diagnosis in 1998 and committed myself to working for Parkinson’s research. I eventually established a Foundation which raises money for research.
Parkinson’s disease (PD) is typically considered a chronic, progressive neurodegenerative movement disorder. However, it is now known to have variety of nonmotor symptoms as well.
Primary Causes

- Idiopathic—majority of cases
- Genetic
- Drug induced—Calcium Channel Blockers
- Toxins—Supported by the geographically varied incidence
- Head Trauma
- Cerebral Anoxia
Major Symptoms: TRAP

- Tremor
- Rigidity
- Akinesia/Bradykinesia (absence or slowness of movement)
- Postural Instability
- Other motor symptoms include:
  - Gait
  - Dystonia: uncontrollable muscle contraction
  - Hypophonia: soft voice
  - Dysphagia: difficulty swallowing
  - Fatigue
  - Akathesia: a movement disorder associated with inner restlessness
Non-Motor Symptoms

- Mood: 20-80% suffer from depression.
- Behavior: may be a result of dementia, depression.
- Thinking: slowed reaction time and executive dysfunction
- Sensation: impaired sense of smell
- Excessive daytime sleep, insomnia, and sleep disturbances.
- Vision problems
- Impaired proprioception (ability to sense stimuli arising within the body regarding position, motion, and equilibrium)
- Oily skin
- Weight loss
- Incontinence
- Constipation
- Drooling
Management

- Requires careful consideration of a number of factors:
  - Age
  - Symptoms and signs
  - Stage of disease
  - Degree of functional disability
  - Level of physical activity and productivity

- Treatment:
  - Pharmacologic
  - Nonpharmacologic
  - Surgical therapy.
Drug Therapy

- Symptomatic
  - Treats symptoms of disease
  - Do not slow or reverse the natural course
  - Nearly all available treatments are symptomatic

- Neuroprotective:
  - Several potential neuroprotective agents have shown some promise in animals and/or humans and are undergoing further investigation.
Symptomatic Therapy

• The decision to initiate is determined by the degree to which the patient is functionally impaired.

• The timing of this decision varies greatly among patients but is influenced by:
  • The effect of disease on the dominant hand
  • The degree to which the disease interferes with work, activities of daily living, or social and leisure function
  • The presence of significant bradykinesia or gait disturbance
  • Patient values and preferences regarding the use of medications
Drugs for Motor Symptoms

- Levodopa
- Dopamine agonists
- Monoamine oxidase (MAO) B inhibitors
- Anticholinergic agents
- Amantadine
- Catechol-O-methyl transferase (COMT) inhibitors
Levodopa

- The most effective drug for the symptomatic treatment of idiopathic PD
- Particularly effective for the management of bradykinetic symptoms
- Tremor and rigidity can also respond
- Postural instability less likely to do so.
- Levodopa is the drug of choice if symptoms, particularly those related to bradykinesia, seriously threaten the patient's lifestyle.
Levodopa: Adverse Effects

• Less Severe:
  • Nausea
  • Somnolence
  • Dizziness
  • headache

• More serious (more common in elderly):
  • Confusion
  • Hallucinations
  • Delusions
  • Agitation
  • Psychosis
  • Orthostatic hypotension
  • Peripheral neuropathy (low B12)
Is Levodopa Toxic To Neurons?

A 1998 consensus conference reached the following conclusions:

• There is no evidence that levodopa causes neuronal death in animal models of parkinsonism
• There is no evidence that chronic administration of levodopa exacerbates the degenerative process in PD
• Late motor complications arise due to the combination of progressive degeneration of dopamine neurons and the reversible effects of levodopa administration

Data from the ELLDOPA trial suggest:

• Rather than being neurotoxic, levodopa either slows the progression of PD or has a prolonged benefit even after the drug has been stopped.
Dopamine Agonists

• A group of synthetic agents that directly stimulate dopamine receptors.
• Drugs currently approved by the United States Food and Drug Administration (FDA):
  • Bromocriptine (Parlodel, Cycloset)
  • Pramipexole (Mirapex)
  • Ropirinole (Requip)
  • Rotigotine (Neupro): transdermal
  • Apomorphine (Apokyn): injectable
Dopamine Agonists vs Levodopa

- Potential that DAs are associated with fewer motor fluctuations
- Evidence that there is a higher incidence of levodopa-related dyskinesia in young-onset PD
- Some experts suggest using DAs as initial treatment for PD in patients younger than age 60
Adverse Effects of Dopamine Agonists

• Similar to those of levodopa:
  • Nausea, vomiting
  • Sleepiness
  • Orthostatic hypotension
  • Confusion
  • Hallucinations.
• Peripheral edema common with chronic use
• Dopamine Agonist Withdrawal Syndrome
• Associated with an increased risk of impulse control disorders:
  • Pathologic gambling
  • Compulsive sexual behavior
  • Compulsive buying
MAO B Inhibitors: Selegiline (Eldepryl)

- Modestly effective as symptomatic treatment
- May have neuroprotective properties.
- In many individuals, monotherapy does not produce a functionally significant benefit.
- A reasonable option in early PD as long as the patient understands its limitations.
Rasagiline (Azilect)

- Neuroprotective properties in animal models
- Modestly effective as symptomatic treatment for PD in human clinical trials
Adverse Effects of MAO B Inhibitors

- Nausea
- Headache
- Insomnia
- Often causes confusion in older adults
- May increase levodopa-induced side effects (dyskinesia, psychiatric toxicity)
Anticholinergics

- Most useful as monotherapy for patients <70 with disturbing tremor but do not have significant bradykinesia or gait disturbance.
- May be useful in patients with more advanced disease who have persistent tremor despite treatment with levodopa or dopamine agonists.
- Examples:
  - Trihexyphenidyl
  - Benztropine (Cogentin)
Anticholinergics: Adverse Effects

- Common and often limit their use.
- Older adults and cognitively impaired patients are particularly susceptible to:
  - Memory impairment
  - Confusion
  - Hallucinations
  - Seldom appropriate for older persons
**Amantadine**

- Antiviral agent with mild antiparkinsonian activity
- Mechanism of action uncertain
- Increases dopamine release
- Inhibits dopamine reuptake
- Stimulates dopamine receptors
- Possibly exerts central anticholinergic effects
- Improvement in bradykinesia, tremor, rigidity
- Best used as short-term monotherapy for mild disease
- Addition of levodopa results in improvement
Amantadine: Adverse Effects

- Ankle edema
- Livedo reticularis
- Confusion
- Hallucinations
- Nightmares
COMT Inhibitors:
Tolcapone (Tasmar), Entacapone (Comtan)

- Ineffective when given alone
- May prolong and potentiate the levodopa effect
- Useful as levodopa extenders
- Mainly used to treat patients with motor fluctuations who are experiencing end-of-dose wearing "off" periods
Tolcapone (Tasmar): Adverse Effects

- Dyskinesia
- Hallucinations
- Confusion
- Nausea
- Orthostatic hypotension
- Managed by lowering the dose of levodopa either before or after the addition of tolcapone
- Diarrhea poorly responsive to antidiarrheal medications in 5 percent of patients
- Orange discoloration of the urine common but benign adverse event
- Elevations in liver enzymes may rarely occur
- Rare cases of liver toxicity
Estrogen

• Low-dose estrogen may be helpful as adjunctive therapy in postmenopausal women with motor fluctuations on antiparkinsonian medication
• No evidence that estrogen has a specific effect on dopamine receptors
• Benefit may be related to an overall sense of well-being.
Neuroprotective Therapies

• Based on the concept that dopaminergic neurons in the substantia nigra can be protected from the complex degenerative process that causes premature cell death and depletion of dopamine.

• Neuroprotective drugs could be used in patients with early clinical signs of disease or potentially even prior to the appearance of disease in those shown to be at genetic risk.

• No treatment to date has proven to be effective for neuroprotection in PD.
Levodopa

- Slows the progression of PD
- Prolonged benefit even after the drug has been stopped
MAO B Inhibitors: Selegeline, Rasagiline

• Ability to block free radical formation from the oxidative metabolism of dopamine
• May also inhibit apoptosis (programmed cell death)
• Provide mild symptomatic benefit
• Rasagiline’s benefits in animal models not confirmed in humans
Dopamine Agonists

- Neuroprotective in the laboratory because they are antioxidants and free radical scavengers
- Feedback reduction of endogenous dopamine turnover
- Benefits in humans unproven
Coenzyme Q10

- Interest arose because mitochondrial dysfunction may play a role in PD
- Available evidence suggests that coenzyme Q10 has no neuroprotective effect for patients with PD
Vitamin E

• DATATOP Trial of patients with early PD
• No beneficial effect of vitamin E compared with placebo for the primary end point of average time to onset of disability requiring levodopa use.
• In 2006, American Academy of Neurology (AAN) concluded that vitamin E should not be considered for neuroprotection
Uric Acid

- Antioxidant properties suggesting that it may prevent oxidative damage and cell death in PD.
- Association between uric acid concentration and the risk of PD does not prove that urate is neuroprotective.
- Therapeutic utility of urate (and diets designed to increase plasma uric acid) is likely to be limited by adverse effects (gout and kidney disease).
- A preliminary trial of the urate precursor inosine demonstrated safety in patients with PD, supporting further trials to study its possible neuroprotective effect in PD.
Isradipine

• Calcium channel antagonist for the treatment of hypertension
• Neuroprotective properties in animal models of Parkinson disease
• A preliminary trial demonstrated its safety in patients with PD
• Larger trial will be needed to assess efficacy
Nilotinib

• Treatment for chronic myeloid leukemia.
• Preclinical studies suggest reduces oxidative stress, and protects dopaminergic neurons
• Very expensive drug
• Cardiovascular toxicity
• Suppression of the bone marrow
• Should not be used to treat PD except in a clinical trial.
Ursodeoxycholic Acid (UDCA)

- Research reported in 2015 from the University of Sheffield
- Marked rescue effect of the drug UDCA on cell batteries (mitochondria) in patient tissue
- First study to demonstrate beneficial effects of UDCA on the nerve cells affected in Parkinson's disease in an animal model of Parkinson's disease
- UDCA is already approved for use in human liver disease
- Results support fast track of UDCA to clinical trials
Nonpharmacologic Therapies

- Education is essential to provide understanding and control over the disorder.
- Emotional and psychological needs of the patient and family should be addressed.
- Support groups are a valuable resource.
- Regular exercise and physical therapy modalities appear to offer benefit for improving function in patients with PD.
- Speech therapy may be helpful in improving speech volume and maintaining voice quality.
- A high fiber diet and adequate hydration help to reduce the constipation of PD.
- Large, high-fat meals that slow gastric emptying and interfere with medication absorption should be avoided.
Why Exercise Is Important?

• One of the best ways to counter the negative effects of Parkinson’s disease
• Enhances oxygen delivery to brain inhibiting further cell damage, cognitive decline, and loss of muscle control
• Improves flexibility and endurance
• Reduces risk for falls
• Eases depression, constipation
Action Steps

• Early referral for physical therapy and/or an exercise program can prevent or delay disability
• Age or stage of disease do not preclude exercise
Movement Is Fun!

- Walking
- Dancing
- Group yoga or Tai Chi
- Gardening
- Aqua aerobics
- Bicycling
- “Wii-hab”
Movement RX

• Moderate-intensity physical activity for 30 minutes on most, if not all, days of the week
  • Can be done at one or more times during the day
  • Start slowly and build up if you have not been active

• Muscle strengthening activity 2 days per week
  • 8-10 Exercises with major muscle groups
  • Newly added to the recommendations for older adults

• Flexibility

• Balance 2 days per week
What Exercise Is Right for You?

“The handle on your recliner does not count as an exercise machine.”
Your Unique Movement RX

• Walking is easiest and most practical for many older adults
• Other: stationary or recumbent cycles, rowing, swimming, chair aerobics, exercise classes/videos, upper-body exercisers, dancing, gardening, tennis, golf, playing with children
• Join a class for strength training
Walking Well

- Consult with your doctor
- Prepare for “off periods”
  - Walking companion
  - Even surfaces and familiar territory
  - Pill box
  - Cell phone
- Stay hydrated
  - Non-carbonated water
  - Sports drinks, fruit juices
- Consider assistive aids for balance; hip protectors
- Environmental prophylaxis
  - Sunscreen, sunglasses, hat, insect repellant, rain gear
- Proper footwear
  - Velcro closure, wide toe box
- Walk with a purpose
Can Dancing Help Me?

- Helps find a consciousness in movement
- Helps regain balance
- Helps fight depression
- Socially engaging
- Intellectually challenging
- Music and dance can be spiritually uplifting

"This is a transporting exercise. When I come here, I don't have Parkinson's."

- Joel Marsh
Surgical Treatment

• Good evidence from randomized controlled trials to endorse deep brain stimulation (DBS) as an effective therapeutic option for well-selected patients with medically intractable symptoms of PD.
• DBS is non-destructive, can be performed bilaterally with low neurologic morbidity, and can be modified over time to deal with changing or progressing patient symptoms.
• Disadvantages:
  • Greater cost
  • Risk of infection, hemorrhage, or mechanical breakdown
  • Need for periodic reprogramming.
  • Does not help postural instability or speech and swallowing problems
  • No evidence that DBS slows progression of the underlying neurodegenerative process.
• Tissue transplantation and intracerebral infusion treatments for motor fluctuations cannot be recommended pending future research concerning these approaches.
Algorithm For Management

Source: American Family Physician, December 2006
Resources

- Parkinson’s Disease Foundation:  
  - www.pdf.org

- National Parkinson’s Foundation:  
  - www.parkinsons.org

- National Institutes of Neurological Conditions and Stroke:  
  - www.ninds.nih.gov
“Alone we can do so little; together we can do so much.”
—Helen Keller
Questions?