

2018 Update in Parkinson's Disease: Treatments and Future Plans

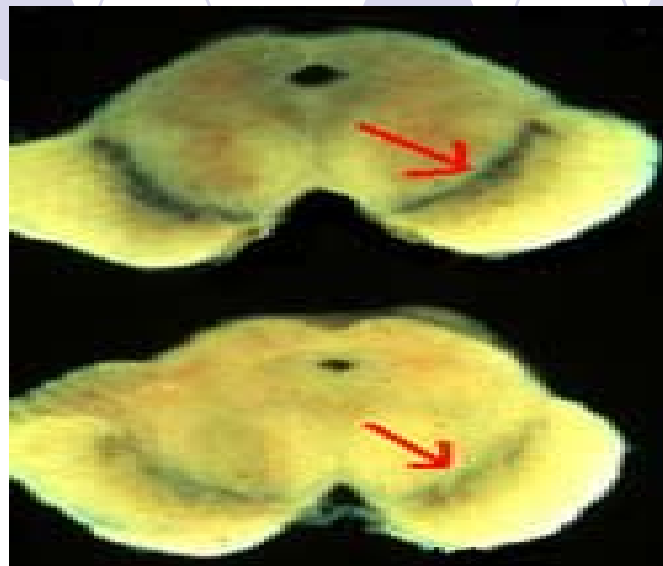
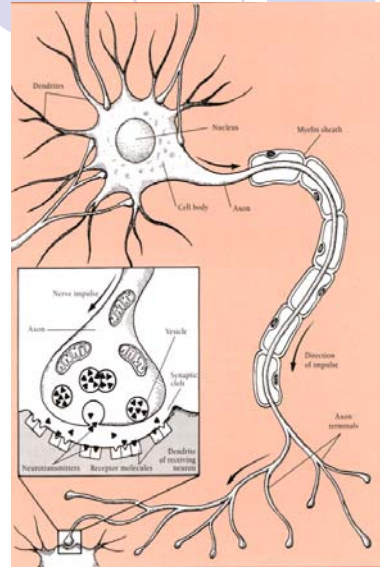
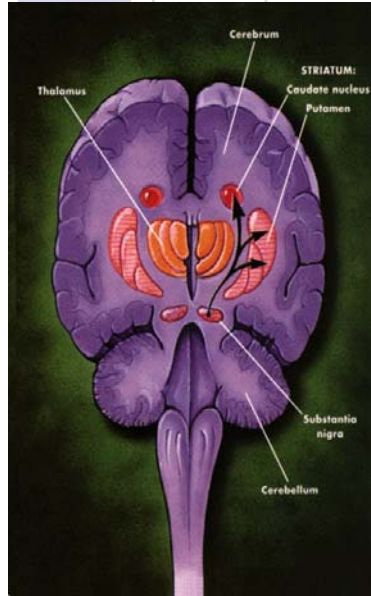
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A National Parkinson Foundation Center of
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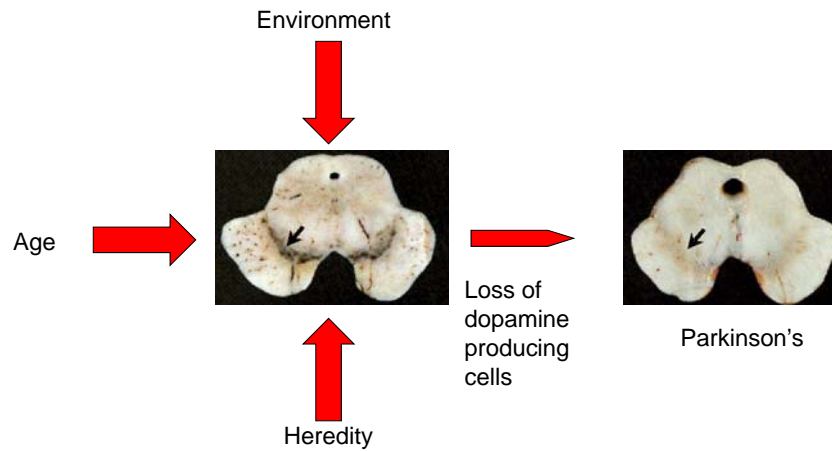
What is Parkinson's Disease?

- A **progressive, chronic**, complex, **neurological** disorder
- Caused by the **degeneration** of cells that produce dopamine
- **Dopamine** is a Neurotransmitter (chemical messenger)
- Dopamine is produced by the cells within the **Substantia Nigra** (black substance)
- One of the few progressive neurological diseases whose symptoms can be alleviated with medications

Dopamine System in Human Brain



What Causes Parkinson's Disease?



Cardinal Signs & Symptoms

- Tremor
- Rigidity
- Bradykinesia
- Impaired Balance (often later in disease)

Other Signs and Symptoms

Micrographia (Small Handwriting)

Stooped Posture

Shuffling Gait

Hypomimia (Masked Face)

Constipation

Urinary Urgency, Frequency,
Incontinence

Drooling

Heat Intolerance

Increased Perspiration

Dandruff

Excessive Skin Oiliness

Low Blood Pressure

Sexual Functional Problems

Fatigue

Speech and Swallowing Difficulties

Sleep Abnormalities

Vivid Dreams

Restless Leg Syndrome

Neuropsychological Problems

Depression

Anxiety

Bradyphrenia (Slowness
of thinking)

Dementia

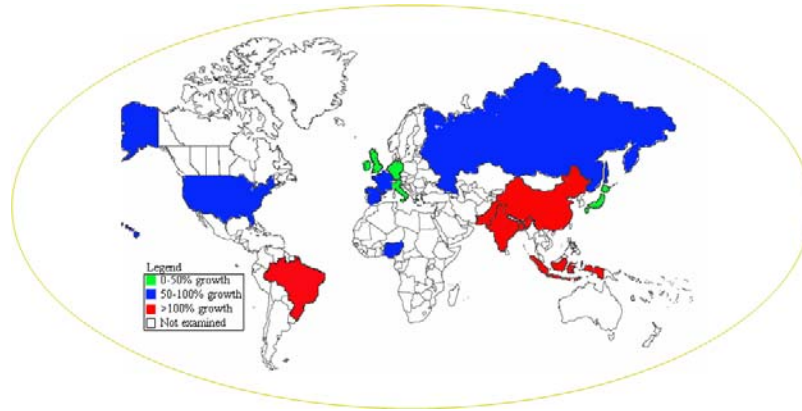
Psychosis (Hallucinations
and Delusions)

Incidence of Parkinson's Disease

- Parkinson's Disease affects about **1,000,000** Americans
- **50,000-60,000** Americans are diagnosed each year
- Average age of onset is **55-65 years of age**
- Present worldwide in all races and socioeconomic groups
- Slightly higher incidence in men
- Few go into nursing homes and reach end stage of disease

The burden of Parkinson disease is growing

Change in number of people with Parkinson disease in the world's most populous nations from 2005 to 2030*

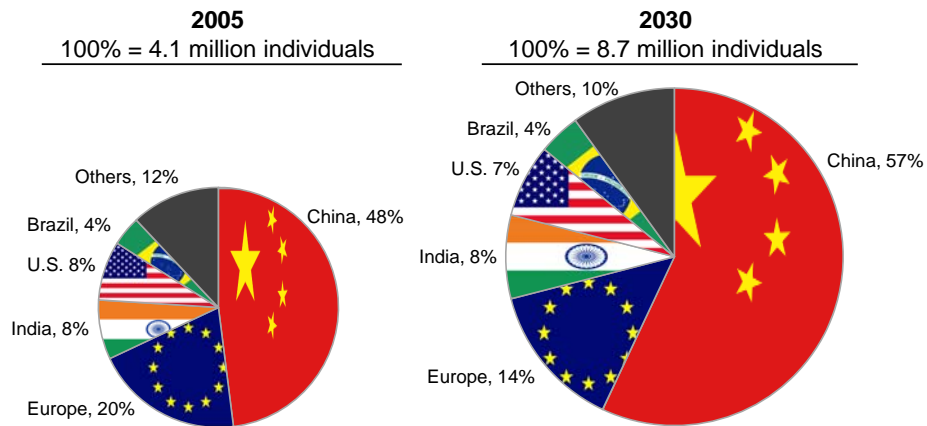


*Among individuals over 50 in the world's ten most and Western Europe's five most populous nations

Source: Neurology 2007;68:384-6

The burden affects the whole world

Distribution of individuals with Parkinson disease by country, 2005 and 2030*



*Among individuals over 50 in the world's ten most and Western Europe's five most populous nations

Source: Neurology 2007;68:384-6

Medications

- MAO-B Inhibitors
 - Azilect (rasagiline)
 - Eldepryl (selegiline)
- Dopamine Agonists
 - Requip (ropinerole) IR and ER
 - Mirapex (pramipexole) IR and ER
 - Neupro Patch
 - Apokyn (apomorphine)
- Levodopa
 - Sinemet (carbidopa/levodopa) IR and ER
 - Stalevo (carbidopa/levodopa/entacapone)
 - Parcopa
- Anticholinergics
 - Artane (trihexyphenidyl)
- COMT-Inhibitor
 - Comtan (entacapone)
- Amantadine
 - Symmetrel

May be used independently or together!

So What's New?!

- In the past 3 years, **6** new treatments were FDA approved for Parkinson's disease
- Improvements in drug delivery, treatment for secondary signs and symptoms and research innovations

Rytary™



- New formulation of extended release carbidopa/levodopa
 - “Accordion-style” capsule
 - Contains beads of C/L that dissolve and absorb at different rates
- Designed to last longer (6 hour doses)
- Early PD: improved movement/ADL activities
- Advanced PD: Reduced motor fluctuations and improved UPDRS scores when compared to Stalevo

Duopa

Duopa
carbidopa/levodopa
enteral suspension

- Unique delivery system for carbidopa/levodopa
- Delivers drug directly to the site of metabolism in the small intestine via external pump
- Brain receives constant supply of medication, reducing on/off time and fluctuations as compared to oral Sinemet

How is Duopa delivered?



- A Duopa cassette
- B CADD-Legacy® 1400 pump
- C Cassette tube
- D Stoma
- E PEG tube
- F J tube

Please see Important Safety Information (Medication Guide) on page 9 and full Prescribing Information at RxAbbVie.com.

Duopa
carbidopa/levodopa
enteral suspension

Other Recent Additions to Drug Marketplace

- Northera (droxidopa)
 - Derivative of norepinephrine (a chemical which regulates our nervous system)
 - Used in treatment of orthostatic hypotension
 - Granted accelerated FDA approval, but only studied in PD for two weeks
 - Needs further review to learn more long-term use

Other Recent Additions to Drug Marketplace

- Nuplazid (pimavanserin)
 - Medication approved for use for psychosis (hallucinations and delusions) in Parkinson's disease
 - Blocks 5HT_{2A} receptors specifically, which are often responsible for psychosis in PD
 - May have less effect on the motor symptoms of PD than other antipsychotics currently on the market

Other Recent Additions to Drug Marketplace

- Xadago (safinamide)
 - MAO-B inhibitor
 - Approved for improvement of “on” time without troublesome dyskinesia in PD
 - Used in conjunction with other PD medications (not monotherapy)
 - In clinical trials, PD patients overall did not require a reduction of their C/L doses when combined with Xadago

Other Recent Additions to Drug Marketplace

- Gocorvi (amantadine ER)
 - Extended release amantadine
 - Approved for treatment of dyskinesia in people with PD who are also taking levodopa
 - Once/daily solution for dyskinesia management and reducing “off” time, drug is currently taken 3-4 times daily
 - May also reduce side effect profile of those who may not tolerate repeated doses of amantadine

Pipeline Plans

- Clinical trials in Parkinson’s disease are essential to discovering new treatments and potential disease modifiers
- Involve medication, surgical, biomarker, exercise, care delivery and dietary interventions



Disease Modifying? SURE-PD

- Inosine
 - Antioxidant supplement which raises urate level in the body
 - May potentially slow the progression of PD
 - Previously studied in smaller group of patients
 - Determined to be safe and well tolerated
 - Double-blind, placebo-controlled Phase III study to last around 2 years in people with early PD, not yet taking many medications
 - Can not include those with gout, recurrent kidney stones, heart attack or stroke

Disease Modifying? NILO-PD

- Nilotinib
 - c-Abl inhibitor
 - Drugs in this class are currently treatment for leukemia and gastrointestinal tumors
 - 15 years clinical experience shows safety and low side effect profile
 - Initial clinical trial of nilotinib was presented in 2015
 - NILO-PD currently enrolling as a multi-center, multi-arm, placebo-controlled, randomized clinical trial internationally to better understand the effects of this treatment
 - Looking for individuals with moderate to advanced PD with a limited cardiac history

Disease Modifying?

● Exenatide

- Glucagon-like peptide 1 agonist, currently used in diabetes
- May potentially be a treatment for PD as there is evidence for a relationship between insulin resistance and neurodegeneration
- Once weekly subcutaneous injection for 48 weeks
- Individuals on active drug compared to placebo group had a 3.5 point advantage on UPDRS while “off”
- More clinical studies are needed to assess global benefit – patient selection in the initial study was limited to 60 participants for 48 weeks



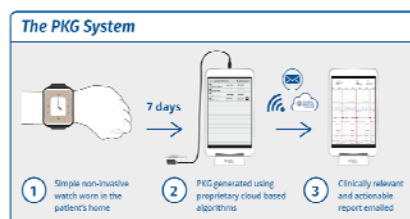
Symptom Management APL-130277

- In open-label clinical trial enrollment phases
- Sublingual (under the tongue) formulation of Apokyn, which is currently only available as a subcutaneous injection
- Designed to help with “unpredictable off-times” of PD when regular medication regiment may not help symptoms
- Submitted for FDA approval in March 2018



Symptom Measurement Parkinson's KinetiGraph (PKG)

- APPRISE Study
- In conjunction with the Parkinson's Foundation's Parkinson's Outcomes Project
- Wearable wrist device to measure PD variables (on-time, off-time, motor fluctuations and medication administration)
- Studying whether using the PKG device can help to guide treatment decisions and optimize therapy



Global Clinical Research in PD

- Vitamin D
 - Vitamin D levels have been shown to be lower in the PD population, similar to other diseases
 - Low levels are associated with slower walking speed, worse memory/thinking and depression
 - Vitamin D may also affect low bone mineral density in PD, increasing risk of osteoporosis
- Neuroderm
 - Phase II Clinical Trial of carbidopa/levodopa in liquid form which is administered through the skin in a patch/pump system
 - Has shown promise in early trials as another way to deliver continuous carbidopa/levodopa through a belt-worn pump
- Stem Cell Therapy
 - Inducible pluripotent stem cells, amongst others, are currently being studied in PD
 - Still in animal stages - not yet perfected for use in humans
 - Other countries may be studying with less rigorous regulations/standards
 - "For-profit" agencies generally are not reputable
- Gene Therapy
 - ProSavin (lead in France)
 - Surgical intervention to "reprogram" brain cells so that they produce dopamine
 - Inserts large quantities of three enzymes which manufacture dopamine into the basal ganglia
 - Was shown to be safe and improve movement symptoms in advanced PD
 - Was not placebo-controlled, only studied for 12 months
 - New trial of glial cell line-derived neurotrophic factor (GDNF) at NIH to attempt a new delivery system of gene transfer

Clinical Trial Resources

- **Clinicaltrials.gov**
 - National Institutes of Health regulated and monitored trial database
 - Registers trials worldwide
 - Highly reputable source of clinical trial information
- **Fox Trial Finder**
 - Specifically for PD research
 - “Match.com” style system
 - Sponsored and managed by Michael J Fox Foundation
- **Johns Hopkins PD Research Database**
 - For healthy controls and PD patients
 - Will collect information from you and contact when there are trials that you may be eligible for

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 - American Parkinson Disease Association
 - National Parkinson Foundation (NPF)



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