

# Best Treatments for Parkinson's Disease

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# What is Parkinson's Disease (PD) ?

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- Progressive neurologic disorder that results from the loss of specific cells in your brain that produce a chemical called dopamine
- Loss of dopamine leaves patients less able to control their movement
  - Slow
  - Stiff
  - Shaky

# How is PD Treated?

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- Since most symptoms of PD are caused by the lack of dopamine, many PD drugs are aimed at either temporarily replenishing or mimicking the effects of dopamine
- Debate over how and when to start
  - Depends on age of the patient, severity of PD and the presence of other co-morbidities
  - Most important factor:
    - » The need to maintain quality of life/ability to carry out activities of daily living

# Treatment does not = Medication

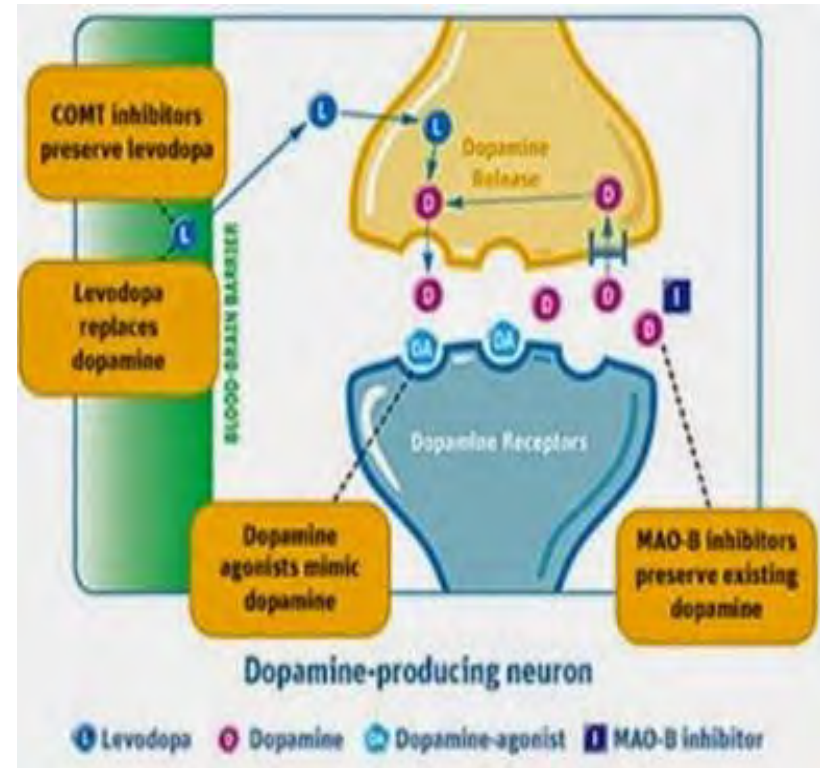
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- Supportive therapies
  - Exercise
  - Physical therapy
  - Occupational Therapy
  - Speech Therapy
  
- Pharmacotherapy  
(medications)

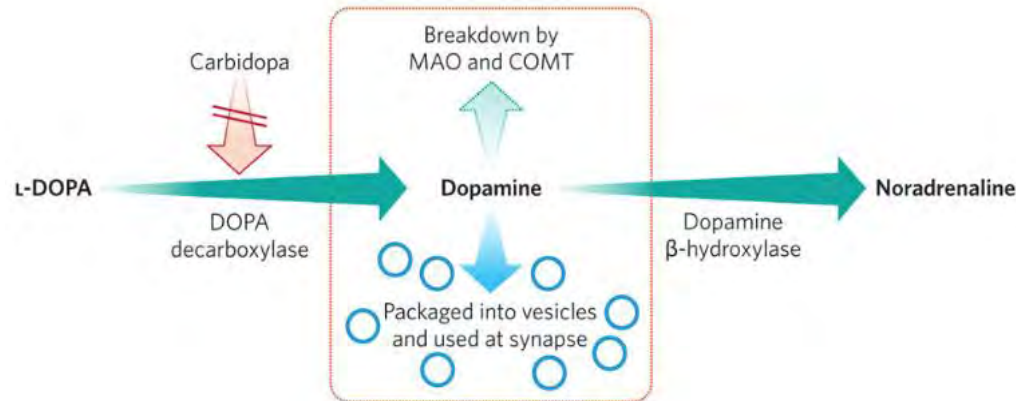


# How Do PD Medications Work ?

- Dopaminergics
  - Levodopa
  - Dopamine Agonists
  - MAOB Inhibitors
  - COMT Inhibitors
- Others
  - Amantadine
  - Trihexiphenidyl



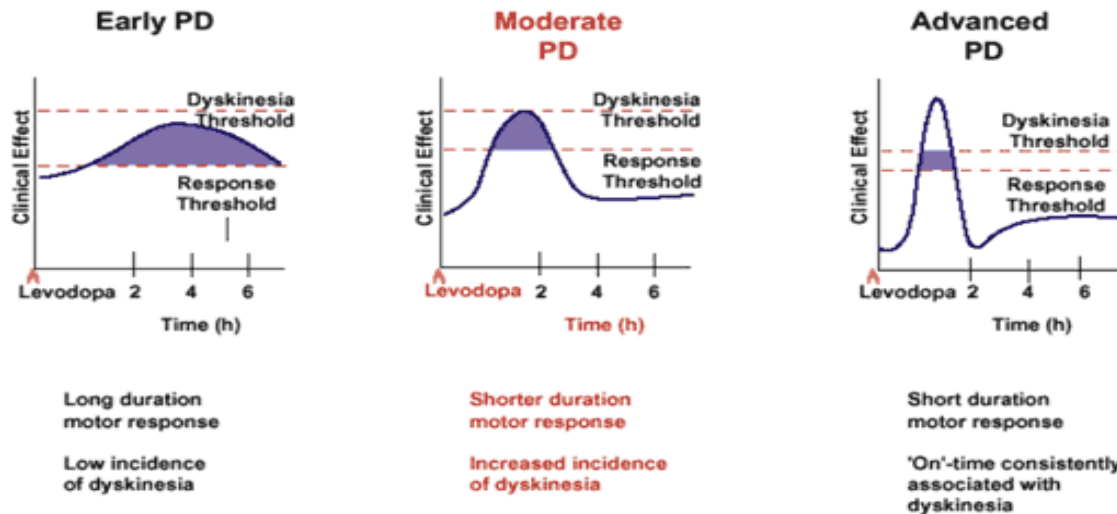
# Levodopa



- The most efficacious drug therapy at all stages of PD
- Combined with carbidopa to slow its breakdown before it reaches the brain, therefore reducing side effects and increasing its availability
- In the US, known as “sinemet”
- Exists in immediate release, controlled release and IR/CR combo preparations
- Should be taken on empty stomach

# Side Effects of L-dopa

- Short term: nausea, sleepiness, lightheadedness, confusion, hallucinations
- Long term: motor fluctuations and dyskinesia



# Treatment of Motor Fluctuations

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- Fluctuations can be reduced by maximizing “On” time
  - Increase levodopa dose
  - Increase frequency of levodopa administration
  - Addition of long acting levodopa
  - Addition of long acting DA
  - Extend the half life of levodopa by slowing the breakdown of dopamine
    - » MAOB inhibitors
    - » COMT inhibitors



# Treatment of Motor Fluctuations

## Extended Release Levodopa (Rytary)

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- FDA approved in January 2015
- Contains IR & ER beads
- Designed to provide longer lasting benefit for patients
- When compared to standard c/l
  - Less frequent medication dosing (3.6 vs 5 doses per day)
  - The daily total “off time” improved over an hour each day
  - Caution with long term effects (dyskinesia)



# Treatment of Motor Fluctuations

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## MAOB - inhibitors

- Selegiline, Rasagiline  
Safinamide
  - Inhibit an enzyme that breaks down Dopamine
  - Used alone or in combination with Levodopa
  - Mild symptom improvement
- Side effects:
  - Restlessness, agitation, insomnia
  - Interactions



## COMT-inhibitors

- Entacapone, Tolcapone
  - Inhibit an enzyme that breaks down levodopa
  - Has to be used with levodopa (not effective alone)
- Side effects
  - Reddish discoloration of urine
  - Exaggerate levodopa side effects (confusion, hallucinations, dyskinesia)

# Dopamine Agonists

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- Pramipexole (Mirapex), Ropinirole (Requip), Rotigotine (Neupro), Apomorphine
  - Mimic the effect of dopamine in the brain
  - Available in immediate and controlled release formulations
  - Can be used alone or in combination with levodopa
  - Less effective than levodopa

# Dopamine Agonists

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- Side effects:
  - Nausea, lightheadedness, leg swelling, hallucinations
  - Daytime sleepiness & sleep attacks (~ 5%)
  - Impulse control disorders (~10-15%)
    - » Compulsive gambling, shopping, eating or hypersexuality

# Levodopa vs DA

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## DA Pros

- Less motor fluctuation and dyskinesia
- No dietary restrictions

## Levodopa Pros

- More effective
- Cheaper
- Fewer side effects

Long term disability and quality of life are similar whether started on initial levodopa or dopamine agonist

# Non-Dopaminergic Therapies

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- Amantadine
  - In early stages to treat tremor, fatigue, bradykinesia
  - In later stages to reduce dyskinesia
  - Side effects: Decrease concentration, agitation, hallucinations, leg swelling & skin changes (livedo reticularis)
- Trihexyphenidyl (Artane)
  - Most useful for tremor in early stage or in young patients with dystonia (cramping)
  - Side effects: Dry mouth, blurred vision, drowsiness, confusion

# What About Cannabis ?

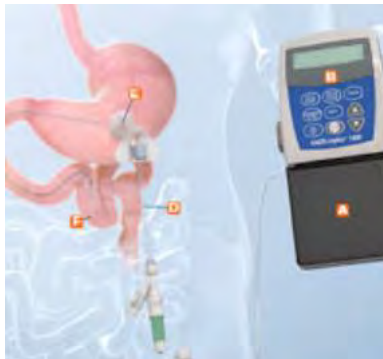


- Endocannabinoid system: Humans make cannabinoids that bind to receptors in body and brain (Basal Ganglia)
- Social media has popularized use of marijuana as a treatment for multiple conditions
- Marijuana consists of THC & CBD
  - Ratio of THC/cannabinoids varies
- Approved in 29 states in US, including Illinois
- Clinical studies have demonstrated *inconsistent results* in regards to symptom control
  - Observational studies: self reported, uncontrolled and open label
- Approved through legislation and not regulation (FDA)
- Research is needed to determine how & when it should be administered and how long term use can effect PD

# What Can We Do When Medications Are Not Enough?

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**Duopa**  
carbidopa/levodopa  
enteral suspension  
4.63 mg/20 mg per mL





# Duopa (Intestinal Infusion of Levodopa)

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- Available in Europe since 2004
- FDA approved in January 2015 for patients with advanced stage PD
- When compared to standard medical therapy
  - » Total daily “off” time improved by 2 hours
- Draw backs
  - » Need for small feeding
  - » Complications related to the tube or the pump
  - » Pump requires changing dopamine cassette once or twice per day

# Surgical Interventions

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- Ablative Procedures
  - » Thalamotomy
  - » Pallidotomy
  - » Ultrasound guided therapy
- Stimulation Procedures (DBS)

# Ablative Procedures

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- “Lesioning Procedures”
- Thalamotomy/Pallidotomy
  - Surgical procedure which uses a small probe to create a scar in the thalamus or globus pallidus
  - Typically only performed on one side of the brain
  - Effective ...HOWEVER cannot not be adjusted over time to address change in symptoms
  - Rarely performed

# Focused Ultrasound

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- Combining ultrasound with MRI scanning for the treatment of ET and potentially PD has recently generated a lot of enthusiasm
- Why?
  - Does not require surgery
  - No permanent hardware (electrodes, battery, IPG)
  - No follow up visits for programming
- Risk of ultrasound guided therapy are same as other “lesioning” procedures
  - Irreversible
  - Cannot be performed on both sides
  - Cannot be refined/adjusted
- Currently, NOT FDA approved for PD

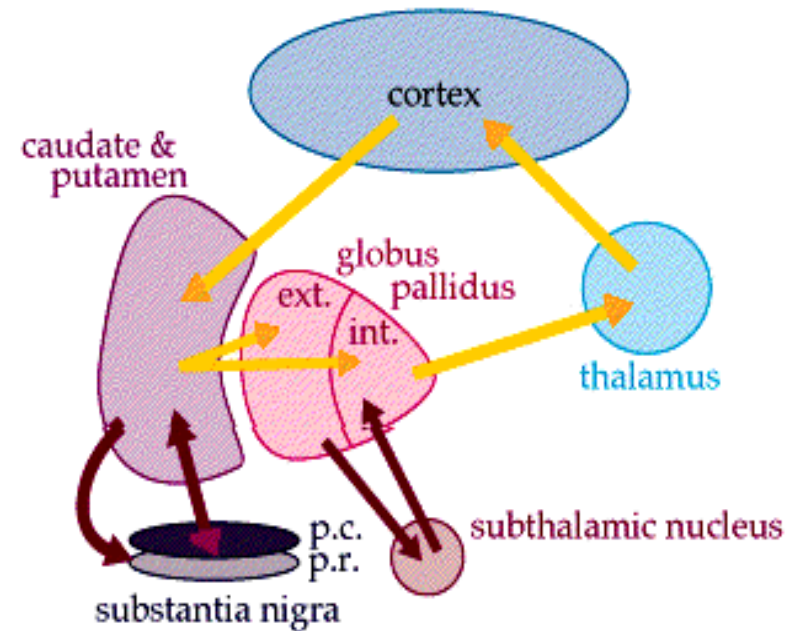
# Deep Brain Stimulation (DBS)

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- FDA approved in 1997
- Although it has provided significant benefit for some patients, DBS is not for everyone
- Candidate Selection is critical to allow for best possible outcome

# How Does DBS Work?

- Basal Ganglia
  - Connections to important areas of the brain that control movement, thinking and mood
- In PD – some of these circuits are faulty, producing sx of PD (slowness, stiffness, tremor)



# Speech Therapy for Parkinson's Disease

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# Would I Benefit From Speech Therapy?

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- Are people asking you to repeat yourself or speak up?
- Have you noticed a change in your voice? (e.g. quiet, hoarse, raspy)
- Have you noticed a change in your speech? (eg. slurred, mumbled, stuttering)



# Speech Difficulty in Parkinson's Disease Can Include:

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- Quiet speech
- Monotone
- Slurred/mumbled speech
- Hoarse vocal quality
- Reduced intelligibility
- Short rushes of speech
- Running out of breath when speaking

# Therapy Approaches

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- Lee Silverman Voice Treatment-4 times/week for 16 visits
- Therapy targeting increasing voice projection with less frequency (2 times/week)
- Communication tips for you and your conversation partners
- Alternative means of communication-examples include IPAD, writing, letter board, communication device”

# Lee Silverman Voice Treatment

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## **LSVT® Program:**

- 16 intensive individual sessions, 4 times a week for 4 weeks
- Focus on improved speech clarity by increasing loudness
- Repeated exercises and speech tasks are designed to strengthen the vocal cords and train the individual to habitually speak louder, therefore more clearly
- Speech Therapist may ask you to have an evaluation by an otolaryngologist to clear you for LSVT

## **Research Has Demonstrated:**

- Improved vocal loudness
- Improved intelligibility
- More facial expression
- Improved ability to swallow

# Lee Silverman Voice Treatment

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<https://www.youtube.com/watch?v=gNldxYjGVV8>

# General Strategies For Speech

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- S- Slow
- L- Loud
- O-Over articulate
- B-Breathe

# Communication Tips For You and Conversation Partners

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- Slow down. Give them time to respond
- Limit background noise and distractions
- Only one person should speak at a time
- Remind them to take deep breaths and pause between words
- Encourage them to use other methods of communication (gesture, pointing and writing) to help get their ideas across
- Confirm what the person is saying by repeating the information back (example: “Oh, you want something to eat”)

# Other Services Provided by Speech Therapy: Swallowing Therapy

# Signs of Dysphagia (Disordered Swallowing)

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- Coughing or throat clearing when eating or drinking liquids
- Food or pills sticking in mouth or throat
- Difficulty chewing food
- Frequently feeling that food or drink “go down the wrong pipe”
- Recurring pneumonia or chest congestion



# Dysphagia-Testing

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- Clinical swallow evaluation: Assessment of oral-facial structures and function. Presentation of food and liquid in an office setting to look for signs or symptoms of aspiration
- Your therapist may ask you to complete a video swallow study
  - Short x-ray test ~20 minutes, non-invasive
  - Able to assess swallowing on a moving x-ray
  - Able to see areas of weakness and reduced range of motion
  - Able to make recommendations for diet textures, compensatory strategies, and specific exercises that will help strengthen the affected muscles

# Therapy For Swallowing

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- Exercises
- Compensatory strategies
  - Head/body position when swallowing
  - Pacing
  - Monitoring size of bites/sips
  - Modifying diet texture

# Swallowing-Exercises

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- Swallow exercises in Parkinson's Disease can help to improve:
  - Controlling food and drink in the mouth
  - Strength and range of motion of swallowing
  - Protecting the airway when swallowing
  - Reducing risk of aspiration
  - Reducing coughing with eating/drinking

# Strategies For Safe Swallowing

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- Go slow, one bite at a time
- Avoid talking while eating
- Alternate bites of food with sips of drink
- Small bites and sips
- Meds in applesauce or crushed/liquid form
- Sit upright when eating/drinking and for 30 minutes after meals
- Stop eating/drinking if coughing occurs

# Cognition

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- Language: Strategies to improve daily communication including word-finding and organization of thoughts
- Cognition: Strategies to improve daily communication and function if experiencing difficulty with memory, attention, and/or problem solving

# Strategies for Memory

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- Repetition/Rehearsal: Repeat the information over and over
- Visualization: Make a picture in your head of what it is you are trying to remember
- Develop a schedule and stick to it
- Stay organized: Keep important articles (wallet, keys, checkbook, glasses, medicine, etc.) in the same place

# Strategies for Memory

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- Daily planner/calendar
- Keeping a daily journal
- Alarm clock or alarm reminders on cell phone
- Tape recorder
- Pill box
- Writing notes, Post-it notes

# Next Steps: Maintaining Skills After Therapy is Over

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- Continue voice exercises daily, think of ways to keep it fun!
  - Reading material of interest using loud voice (articles, book, newspaper, the Bible, etc.)
  - Play a board game using your loud voice
  - Participate in book club and work on loud voice while having conversation
  - Communication Circle- schedule 15 minute conversations with family/friends in person or over the phone routinely for practice
- Continue swallow exercises, follow strategies as provided by therapist
- Check-in with your therapist in 6 months-one year or when you notice a change in voice or swallowing. Therapist will complete a “tune-up” program.



# References

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- Ramig, L.O., Pawlas, A.A., Countryman, S. 1995. The Lee Silverman Voice Treatment: A practice guide for treating the voice and speech disorders in Parkinson's Disease. National Center for Voice and Speech.
- Kalf, H., de Swart, B., et al. (2011). Nijmegen (The Netherlands); Miami (U.S.A.): ParkinsonNet (The Netherlands); National Parkinson Foundation (U.S.A.), 1-137.

# 10-Minute Break

# Emerging Therapies in Parkinson's Disease

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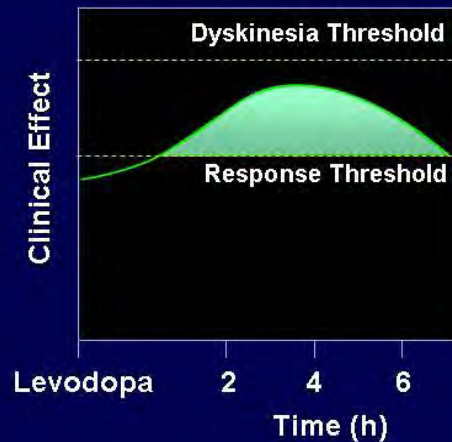
# Complications of Levodopa Therapy

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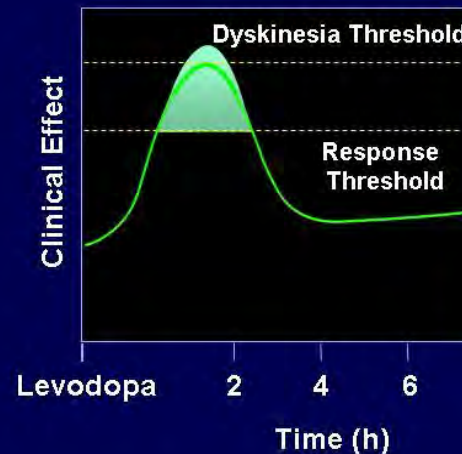
- Dyskinesias (involuntary movements)
  - peak dose (30-60 minutes after a dose)
  - biphasic (occur twice in a dosing interval)
  - continuous (30 minutes after dose and lasting until next dose)
- Motor fluctuations
  - Delayed “ON” response
  - Dose failure
  - End-of-dose wearing-Off
  - Unpredictable “OFF” time
  - Freezing episodes

# Response to Levodopa and Progression of Parkinson's Disease

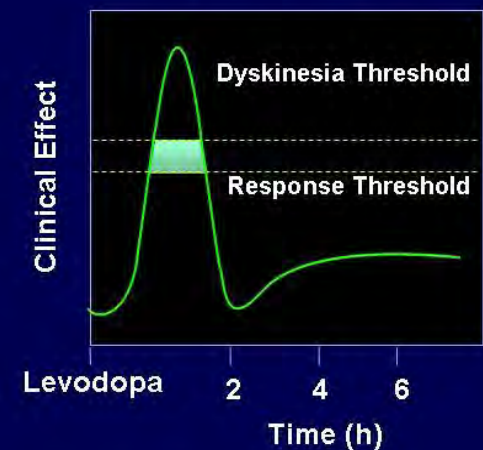
## Early PD



## Moderate PD



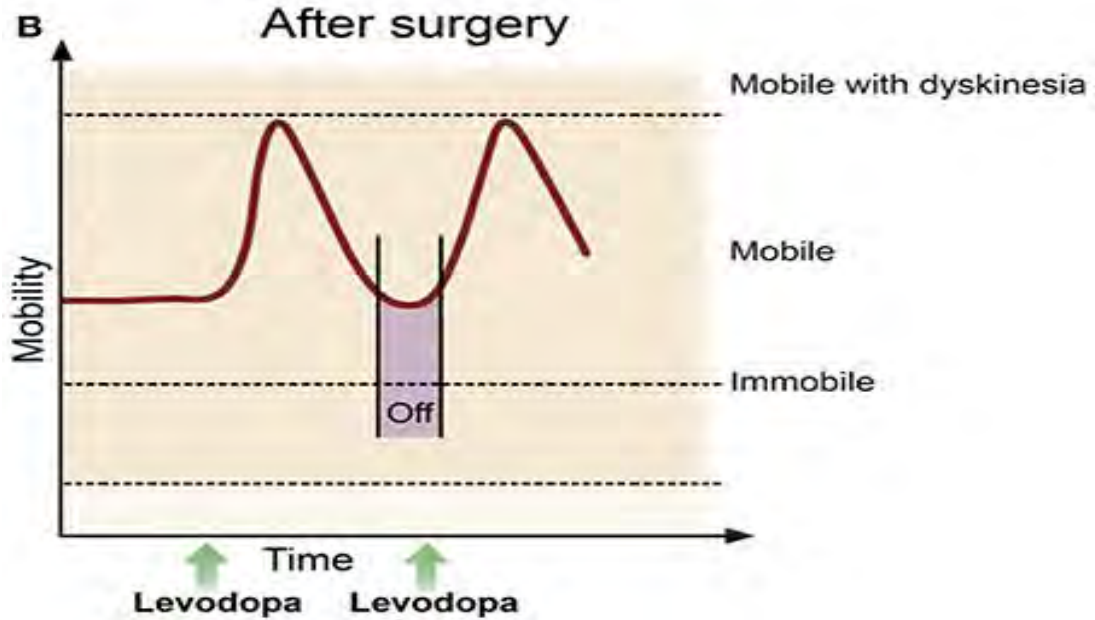
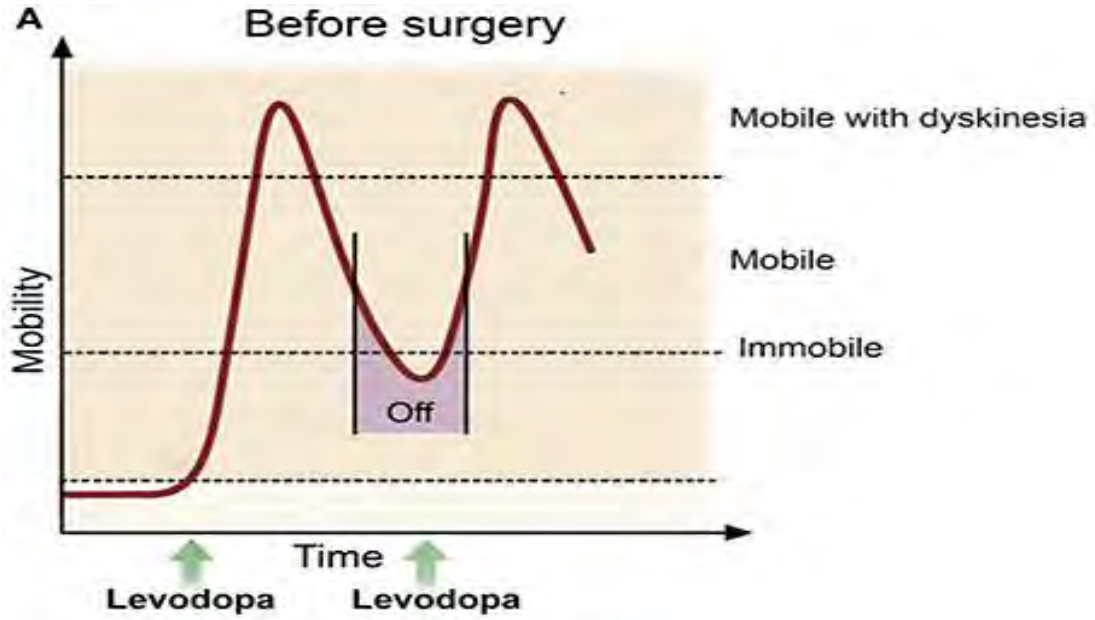
## Advanced PD



- Long duration motor response
- Low incidence of dyskinesias

- Shorter duration motor response
- Increased incidence of dyskinesias

- Short duration motor response
- "On" time consistently associated with dyskinesias

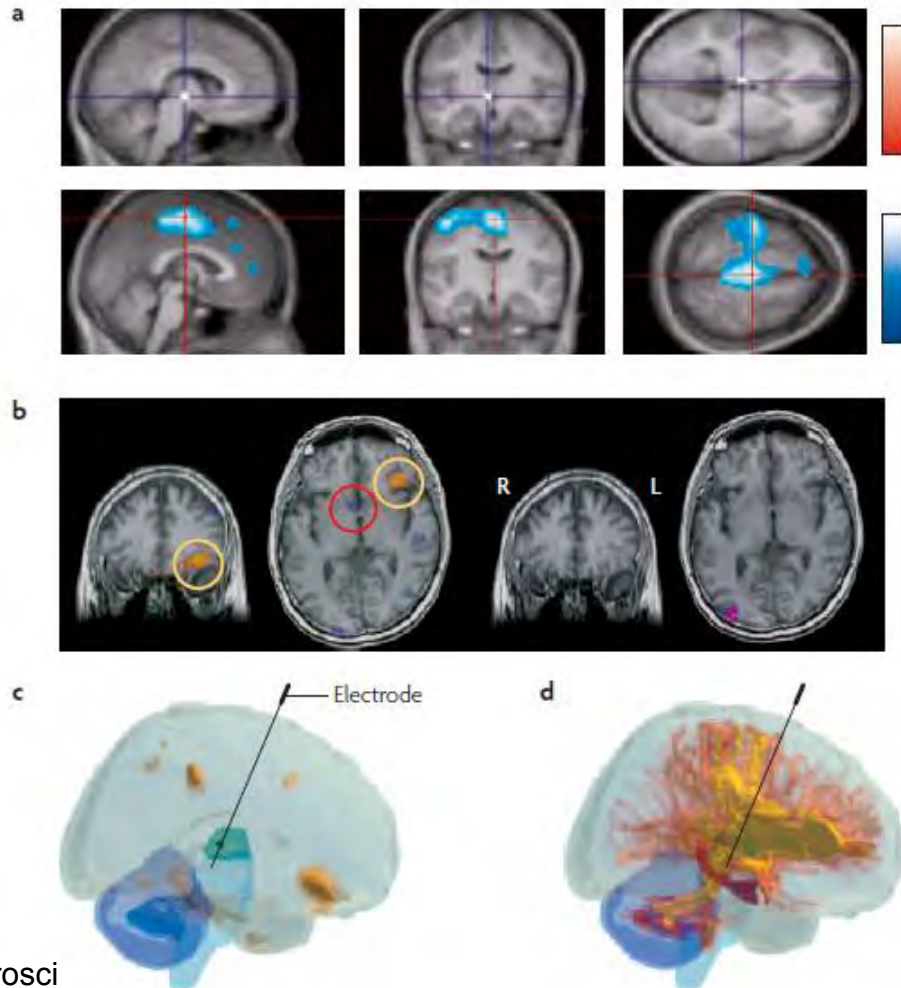


# DBS: How Does It Work?

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- DBS mechanism continues to be a matter of debate
- Inhibition of the stimulation target
- Excitation of the stimulation target
- Combination of inhibition/excitation
- Local production of neurotrophic factors
- Local production of neurotransmitters
- **Modification of brain networks**

# Imaging of DBS effects

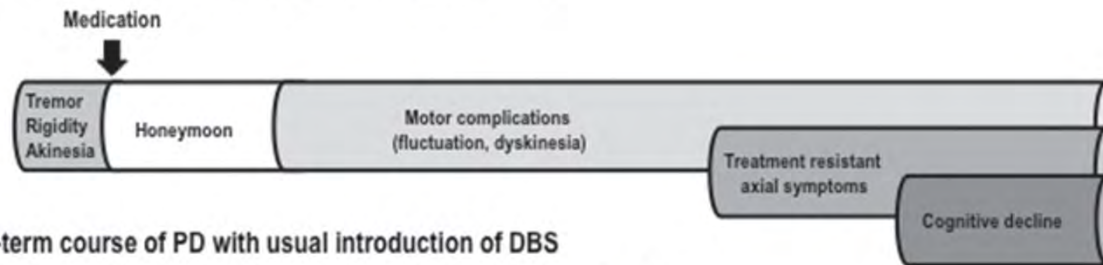


Kringelbach et al. Nat Rev Neurosci  
2007

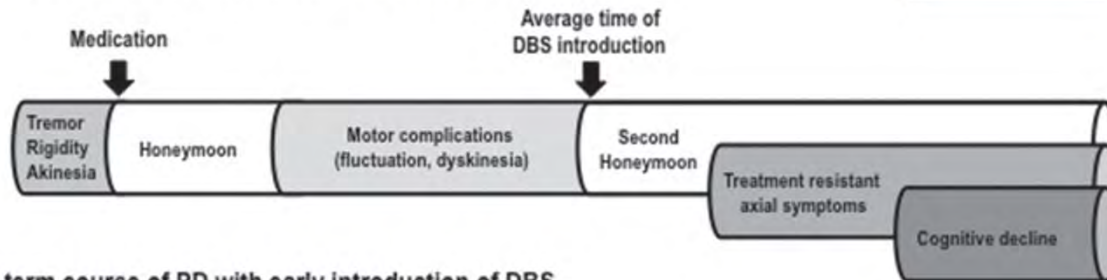


# Long Term Course of Parkinson's Disease

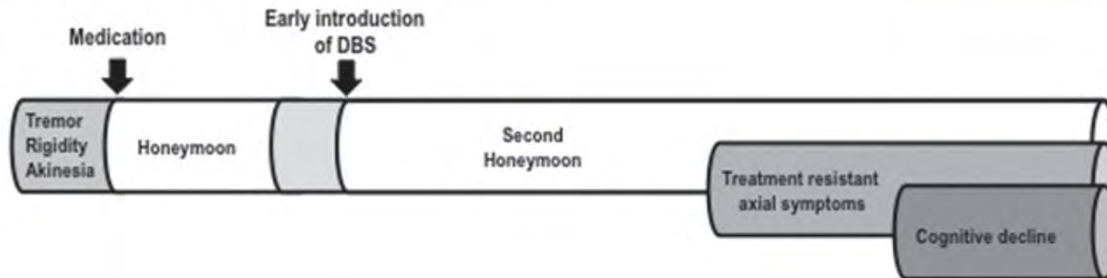
A: general long-term course of PD with medical treatment



B: long-term course of PD with usual introduction of DBS



C: long-term course of PD with early introduction of DBS



Onset                      5 yrs                      15 yrs                      20 yrs

# Investigational Therapies

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- DBS surgery
  - Stimulation on demand
  - Timing of DBS surgery
- MRI-guided Focused Ultrasound
- New medications
  - Add-on therapy to levodopa
  - New agents
  - Personalized therapy
- Gene therapy
- Stem cell therapy
- Vaccine therapy

# DBS Surgery Timing

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- DBS has been an established treatment for advanced Parkinson's disease
- A recent large clinical trial published in 2013 (EARLYSTIM trial) supports surgery earlier in the disease process
- Study participants with levodopa-induced complications had better quality of life and less motor disability than those who received medical therapy only
- Is DBS neuroprotective?

# DBS Surgery Timing

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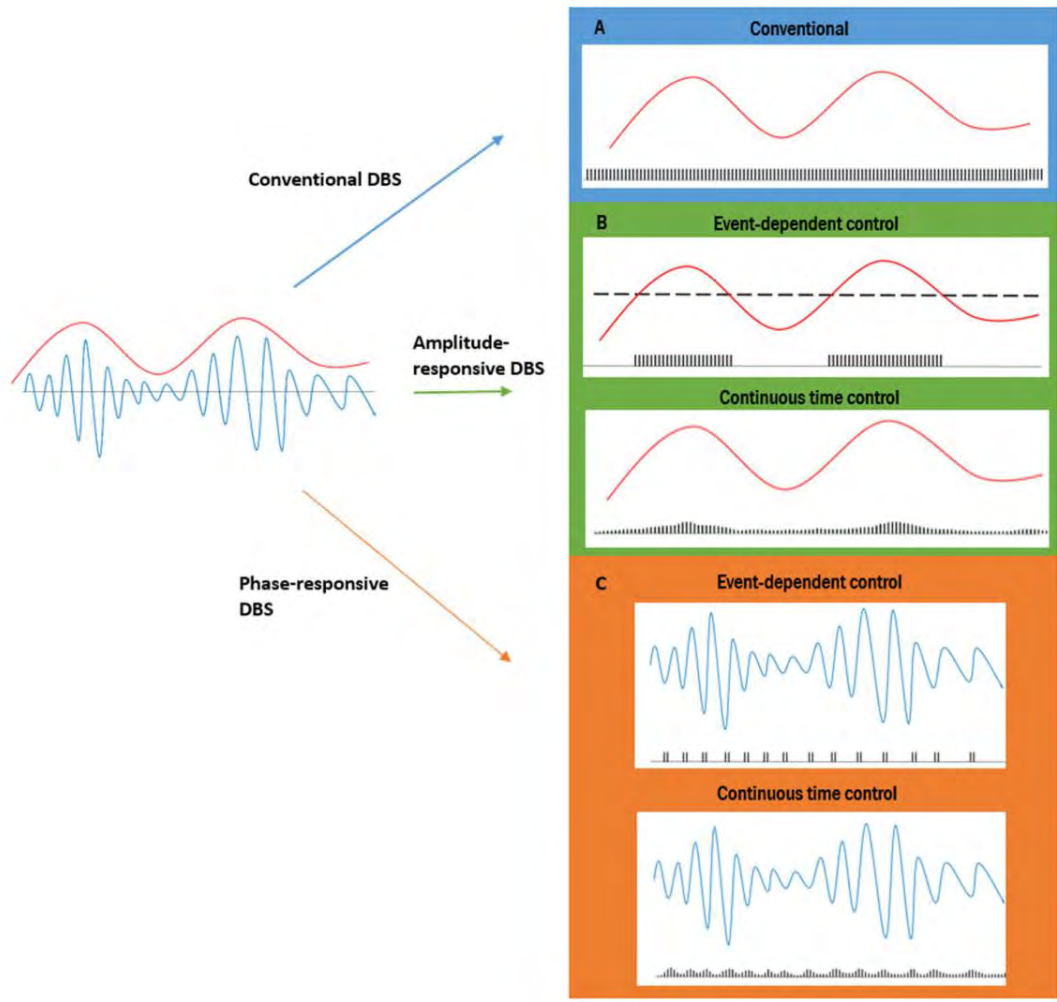
- FDA approved in February 2016 the use of DBS in mid-stage Parkinson's patients
- Risk-benefit and cost-benefit profile analysis favor the use of the DBS in mid-stage disease
- It is unclear at this point whether the FDA decision will affect medical and insurance practices

# DBS Surgery

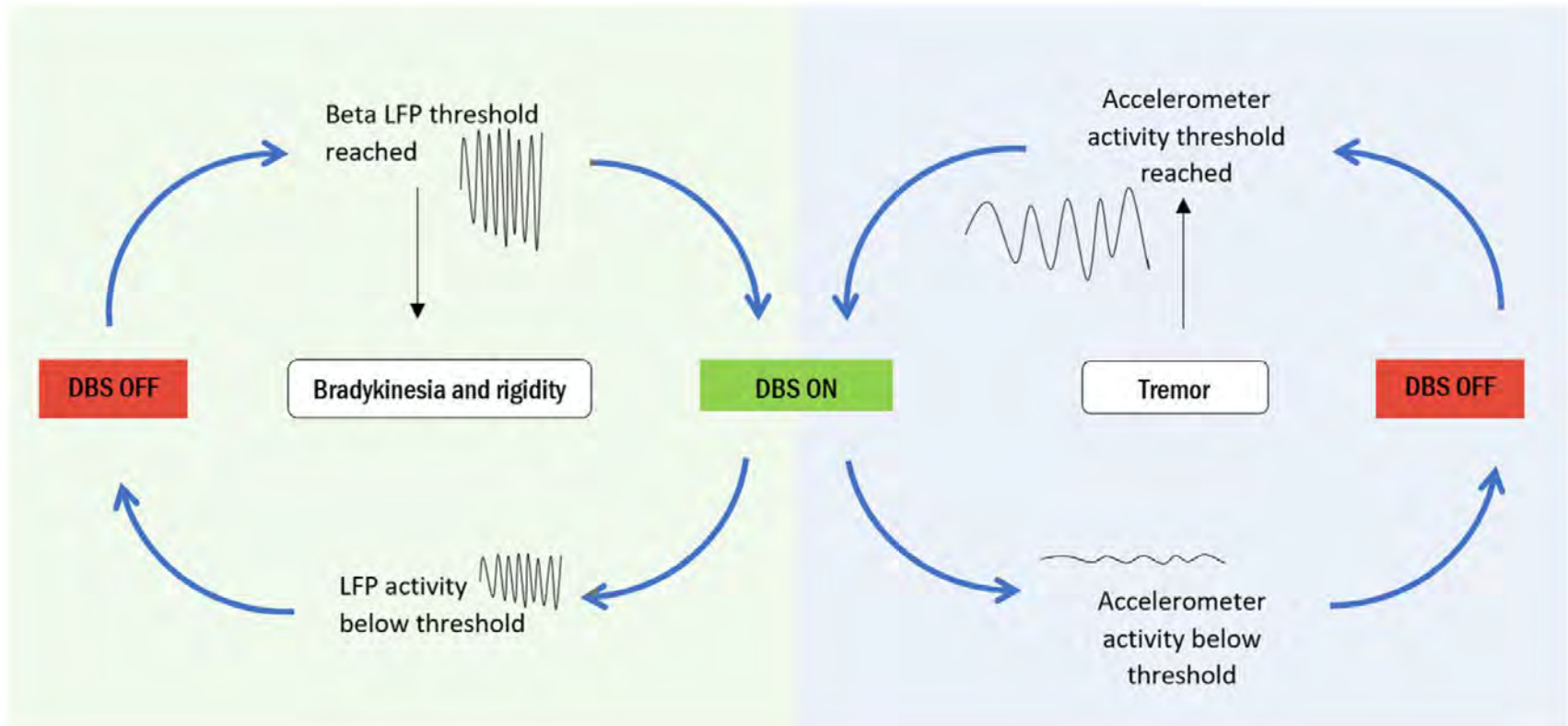
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- Conventional DBS
  - Continuous stimulation
- Stimulation on demand
  - Stimulation delivered when either a symptom appears or the sensor detects a change in brain activity
  - Saves on battery life

# Difference Between Conventional and On-Demand DBS



# Factors That Will Trigger Stimulation



# High Intensity FUS (HIFUS)

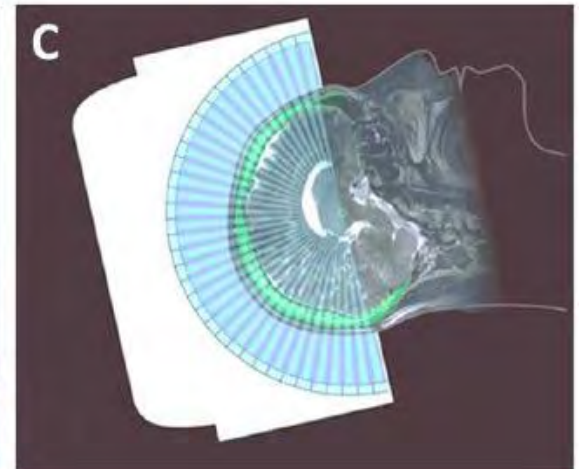
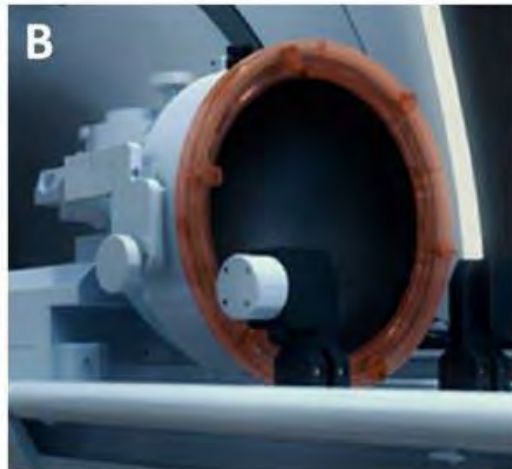
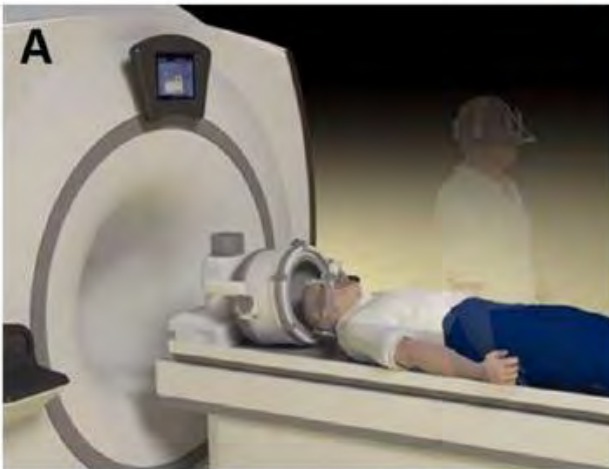
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- FDA approved for the treatment of essential tremor (7-2016)
- It is a non-invasive method to create a stereotactic brain lesion
- Its effect mimics that obtained by previous surgical procedures such as thalamotomy and pallidotomy
- Procedure is usually unilateral given prior experience with bilateral lesional procedures
- Lesion is irreversible



# MRI-Guided Focused Ultrasound (FUS)

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# Gene Therapy

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- Clinical trial of gene therapy with genes involved in the processing of dopamine was tried in 15 individuals with advanced Parkinson's disease (Prosavin)
- Treatment appears safe and well tolerated
- Clinical improvement over a 12 month period was observed in all participants

# Intracerebral Neurotrophic Factor Administration

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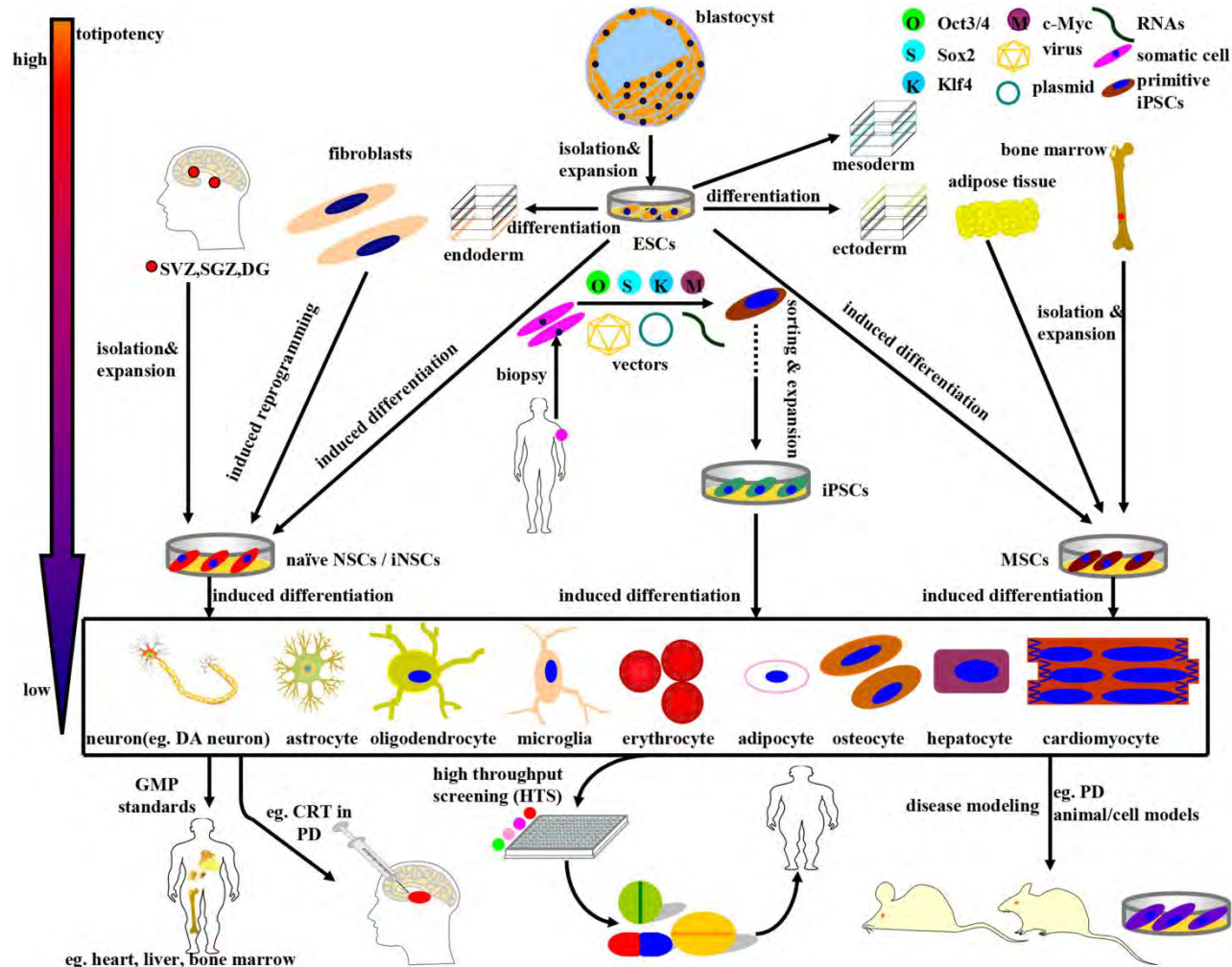
- Neurotrophic factors (NTF) are necessary to maintain and promote function of nerve cells and have been investigated for neuroprotective effects
- Clinical trials have produced mixed results
- Analysis of eight studies with 223 participants showed that NTF administration does not improve motor function in PD

# Stem Cell Transplants

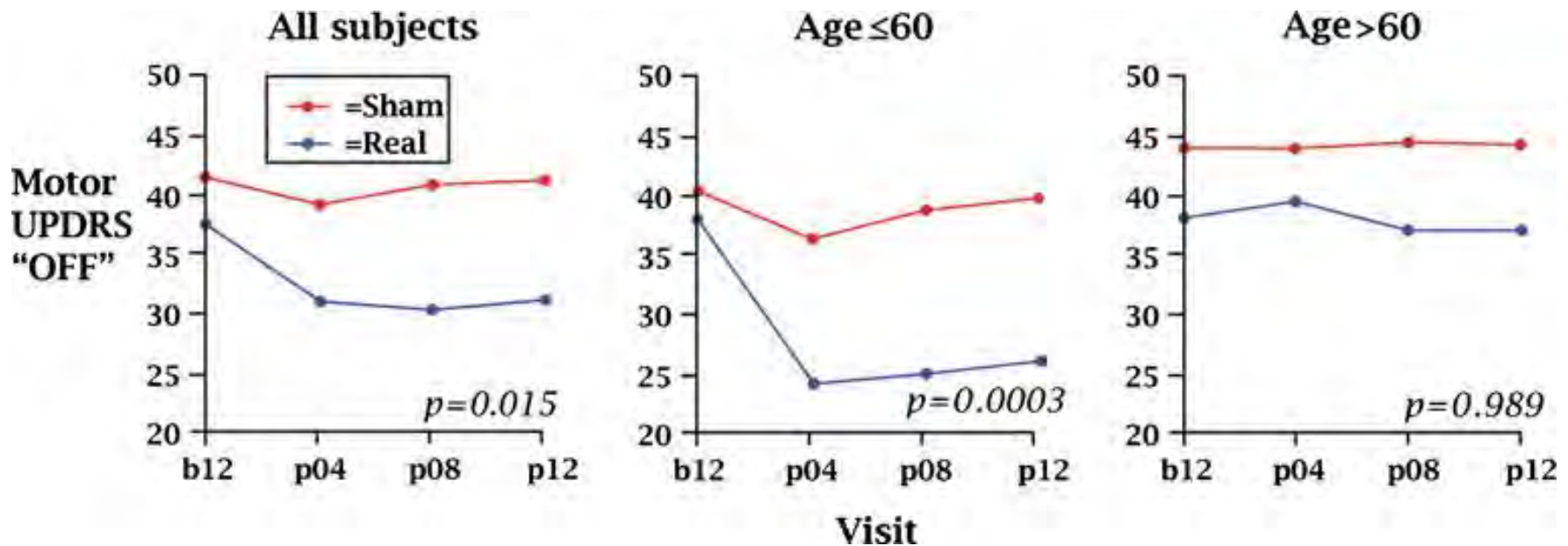
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- Pre-clinical studies suggested that neural stem cell transplantation is effective in animal models of the disease
- A recent study in non-human primates showed successful implantation and development of dopamine producing neurons

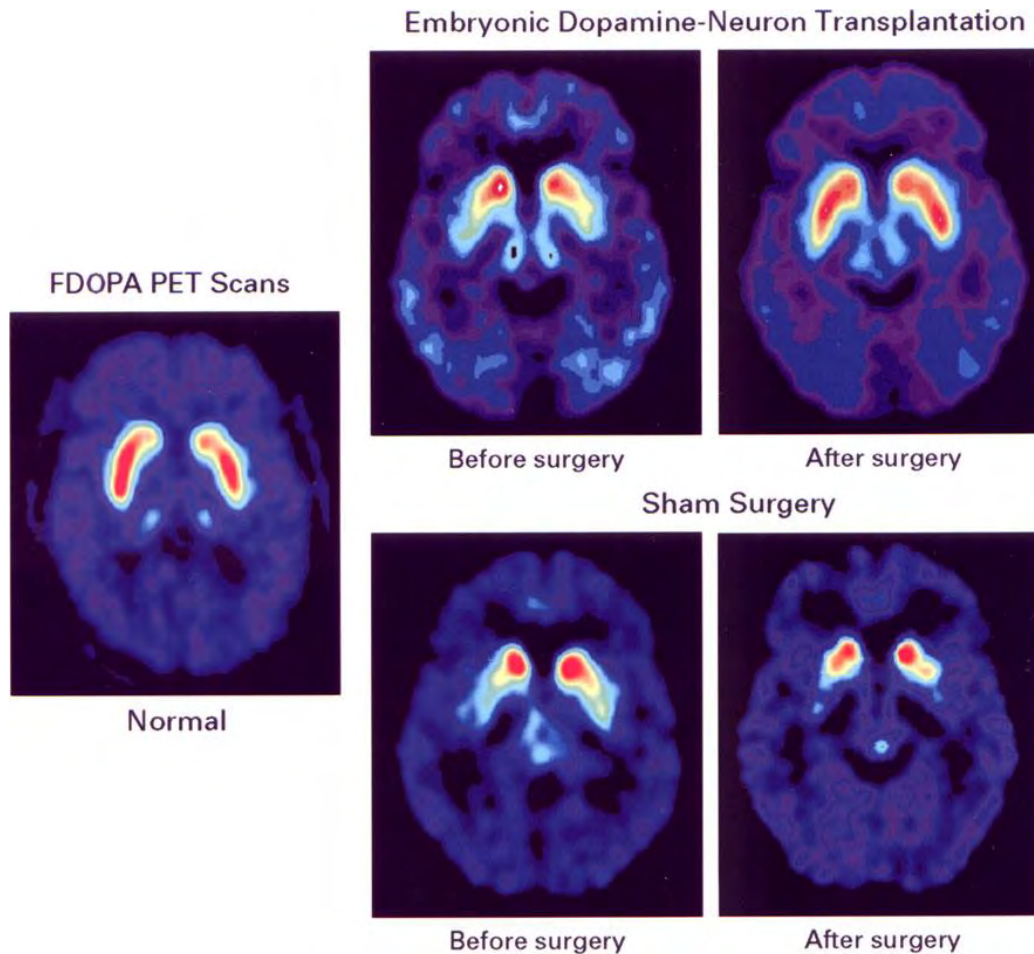
# Currently Available Stem Cells For Research and Therapy



# Improvement of Motor Function in the First 12 Months



# Dopamine Cell Transplantation for Parkinson's Disease



Freed et al. 2011

# Human iPS Cell-derived Dopaminergic Neurons Function in a Primate Parkinson's Disease Model

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- Induced pluripotent stem cell-derived dopaminergic progenitor cells survived and functioned as dopaminergic neurons in a primate model of PD treated with the neurotoxin MPTP
- Score-based and video-recording analyses revealed an increase in spontaneous movement of the monkeys after transplantation
- Mature dopaminergic neurons made connections into the host brain region; this was achieved with cells from patients with PD or from healthy individuals
- The transplanted cells did not form any tumors in the host brains for at least two years
- Brain imaging with MRI and positron emission tomography (PET) was used to monitor the survival, expansion and function of the grafted cells, as well as the immune response in the host brain

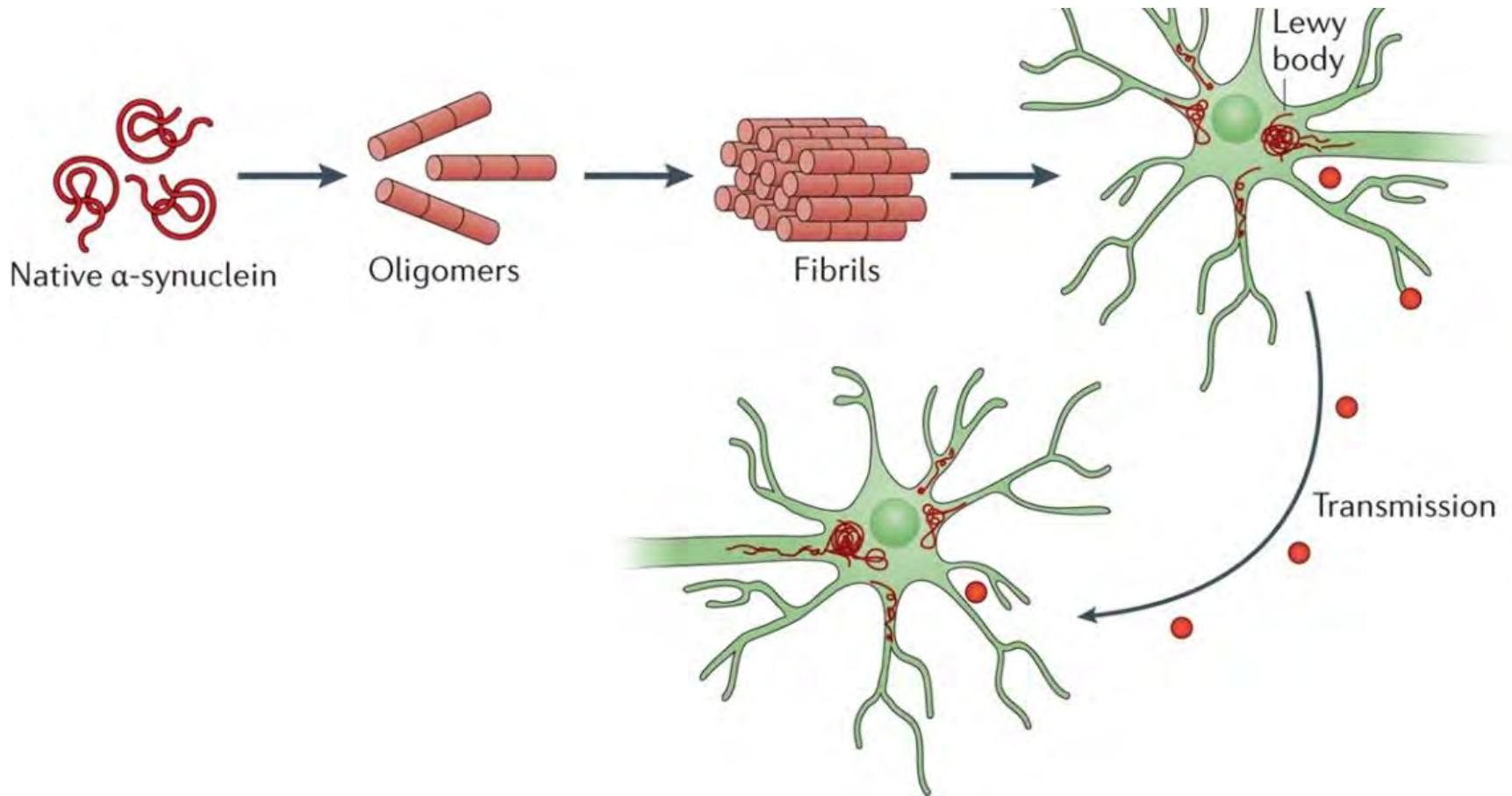


# Stem Cell Transplants-Concerns

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- Stem cell origin has been controversial
- Procedures are unregulated, putting patients potentially at risk
- Stem cell procedures are often not included in a clinical trial protocol and informed consent is not obtained
- Guidelines for these procedures have been issued by the International Society of Stem Cell Research in May 2016

# Alpha-Synuclein in Parkinson's Disease



# Therapies Based on Blocking Alpha Synuclein Cunction

Table 1 | Selected  $\alpha$ -synuclein-targeted therapies in development for Parkinson disease

Drug	Sponsor	Modality	Status
RO7046015	Roche	$\alpha$ -Synuclein-specific antibody	Phase II planned to start by end of June 2017
BIIB054	Biogen	$\alpha$ -Synuclein-specific antibody	Phase II planned to start by end of 2017
PD01A and PD03A	Affiris	Vaccine against $\alpha$ -synuclein	Phase I
NPT200-11	Neuropore Therapies/UCB	Small-molecule inhibitor of $\alpha$ -synuclein misfolding	Phase I
NPT088	Proclara Biosciences	Small-molecule inhibitor of $\alpha$ -synuclein misfolding	Preclinical
SAR402671	Sanofi Genzyme	Small-molecule inhibitor of glycosphingolipid metabolism	Phase II

# New Medical Therapies

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- Agents that modulate dopamine action to ameliorate levodopa-induced complications are in phase I-II trials
  - Eltoprazine
  - Dipaglurant
- Agents that prolong levodopa action
  - Opicapone (once a day dosing)

# Neuroprotective Agents-I

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- Exenatide belongs to a class of drugs used in the treatment of diabetes
- Exenatide has been shown in animal models to have neuroprotective and neurorestorative effects
- Exenatide in humans improved the motor symptoms of Parkinson's disease. This improvement persisted for 12 months after the drug was stopped

# Neuroprotective Agents-II

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- Nilotinib is a drug used in the treatment of leukemia
- A small study in 12 patients with advanced Parkinson's disease or dementia with Lewy bodies hinted to improvement of motor and cognitive symptoms
- There are several concerns about the study:
  - Safety is unclear
  - Effect is questionable

# Summary

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- Extensive ongoing research is aiming at:
  - Improving available symptomatic treatment options
  - Investigating ways to achieve restoration of the affected brain regions
  - Neuroprotection
  - Delaying disease progression

**Thank You!**