EMERGING TREATMENTS FOR PARKINSON'S DISEASE

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Complications of Levodopa Therapy

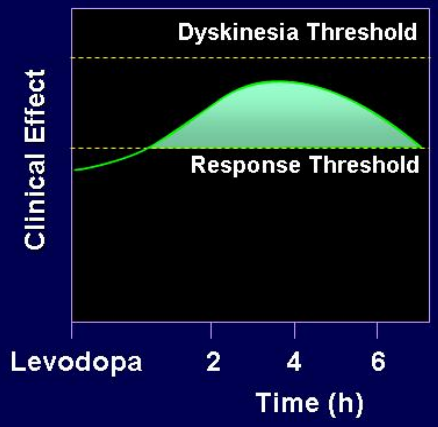
- Motor fluctuations
  - Delayed “ON” response
  - Dose failure
  - End-of-dose wearing-Off
  - Unpredictable “OFF” time
  - Freezing episodes

Complications of Levodopa Therapy

- Dyskinesias (involuntary“wiggly”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)

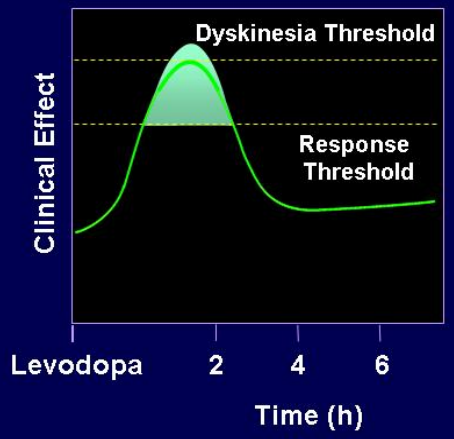
Response to Levodopa and Progression of Parkinson's Disease

Early PD



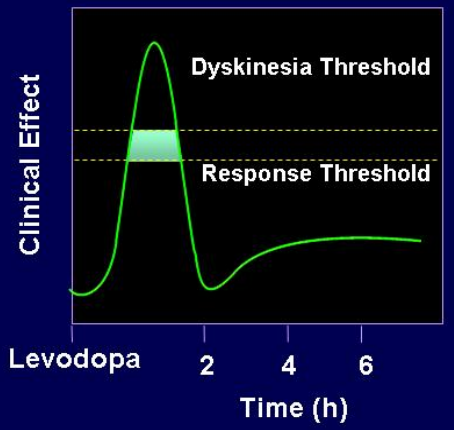
- Long duration motor response
- Low incidence of dyskinesias

Moderate PD



- Shorter duration motor response
- Increased incidence of dyskinesias

Advanced PD



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

Olanow CW, Agid Y. http://www.medscape.com/viewprogrm/1847-pnt.

Surgical Treatments for Parkinson's Disease

- Ablative procedures
  - thalamotomy
  - pallidotomy
- Electrical stimulation procedures
- Deep brain stimulation
  - subthalamic nucleus (STN)
  - globus pallidus internus (Gpi)

Deep Brain Stimulation (DBS)

- High frequency, pulsatile electrical stimulation
- Stimulating electrodes are stereotactically placed into the target region
- It can be activated and deactivated with an external device
- The patient has the option of adjusting stimulation parameters

Surgical Candidate Selection

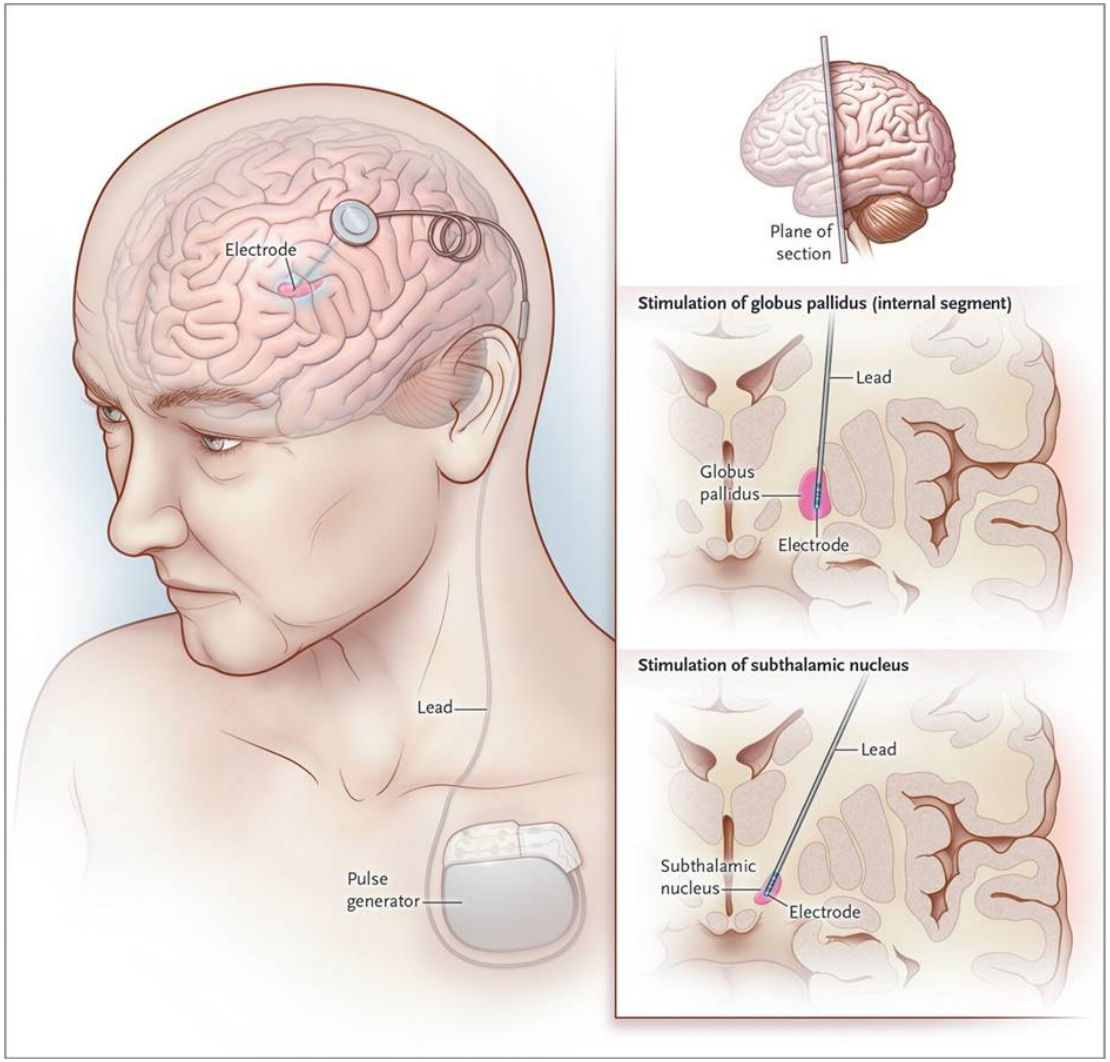
- Disease duration > 5 years
- Confirmed diagnosis of Parkinson's Disease
- Complications of optimal medical therapy
- Continued good response to levodopa
- Absence of dementia
- Absence of severe depression
- Ability to tolerate the surgical procedure

Contraindications to Surgical Treatment

- Blood clotting disorders
- Blood malignancies
- Poorly controlled hypertension
- Overall compromised health status

- Cardiac pacemaker is not a contraindication for DBS surgery

FDA Approved DBS Target Structures



Which is the Optimal Surgical Target?

- Both STN and GPi placement have shown efficacy in treating symptoms of Parkinson's
- STN placement allows for more reduction of medications than GPi
- STN placement is more widely performed and is more effective

Subthalamic Nucleus DBS

- All cardinal features of PD improve
- “OFF” time improved 60%
- “ON” time improved 10%
- Increased “ON” time
- Reduced dyskinesias
- Reduced medication requirements <50%

Subthalamic Nucleus DBS

- Bilateral electrode placement is necessary
- Unilateral placement may be considered in select cases
- Indicated for control of rigidity, bradykinesia and dyskinesias

Globus Pallidus Internus (GPi) DBS

- All cardinal features of PD improve
- Reduced dyskinesia
- Moderate improvement in “OFF” signs
- No medication reduction

Globus Pallidus Internus (GPi) DBS

- Similar benefits to the STN DBS
- Significant improvement in dyskinesia
- Moderate improvement in bradykinesia and rigidity
- Bilateral DBS may be better tolerated than bilateral pallidotomy

Effects of STN, GPi DBS

	STN	GPi
Tremor	+++	++
Bradykinesia	+++	++
Rigidity	+++	++
Gait	+++	++
Dyskinesias	- /+	+++
L-dopa dose decrease	+++	+/0

Symptom Change After Turning on Stimulation

Symptom	Sec.	Min.	Days	Wk/Mo
Rigidity	+++	S	S	S
Tremor	+++	+	(+)	(+)
Bradykinesia/akinesia	+++	+	+	S
Off-phase dystonias	++	+	+	S
Diphasic dyskinesias	(-)	-, (+)	++	+
On-period dyskinesia	(-)	- -	-	++

+ = improvement; - = worsening s = stable

Timing of Surgery

- Are parkinsonian symptoms adequately treated?
- Is the antiparkinsonian regimen optimized?
- Is DBS neuroprotective?

DBS Surgery Timing

- 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 that received medical therapy only

Post-Operative Medication Requirements

GPi DBS	STN DBS
Usually no change Occasional patients with severe preoperative dyskinesias may tolerate higher levodopa doses	Reduction in drug dosage by 50% (range 0-100%)

DBS-Related Adverse Effects

Intracerebral hemorrhage
Seizures
Infection
Breaking of connection lead
Eyelid opening apraxia
Executive dysfunction
Confusion
Weight gain

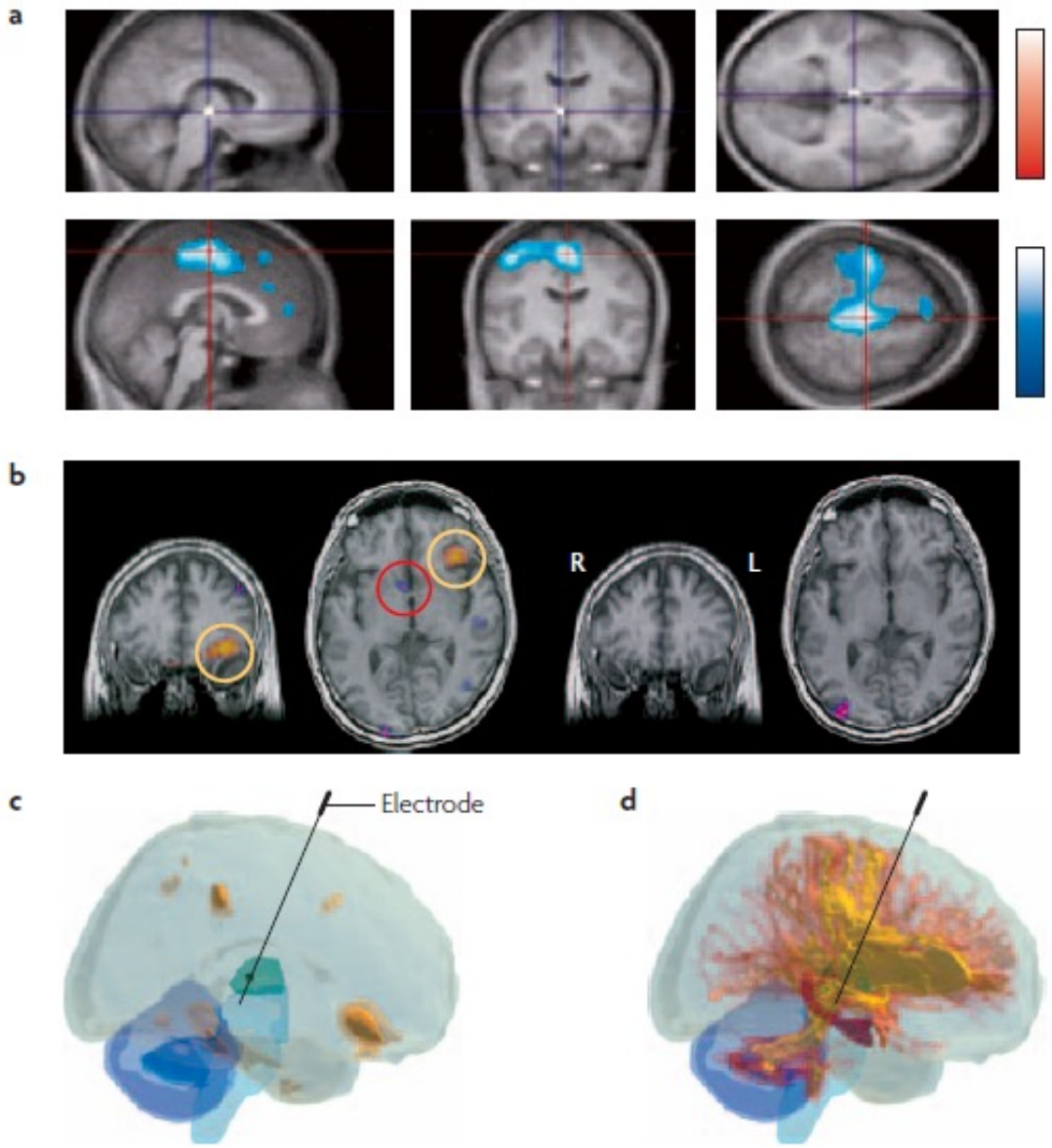
MRI Safety Guidelines (Medtronic)

- MRI field strength: 1.5 Tesla
- MRI type: horizontal bore, not open-sided systems
- DBS leads and extensions should be intact and functional (needs to be checked prior to scan)
- MRI scan parameters:
  - Radio frequency (RF) Specific absorption rate (SAR)
  - Gradient dB/dt parameters

DBS: Mechanisms of Action

- DBS mechanism continues to be a matter of debate
- Inhibition of stimulated region
- Excitation of stimulated region
- Combination of inhibition/excitation
- Modification of brain networks

Imaging of DBS Effects



Summary

- DBS is effective in treating moderate to advanced PD
- Recent studies demonstrate that DBS is effective also early in the disease process
- Stimulation parameter adjustment can be useful to control symptoms effectively.
- DBS effects reflect changes at a systems level rather than an effect on a single brain structure

Regenerative Therapies in Parkinson's Disease

- Infusion of trophic factors (GDNF)
- Infusion of genes involved in dopamine processing
- Stem cells
  - Fetal cell derived
  - Induced pluripotent stem cells (iPSC)
  - Adipose tissue-derived stem cells

Intracerebral Trophic factor infusion

- Glial-derived neurotrophic factor (GDNF) has been shown to be effective in animal models of Parkinson's disease

- Its use in double-blind, placebo controlled human clinical trials however has been associated with significant side effects and lack of efficacy

Gene Therapy Trials

- Recently published phase ½ open label clinical trial in 15 individuals with advanced Parkinson's disease in which genes involved in the processing of dopamine were infused into the putamen, a brain structure severely affected in Parkinson's diseaese (Prosavin)
- The treatment appears safe and well tolerated
- Clinical improvement over a 12 month period was observed in all participants

Vaccines in Parkinson's Disease

- Clinical trial of a vaccine against alpha-synuclein (AFF011)
- It assesses the safety and tolerability of two doses of a vaccine against alpha-synuclein
- trial is ongoing in Europe

Stem cell therapies

- Stem cells derived from fetal tissue have been tried with limited success and conflicting effects
- iPSC are still in the development phase and have not been yet tried in humans
- Stem cells derived from adipose (fat) tissue are being developed to be infused by intravenous injection.
- It is doubtful however, that these cells can reach the nerve cells in the brain, as the brain is protected from the circulation by the “blood-brain barrier”

Information on Clinical Trials

- www.clinicaltrials.gov