Parkinson Disease: Motor fluctuations and treatment

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Conflicts of Interest

- Teva
- Acorda
- Lundbeck

Primary objectives

- Pharmacological treatment of PD motor fluctuations
- Surgical treatment of PD

Pharmacological treatment of motor fluctuations

Dopamine-related medications

1. Carbidopa-levodopa(Sinemet®)
   - 25/100
   - 50/200 CR
- Extended-release Carbidopa-levodopa capsules (Rytary ®)
- COMT inhibitors
  – Entacapone (COMTAN ®)
  – Carbidopa-Levodopa-Entacapone (Stalevo ®)
- Levodopa Oral Inhaler (rescue for wearing off)
  – Inbrija ®

Levodopa oral inhalation powder

Inbrija®

- 42 mg/ capsule: 2 capsules: 2-5 times/day
- Wearing off significantly alleviated in 10-30 min
- cough (contraindicated in asthma, COPD), nausea, URI

Lewitt PA, Hauser RA, Pawa R et al. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo controlled phase 3 trial. *Lancet Neurology.* 2019 Feb;18(2):145-154. doi: 10.1016/S1474-4422(18)30405-8.

Dopamine-related Medications for PD

1. Dopamine agonists
   - Pramipexole (Mirapex®)
   - Ropinirole (Requip ®)
   - Rotigotine (Neupro® patch)
   - Apomorphine (Apokyn® Injections)

Non Dopaminergic Medications for PD

1. Amantadine
   - (regular) Amantadine taken 2-3 times a day
   - Long acting:
     - Gocovri ®
     - Osmolex ®
2. Monoamine Oxidase-B inhibitors (MAO-B)
   - Rasagiline (Azilect ®)
   - Selegeline (Zelapar ®)
   - Safinamide (Xadago ®)
3. Trihexyphenidyl (Artane ®)

Long-acting Amantadine

- Gocovri®
  - 68.5 -274 mg/day
  - Reduce dyskinesias; reduce OFF time
  - Hallucination, Dizziness, Dry mouth, Edema, Constipation, Fall, Orthostatic hypotension, $$

Pahwa R, Tanner CM, Hauser RA, et al. ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dyskinesia in Parkinson Disease (EASE LID Study)A Randomized Clinical Trial. *JAMA Neurol.*2017;74(8):941–949. doi:10.1001/jamaneurol.2017.0943

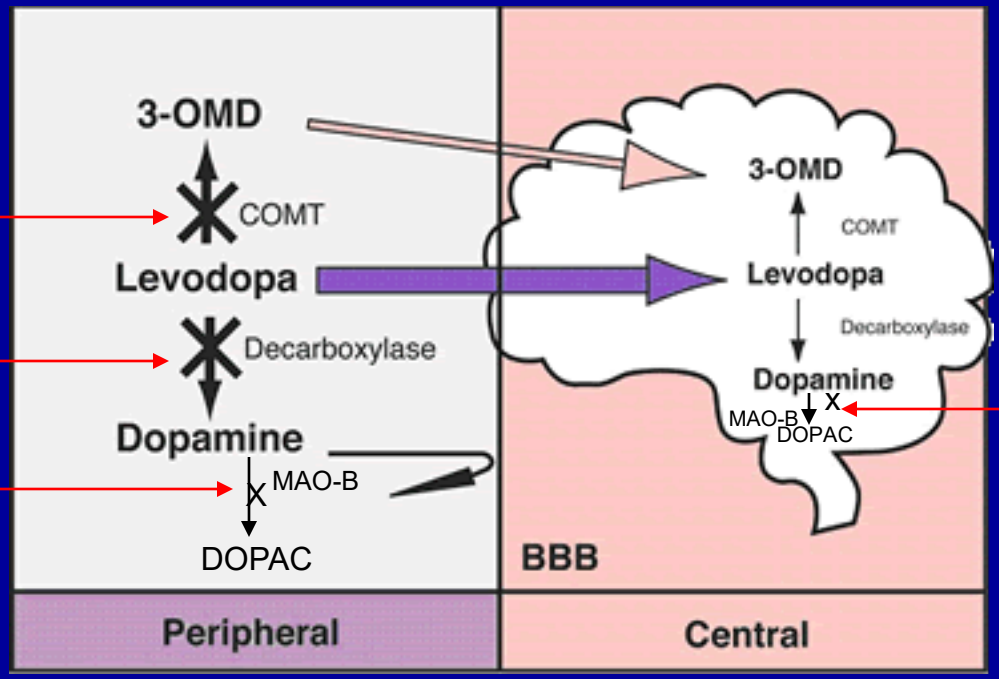
Safinamide (Xadago®)

MAO-B Inhibitor

- 50-100 mg/day
- Improve on time w/o dyskinesias; reduces OFF time ~ 1 hr
- Dyskinesia, Fall, Nausea, Insomnia, $$

Schapira AHV, Fox SH, Hauser RA, et al. Assessment of Safety and Efficacy of Safinamide as a Levodopa Adjunct in Patients With Parkinson Disease and Motor FluctuationsA Randomized Clinical Trial. *JAMA Neurol.*2017;74(2):216–224. doi:10.1001/jamaneurol.2016.4467

L-Dopa metabolism



Entacapone

Carbidopa

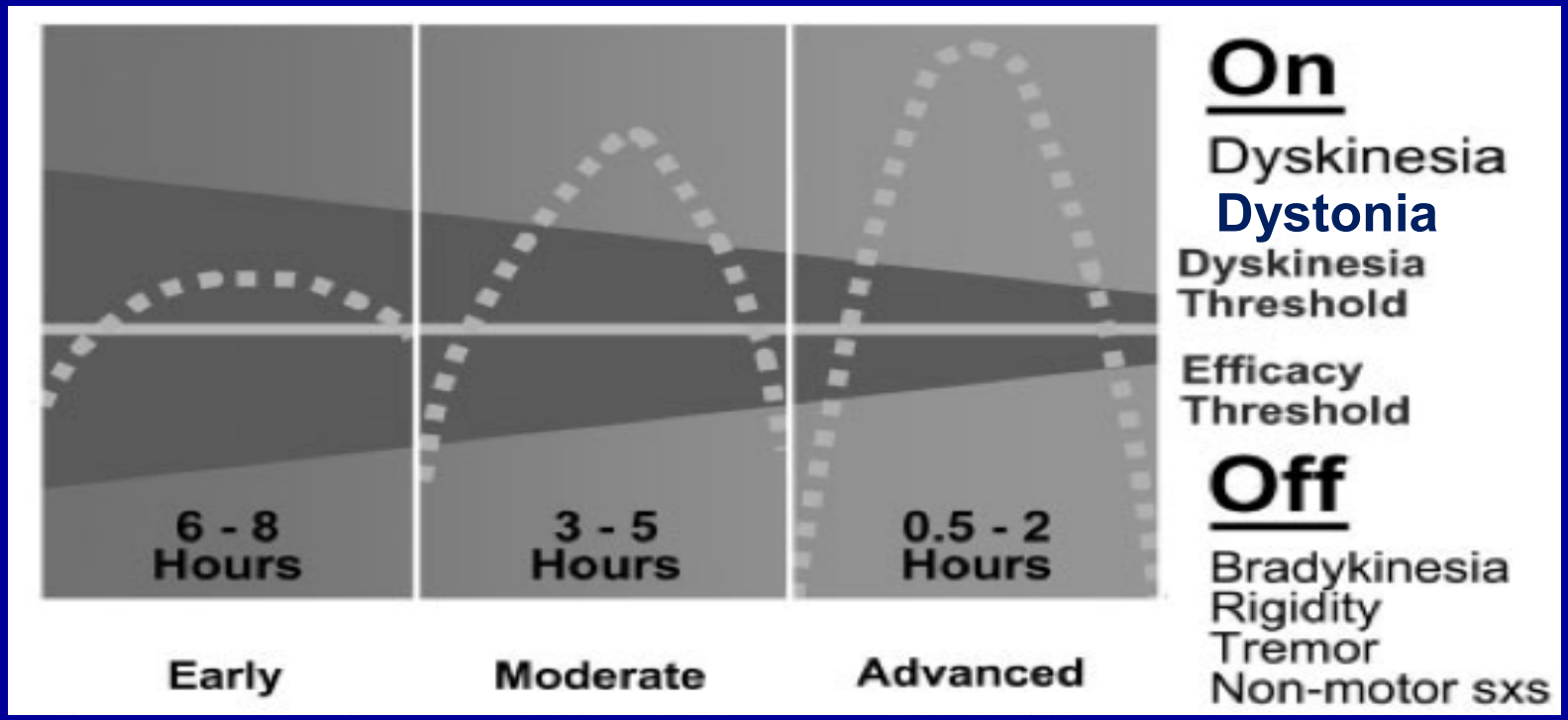
Selegiline
Rasagiline

Selegiline
Rasagiline

Brain: Tyrosine → Tyrosine hydroxylase → L-Dopa → **Dopamine**

Motor Fluctuations and Dyskinesias

Jankovic, *Movement Disorders*, Vol 20, Suppl 11, 2005



Dystonia

- Motor complications after long-term use
  - Wearing off
  - Dyskinesia

Cause of Motor fluctuations

- Loss of dopamine cells
  - Erratic stimulation of dopamine receptors
  - Other biochemical processes
- Individual factors
  - Genetic factors
  - Change in metabolism over time
  - **Severity and frequency variable**
- Dose of levodopa
- Duration of treatment

Motor Fluctuations: Wearing *Off* of Medications (Levodopa)

- Predictable
- Unpredictable and sudden
- Dose failure or delayed or partial response
- Worsening shortly after taking medications
- End of dose rebound (much more severe than expected or in the past)
- Unpredictable Off- state and Unpredictable On-state (dyskinesias)
    - Aquino and Fox, *Movement Disorders*, 2015

Motor Fluctuations: Dyskinesias- excessive movements (Levodopa related)

- Peak dose
- Ocular (eye related abnormal movements)
- Severe jerking after taking medications
- Respiratory dyskinesias
- *On* or *off* dystonia (twisting or turning of limbs, head, torso)
- Diphasic dyskinesias
- Unpredictable dyskinesias
    - Aquino and Fox, *Movement Disorders*, 2015

Minimize Motor fluctuations

- Make levodopa (or dopaminergic medications) *linger longer* in the brain
  - Multi-modal medication treatment
    - (Almost) continuous stimulation of dopamine receptors
    - Minimizing side-effects of the medications
    - Affordable

Predictable Off

- Increase dose & frequency of levodopa
- Extended release ($$$!)
- CR preparations
  - Poor absorption
- Add COMTAN to carbidopa/levodopa
  - [Can worsen dyskinesias!]

Salat & Tolosa, *J of Parkinson's Disease 3* (2013)

Predictable Off

- MAOI: Rasagiline, Safinamide
- Dopaminergic agonists
  - <65-70 years
- Levodopa Inhaler (Inbrija ®)

Unpredictable Off, dose failure, delayed or partial response

- Same strategies as for predictable wearing off, plus
- Address constipation
- Improve gut motility
  - Domperidone (not available in the USA)
- Always take Levodopa on an empty stomach

Unpredictable Off, dose failure, delayed or partial response

- Apomorphine: injectable
- Rescue levodopa
  - Parcopa ® (sublingual)
  - Levodopa Inhaler (Inbrija ®)

Other *Off* symptoms

- Worsening shortly after taking medications
- End of dose rebound (much more severe than expected or in the past)
  - Reduce dosing interval-take medications more closely
- Unpredictable Off- state and Unpredictable On-state (dyskinesias)
  - Surgical treatment
    - Aquino and Fox, *Movement Disorders*, 2015

Peak dose Dyskinesias

- Fractionation:
  - Smaller doses of levodopa IR are more frequent intervals
- Eliminate entacapone
- Eliminate CR
- Extended release carbidopa/levodopa
- Reduce levodopa, add dopaminergic agonists
  - In <65 y of age

Peak dose Dyskinesias

- Amantadine
- Zonisamide (off label)

Other dyskinesias

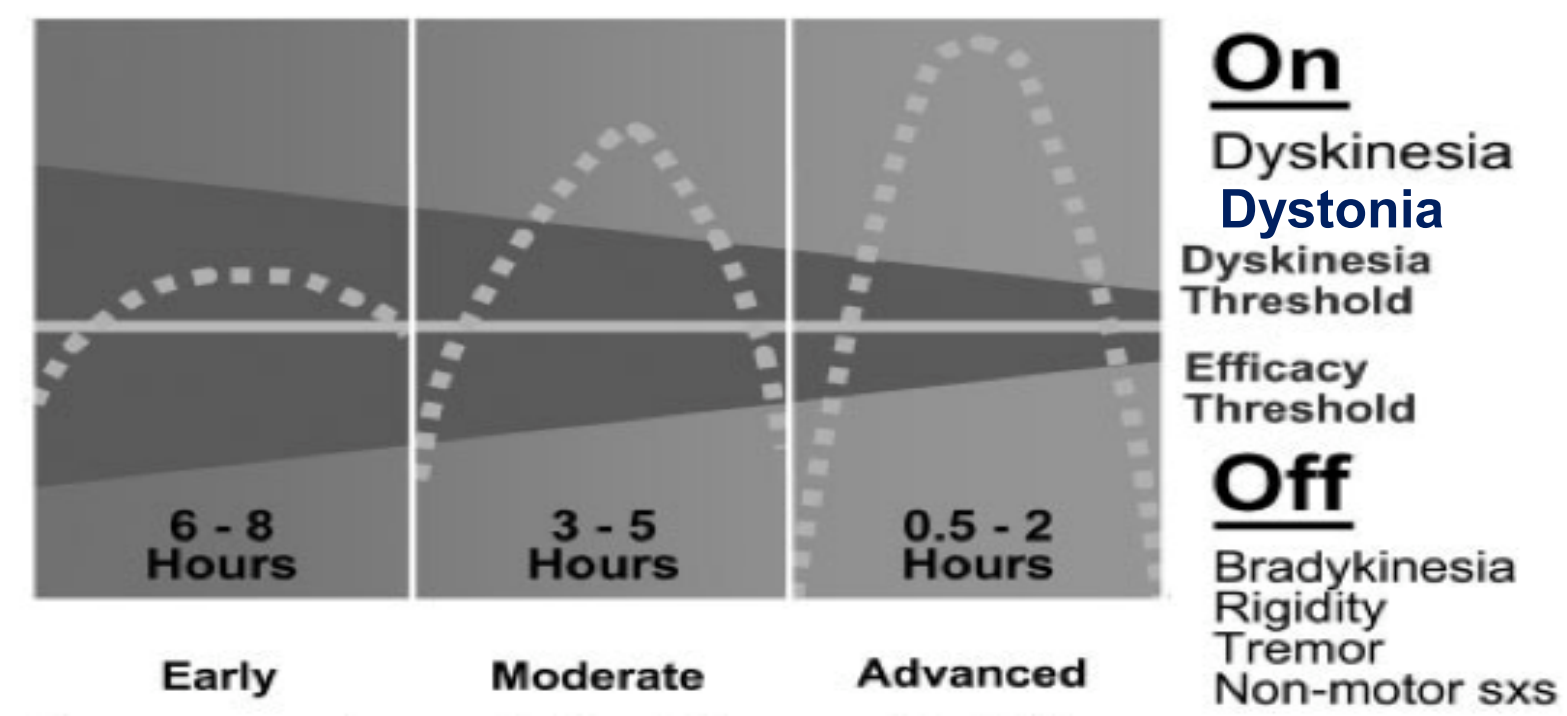
- Ocular (eye related abnormal movements)
- Severe jerking after taking medications
- Respiratory dyskinesias
- *On* dystonia (twisting or turning of limbs, head, torso)
  - No specific strategy, try methods for peak dose dyskinesias
  - ?use of clonazepem, diazepam
  - ?use of botulinum toxin for dystonia
- *Off* dystonia: address wearing *Off* of medications

Other bothersome dyskinesias

- Diphasic dyskinesias
- Unpredictable dyskinesias
  - Try all strategies for dyskinesias
  - Surgical treatment

Motor Fluctuations and Dyskinesias

Jankovic, *Movement Disorders*, Vol 20, Suppl 11, 2005



Dystonia

Persistent and bothersome

– Wearing off, AND/OR

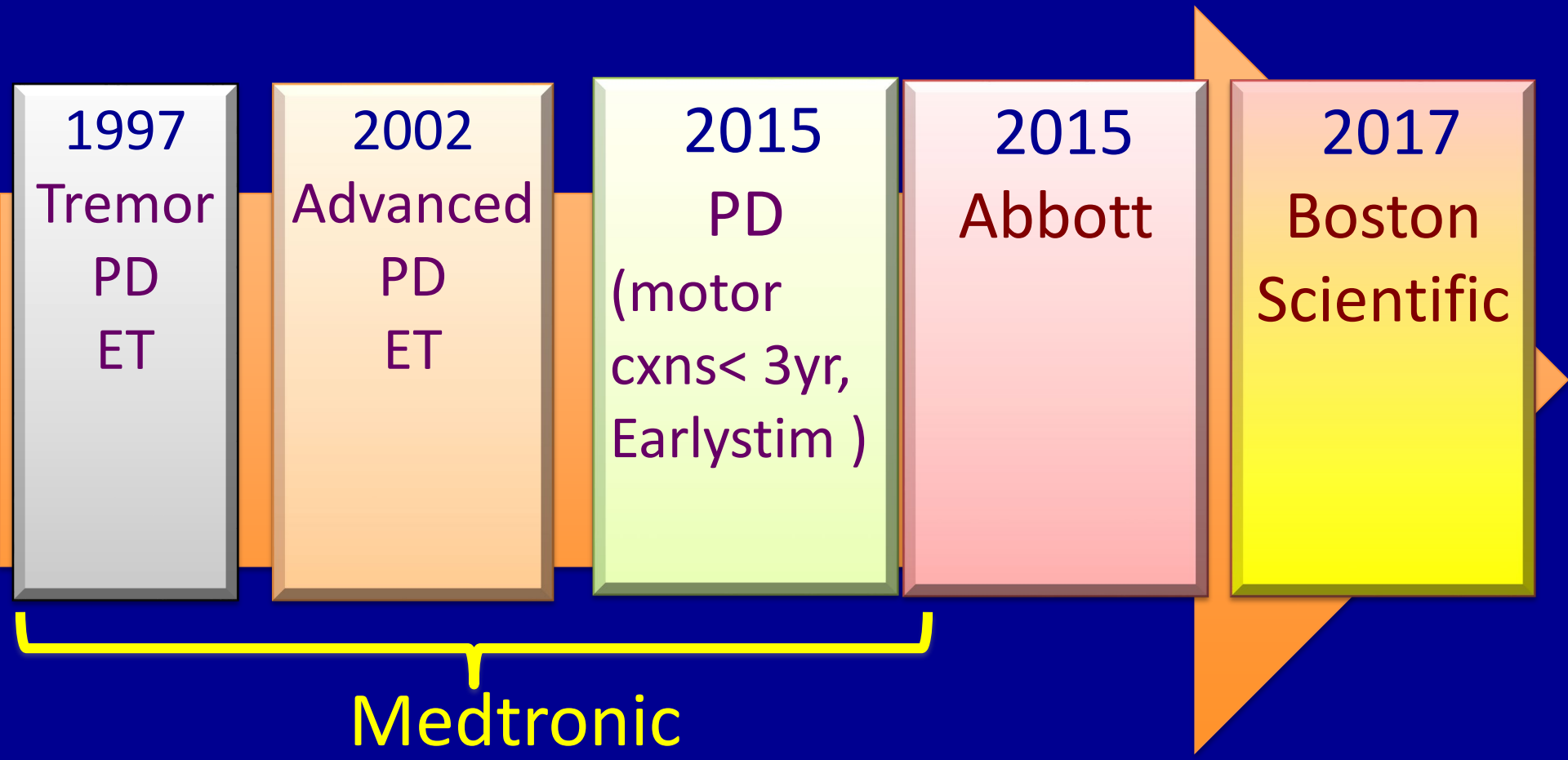
– Dyskinesia/Dystonia

Surgical treatment for PD (Neuromodulation)

1. Deep Brain stimulation (DBS)
   - Subthalamic nucleus (STN)
   - Globus pallidus (Gpi)
2. Levodopa + carbidopa enteral suspension (PEG-J tube)]
3. MRI guided focused ultrasound (MRgFUS)
   - FDA approved for tremor
   - Research

Lee,DJ Dallapiazza, RF, et. al. surgical treatments for Parkinson's disease and potential therapeutic targets. *Neural Engineering research*. 2018. doi: 10.4103/1673-5374.235220

DBS for PD FDA Approval



www.fda.gov

DBS in PD: candidate selection

- Demonstrable levodopa response
  - Diagnosis of PD is secure
- Significant motor fluctuations despite best medical therapy
- No dementia
- Adequately controlled psychiatric symptoms
- Ambulatory
- Acceptable surgical risk/comorbidities
- Reasonable expectations

Effective DBS for PD

- Selection of appropriate candidate
- Multidisciplinary team:
  - **Collaboration between Neurology and Neurosurgery teams**
- Accurate implantation of electrodes
- Effective programming
- **Continue best medical treatment of PD**

Complications of DBS

Surgery related

- Seizure <1% to 3%
- Hemorrhage < 4%
- Superificial infection 2% - 25%
- Permanent deficit < 6%
- Misplaced leads 12.5%

Hardware related

- Device malfunction
- Lead fracture
- Lead migration
- Lead disconnection
- Lead erosion

Stimulation related

- Paresthesias
- Dysarthria
- Diplopia
- Compulsive laughter
- Cognitive changes
  - -Depression
  - -?Dementia
  - -Mania
  - -Anxiety

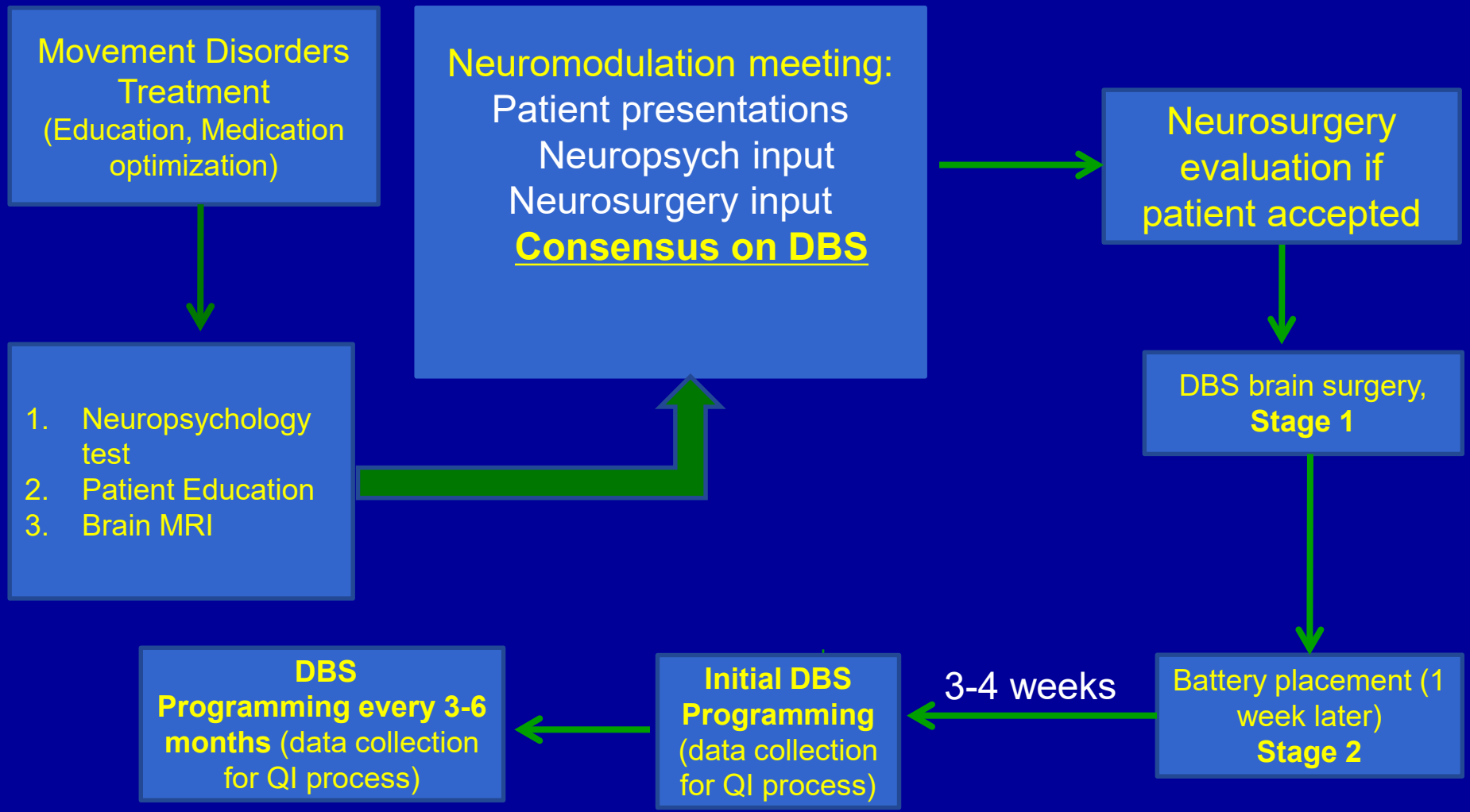
»Continuum, AAN, *Feb 2007*

DBS In PD

- Does not cure (but significantly improves QOL)
- Bilateral DBS usually needed for gait
- Smooths out on-off fluctuations
- Improves
  - tremor, rigidity, dyskinesia;
  - akinesia and postural instability responds least
- Never improves L-dopa unresponsive sx
  - **(Severe tremor is an exception!)**
- Programming requires diligent, frequent followups
- Decreases meds, does not eliminate them

Continuum, AAN, *Feb 2007*

Swedish Neuromodulation



Levodopa-Carbidopa Intestinal Gel (LCIG) Duopa®

- Cassette containing levodopa suspension
- Infusion pump
- Inserted via PEG-J tube into jejunum through stomach

LCIG

- Continous infusion of levodopa during waking hours
- Each Cassette contains 2000 mg of levodopa/100 ml suspension
- Rate of levodopa infusion is identified: X ml/Hr
- Pump delivers infusion at X ml/Hr

LCIG candidate selection

- Demonstrable levodopa response
  - Diagnosis of PD is secure
- Significant motor fluctuations despite best medical therapy
- No dementia or psychosis
- Acceptable GI surgical risk/comorbidities
- **24 hour care-giver who can be educated should be available to help with pump**
- Reasonable expectations

Effective LCIG therapy for PD

- Selection of appropriate candidate
- Multidisciplinary team:
  - **Collaboration between Neurology and Gastrointestinal teams (pre and post operative care)**
  - **Abbvie™ support**
- Accurate placement of PEG-J tube
- Effective titration and regular follow up
- **Continue best medical treatment of PD**

LCIG In PD: LISTEN

- LCIG does not cure (but significantly improves QOL)
- Improves
  - tremor, rigidity, dyskinesia if these are levodopa responsive
  - akinesia and postural instability responds least
- Smooths out on-off fluctuations
- Titration requires diligent follow up
- Every patient needs a good support system
  - Family, Neurologist, GI, Abbvie™
- Never improves L-dopa unresponsive motor symptoms
  - Khemani

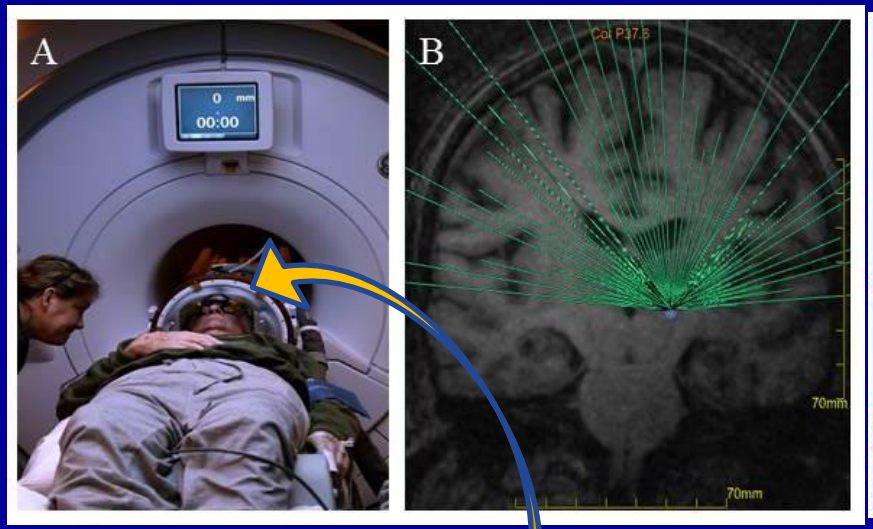
LCIG Complications

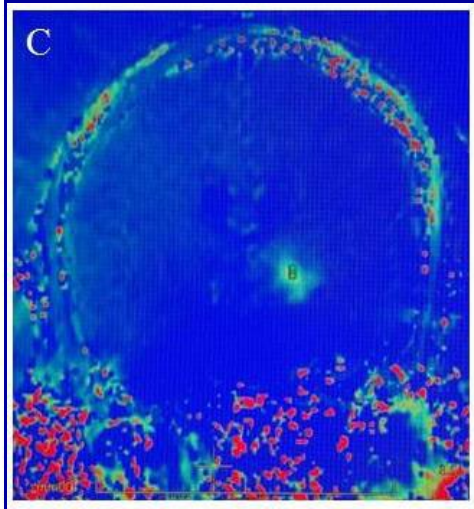
- Hardware related:
  - PEG-J tube separation, blockage, leakage
  - Intestinal perforation
- Infection
- Dyskinesias
- Hallucinations
- Orthostatic hypotension
- Neuropathy

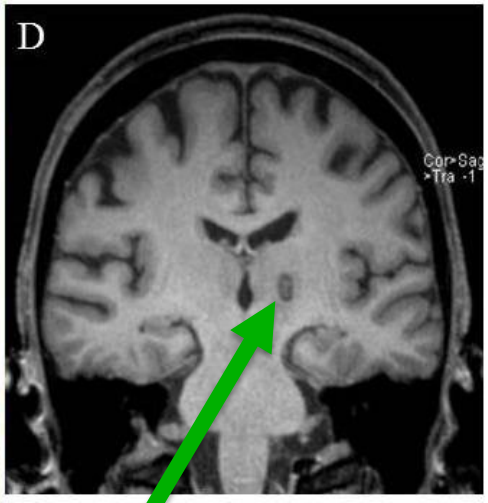
MRI guided Focused Ultrasound (MRgFUS or FUS)

- High-intensity US used to disrupt tremor circuits in brain
  - US waves are precisely transduced and ‘focused’ on Vim seen on MRI
  - US waves create a precise thermal lesion in the nucleus
  - Real-time clinical and radiographic monitoring inform length of procedure and tremor improvement
  - The patient has to remain immobile in a stereotactic frame for precise targeting

What is MRgFUS?







Stereotactic Head Frame

Left thalamic lesion
(treats R hand tremor)

4-5 hours

MRI guided Focused Ultrasound (MRgFUS or FUS)

- PD Tremor : FDA approved but insurance coverage is pending
  - One sided severe tremor
  - Process for candidate selection
- Research:
  - Lesion of Gpi for motor fluctuations and dyskinesias
  - Please contact: Laura.Johnson3@swedish.org
  - Flyers: please contact APDA

Future Therapies

- **Clinicaltrials.gov**
- Michael J Fox Trial Finder
- APDA

Surgical options in Movement Disorders	LC Insestinal Gel Pump PEG-J	Medtronic® DBS system	Abbott® DBS system	Boston Scientific® DBS system	MRI Guided Focused Ultrasound MRgFUS
PD	✓	✓	✓	✓	**Unilateral Tremor***
Brain Targets					
• STN	**n/a**	✓	✓	✓	No
• Gpi	**n/a**	✓	No	No	**Research Trial**
MRI Compatibility	✓	✓ **Brain, Body**	✓ **Brain, Body**	**?**	**n/a**
Directional Lead	**n/a**	No	✓	✓	**n/a**
MICC (multiple independent current control)	**n/a**	No	No	✓	**n/a**
Rechargeable IPG	**n/a**	✓	No	✓	**n/a**

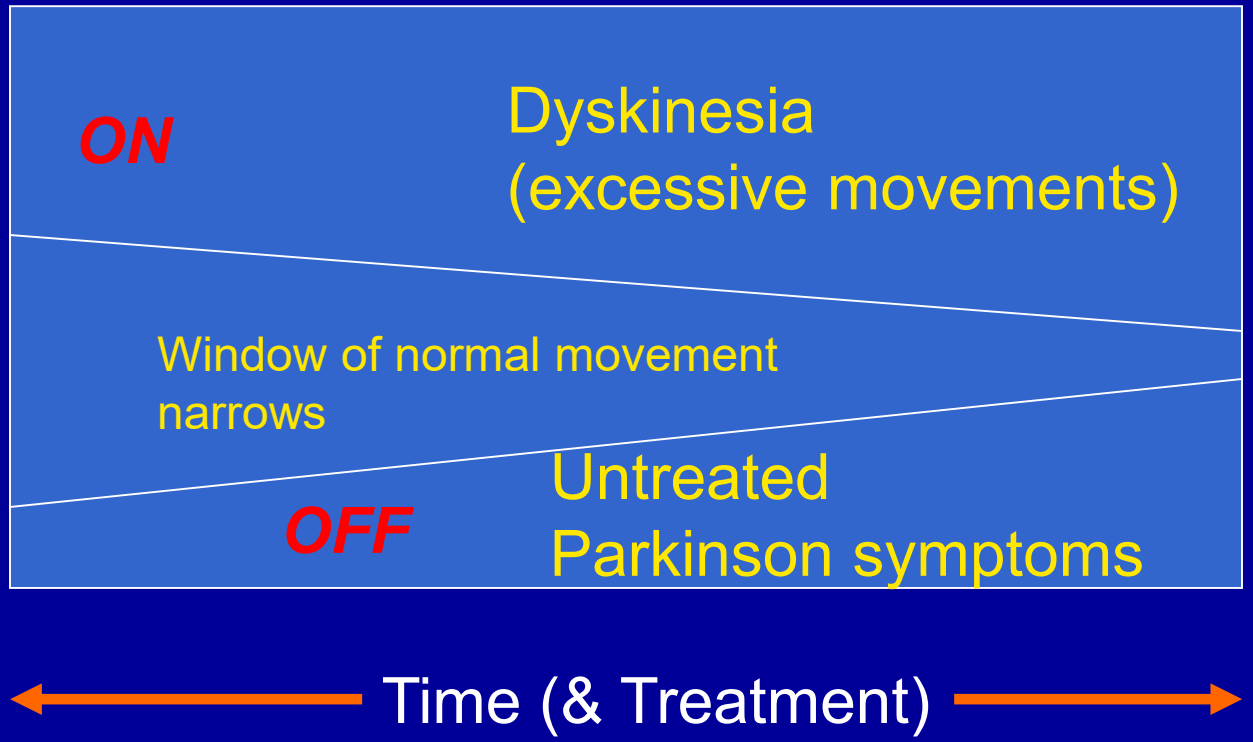
***Medication Refractory Tremor**

http://www.bostonscientific.com/enUS/Home.html

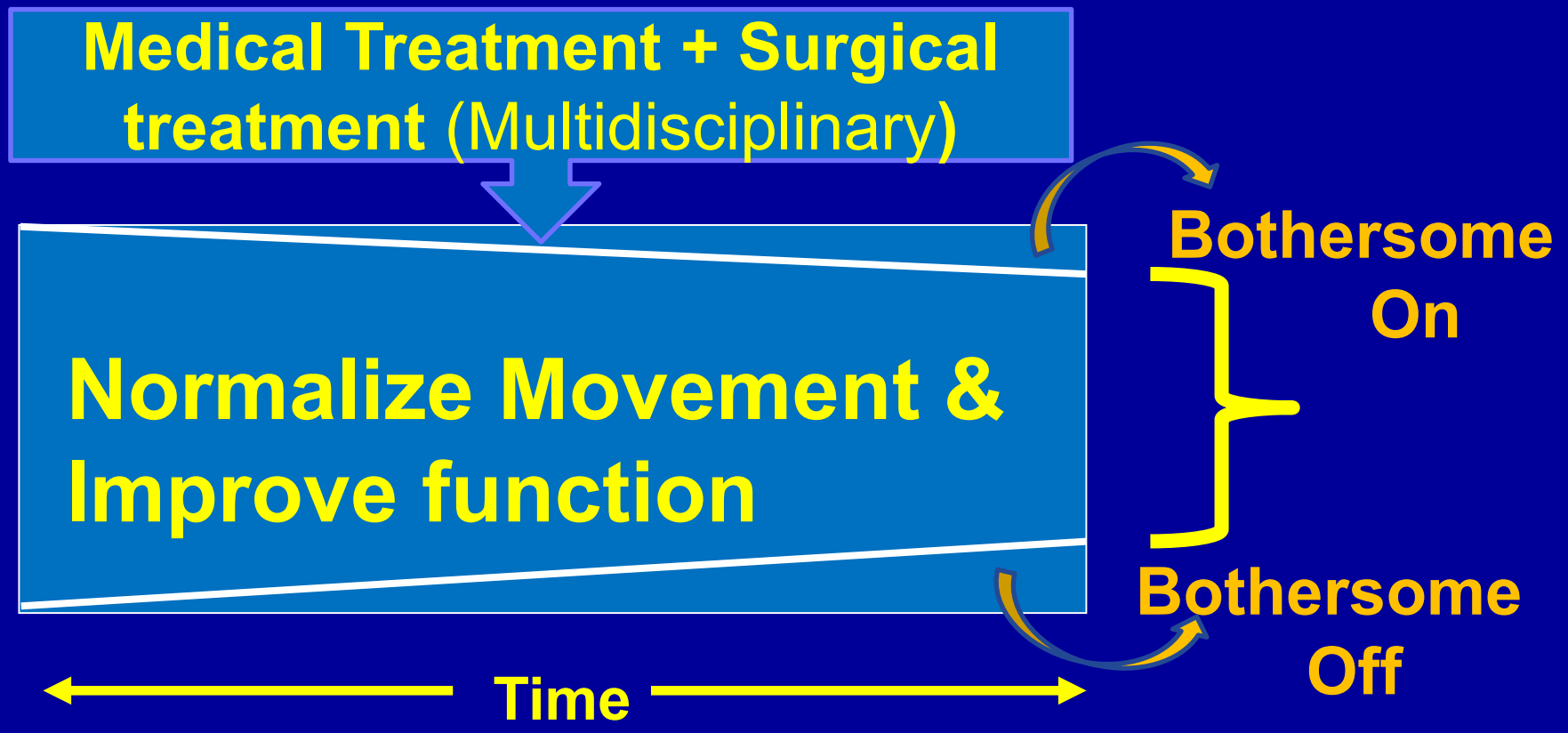
https://www.abbott.com

https://www.medtronic.com/usen/index.html

PD: motor fluctuations



PD Treatment



Thank you!

MRI guided Focused Ultrasound (MRgFUS or FUS)

- Medication unresponsive Tremor (asymmetric)
- Patient Education about DBS vs MRgFUS
  - MRgFUS improves tremor but not the other symptoms of PD: slowness, stiffness, dyskinesias
- CT head (SDR >0.45)
- Ability to lay in scanner for 4-5 hours
- Risk assessment by Neurosurgery
- Neuropsychological testing

Dopaminergic agonists (Pramipexole, Ropinirole, Rotigotine)

- Lower risk of dyskinesias
- Less potent than levodopa for motor symptoms
- More potential side-effects than L-dopa in older & sicker patients
  - Hallucinations
  - Pedal Edema
  - Somnolence, sudden sleep attacks
- Extended release formulations: Pricey!

Dopaminergic agonists

- Impulse control disorders
  - Gambling, shopping, binge-eating, hypersexuality
  - More common in younger patients (?related to frequency of use)
  - 2-3.5 fold increased when treated with agonists

Weintraub 2010

Drug Selection in PD: **Age and Stage**

Drug	Age (physiological)	Stage (severity)	Caution!
Levodopa formulations	Any	Any	Dyskinesias (in younger pts)
Dopaminergic Agonists	"Younger"(<65)	Usually mild-moderate (H and Y <3)	• Hallucinations • Somnolence • Pedal Edema • Compulsive behaviors
MAO B Inhibitors (Rasagiline)	Any	Any	Drug Interactions
Amantadine	Any (Be cautious in folks >75)	Primarily for dyskinesias	• Hallucinations • Pedal Edema • CHF • Renal Failure