

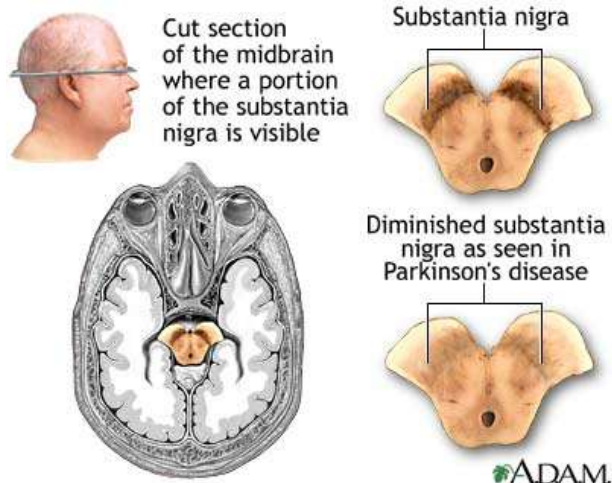
PD & YOU

Managing your Parkinson's disease

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January 24th, 2014

Introduction

When thinking about motor symptoms we are thinking primarily about **dopamine**.



Introduction

- Will present in a case-based format
- Will include older medications as well as newer ones
- Older medications are still are some of the best treatments we have

Case

- JH is a 46yo RH woman
- Presents with possible Parkinson's disease.
- She has:
 - mild tremor when her left hand is resting
 - some slight slowness in the left hand
- She is concerned about the diagnosis but feels at the moment she is functioning really well.

Her Doctor Recommends

- Referral to physical therapy
- A support group (if she can find a young onset one)
- They also talk about starting Selegiline or Rasagaline
- Tells her there is no evidence for Coenzyme Q10 and
- **An exercise program**

Neuroprotection/ Disease Modification

- Ideally medications would slow the progression of Parkinson's disease, but to date no medications have clearly been shown to do this
- It is often called neuroprotection or disease modification

Neuroprotection

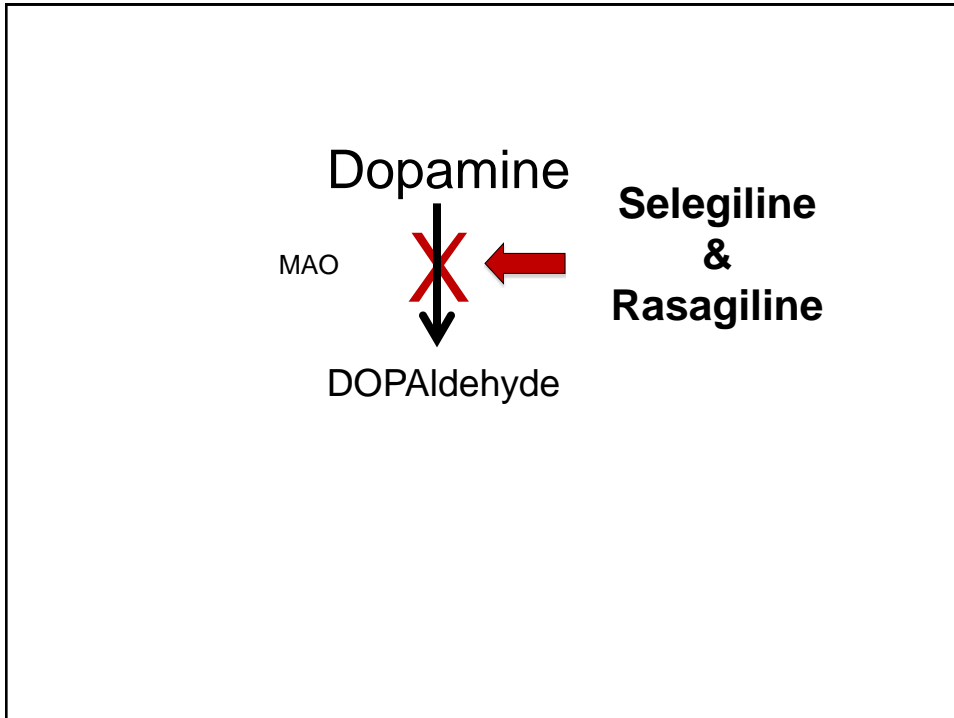
- ~~Vitamin E~~
 - Large multicenter trial
 - Not neuroprotective for PD
- ~~Coenzyme Q10~~
 - Pilot study indicated possible benefit to slow symptom progression in early disease
 - Larger study was stopped in June 2012 of this year because it did not show beneficial effects

Neuroprotection

- Selegiline ?
 - Treatment benefit for motor symptoms of PD
 - Small trend towards delayed onset of symptoms after washout
 - Neuroprotective qualities still being debated
- Rasagaline ?
 - May slightly slow disease progression
 - Again some debate over interpretation of results

Parkinson's Disease Treatment

- Dopamine is the primary neurochemical deficient in Parkinson's
- Most of the medications work to increase the amount of dopamine in the brain



Mao-Inhibitors

- Rasagiline (Azilect) &
- Selegiline (Eldepryl)
- ? slow progression of disease
- **Modest** symptomatic benefit
- Dietary restrictions are often over exaggerated



Neuroprotection - Exercise

- Reasonable data of benefits of exercise in regard to:
 - Physical functioning
 - Health-related quality of life
 - Strength, balance, gait speed
 - Risk of developing PD
 - Cognitive function in a non-PD populations
 - Neuroprotective effects in animal models of PD

Ahlskog, J.E. Neurology. 77(3):288-94. Goodwin VA, et al. Movement Disorders. 23(5):631-40, 2008 Apr 15.

Case con't

- JH is seen in a return visit she is now 48yo.
- She started rasagaline after her first visit.
- Helped a little at first, but says the tremor is really bothering her.
- She has a good exercise program in place
 - biking at the gym 3 days a week and doing a tai chi class twice a week.
- She feels like aside from the tremor she is managing well.

Her doctor talks about the following

- Start one of the following medications:
 1. Ropinirole (Requip)
 2. Carbidopa/levodopa (Sinemet)
 3. Trihexyphenidyl (Artane)
 4. Amantadine
- Refer her to occupational therapy to work on finding her assistive devices to help with tremor and
- **Continuing her exercise program**

Anticholinergics

Trihexyphenidyl (Artane)

- Generally most effective for tremor
- Significant confusion and urinary retention
 - Do not give to those with cognitive complaints or > 65 yrs old

Watts R, Koller W. Movement Disorders. 2004

Case Con't

- JH returns 6 months later. She tried the trihexyphenidyl which helped with the tremor, but when she got to a higher dosage she felt she was in a bit of a “fog.” She had trouble getting everything done during a busy work day. She also has noticed that she has some trouble typing with her left hand and that her left leg does not always move as well during her Thai Chi classes.

Her doctor tells her

- She should start an additional medication if her symptoms are bothersome
- A dopamine agonist – ropinirole (Requip) is probably the best choice and
- **Continue her exercise program**

Dopamine Agonists

- 2 oral forms available:
 - Ropinirole (Requip)
 - Pramipexole (Mirapex)
 - Doses are not equivalent (about 4-5 to 1)
- Usually given three times a day
- There are also once a day (XL) formulations



Dopamine Agonists

- Often first medication used in younger patients (< 60 yo)
- Rarely used in persons over 70 yo because of concern for worsening confusion



Dopamine Agonists

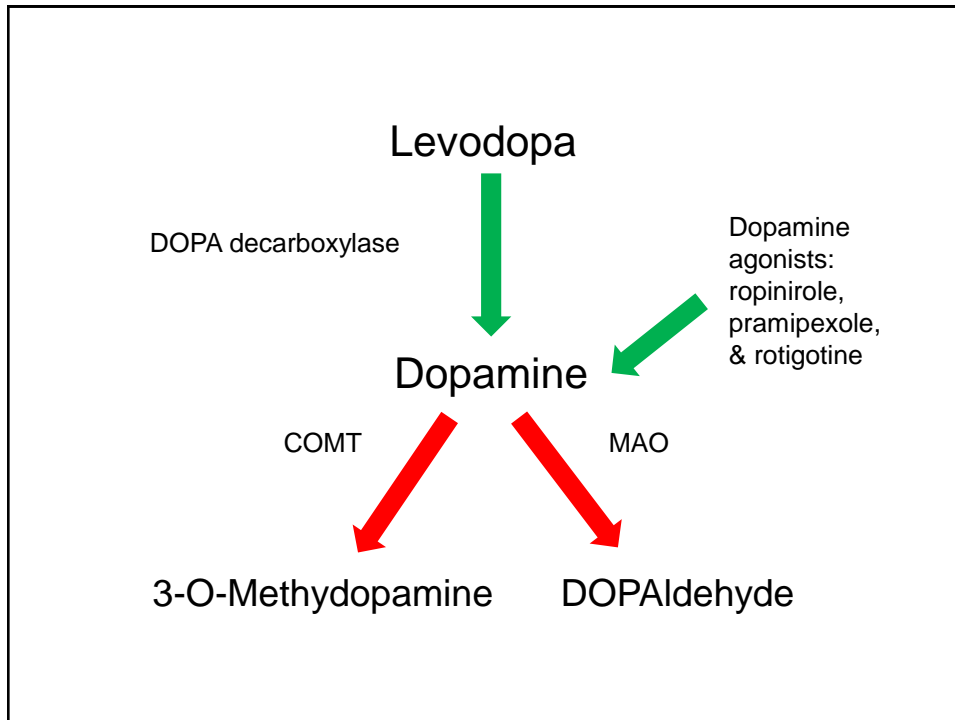
- Used in younger people because
 - Delay onset of dyskinesias (extra movements)
- Used less often in older people because
 - Cause more confusion and give less benefit than levodopa



Dopamine Agonist

- Rotigotine (Neupro)
 - Is a patch form of a dopamine agonist
 - Similar side effects to other dopamine agonists
 - Also can have skin reaction





Case con't

- JH is now 52 yo and has had Parkinson's for 6 years. The ropinirole has been working OK, but as she increased the dosage up she got sleepy at work. She is not forthcoming about it, but when asked she admits she has been gambling recently and that her relationship with her husband is strained a bit largely related to her recently increased sex drive.

Her Doctor talks about:

- Decreasing her ropinirole till her side effects are better and if needed
- Starting carbidopa/levodopa and
- **Continue her exercise program**

Dopamine Agonists

- Side effects include:
 - Fatigue
 - Sleep attacks
 - Nausea
 - Confusion
 - Postural hypotension
 - Leg edema
 - Hallucinations
 - Impulse control d/o's



Carbidopa / Levodopa (Sinemet)

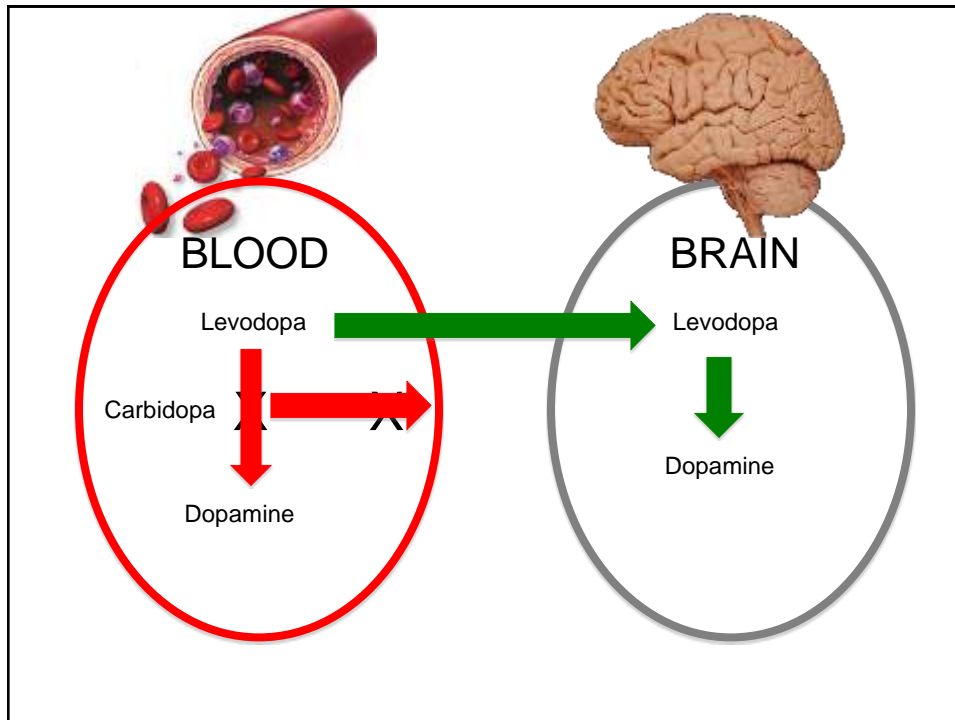
- Levodopa
 - Treats symptoms the most effectively
 - Combined with carbidopa
 - Starting dosage is 25/100 three times a day



25/100 – YELLOW
10/100 – DARK BLUE
25/250 – LIGHT BLUE

Carbidopa / Levodopa

- Levodopa
 - Most patients end up on levodopa
 - Ideally give about 30 minutes before meals
 - Side Effects:
 - Fatigue
 - Confusion
 - Hallucinations
 - Leg edema
 - Dyskinesia
 - Worsening orthostasis



Carbidopa / Levodopa

- Controlled Release
 - Irregular absorption
 - Unpredictable effects
 - Recommended mostly in evening to improve rigidity interfering with normal sleep
 - Can improve early morning symptoms

Case Con't

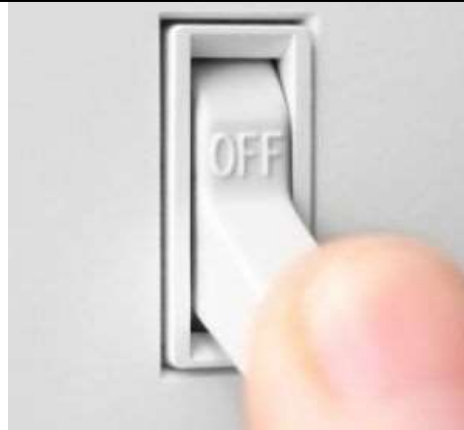
- JH returns after 12 months on a lower dosage of the ropinirole and 1 carbidopa/levodopa 25/100 TID. She has stopped gambling and her relationship with her husband is better. She feels the carbidopa/levodopa works well but she starts to “wear off” about an hour before she is due to take another dose.

She and her doctor discuss

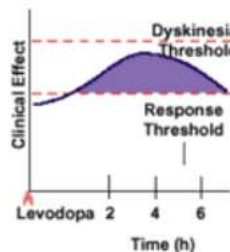
- Taking 1.5 carbidopa/levodopa three times a day
- Taking 1 carbidopa/levodopa four times a day
- Changing to carbidopa/levodopa CR 1 - 25/100 3 times a day
- Adding entacapone (Comtan) to each dose of carbidopa/levodopa and
- **Continue her exercise program**

PD Definitions

- “off”: when medications are not working (tremor, shuffling, stiffness, slowness present)
- “on”: when medications are working
- Motor fluctuations: when someone goes back and forth between the above

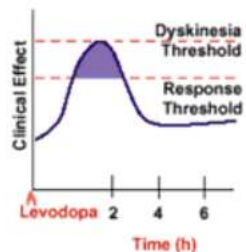


Early PD

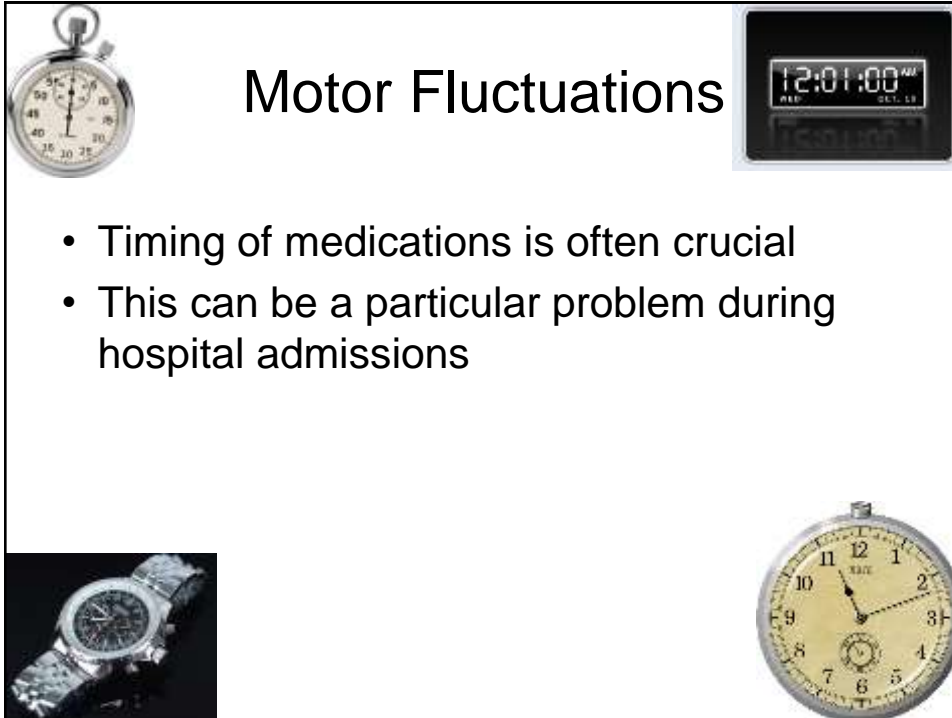


Long duration
motor response
Low incidence
of dyskinesia

Moderate PD

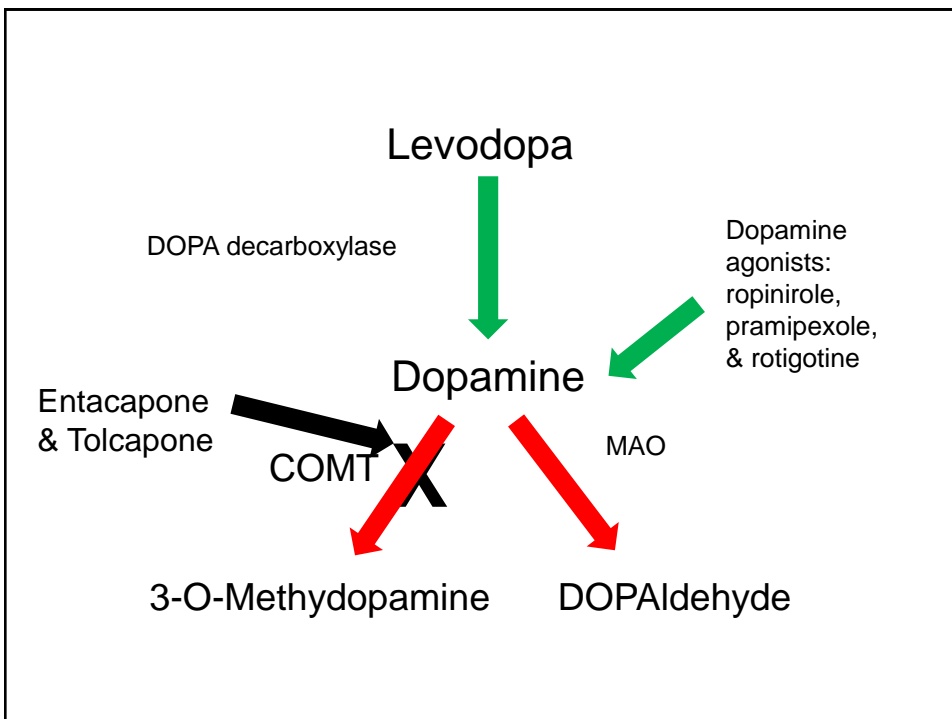


Shorter duration
motor response
Increased incidence
of dyskinesia



Motor Fluctuations

- Timing of medications is often crucial
- This can be a particular problem during hospital admissions



Carbidopa/Levodopa

- Motor fluctuations
 - Effects wear off
 - Slowness and tremor worsens
 - Unpredictable ON/OFF
 - 25-50% develop within 5 yrs
 - 90% of young onset pts within 5 yrs

COMT Inhibitors

- Results in increased ON time
- Allows reduction of levodopa
- Can worsen dyskinesias
- entacapone (Comtan)
 - Most widely used
 - Take at same time as carbidopa/levodopa



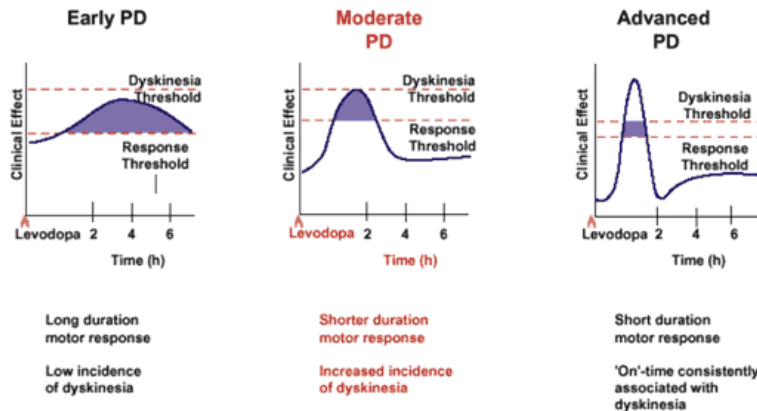
Case Con't

- JH is now 56 years old and ten years into the disease. She takes ropinirole 3mg 3 times a day, 2 - carbidopa/levodopa 25/100mg four times a day (plus a 50/200 CR at bedtime) and 200mg of Comtan with each dose of carbidopa/levodopa (5 times a day). She is having little off time, but is having some extra movements and weight loss. Her husband says she can never seem to be still.

She and her doctor discuss

- Decreasing her carbidopa/levodopa
- Decreasing the entacapone
- Adding amantadine and
- **Continuing her exercise program**

Changes in Levodopa Response Associated With Progression of PD



Medication Diary

Time	"off"	"on"	"on with dyskinesia"	asleep	Meds taken
6:00 a.m.					
6:30 a.m.					
7:00 a.m.					
7:30 a.m.					
8:00 a.m.					
8:30 a.m.					

Amantadine

- Only medication that decreases dyskinesias
- But also does improve other symptoms
- Side effects
 - Urinary hesitancy
 - Leg edema
 - Livedo
 - Insomnia
 - Confusion



Case con't

- JH felt like the amantadine was helpful for a couple of years, but is getting really frustrated by her “off” time and dyskinesias. She feels like even with medications adjustments she has a few hours a day where she is “off” or “on” & really dyskinetic. She has also started to have vivid dreams and sometimes misinterprets objects.

She and her doctor discuss

- Apokyn injections
- Deep brain stimulation – a surgery for Parkinson's
- Having her keep medication diaries and try to tweak her medications and
- **Continuing her exercise program**

Apokyn (apomorphine)

- A subcutaneous injectable medication
- Have to premedicate with antiemetic – generally Tigan
- Takes effect within minutes
- Generally lasts ~30-60 minutes per dose
- Generally take for sudden off's or in am



Case continued

- You go over the risk and benefits of DBS and JH agrees that she is ready to pursue the surgery. At the end of the visit she has plans to see neurosurgery, PT (for a gait & balance evaluation), and a neuropsychologist for neuropsych testing.

Deep Brain Stimulation

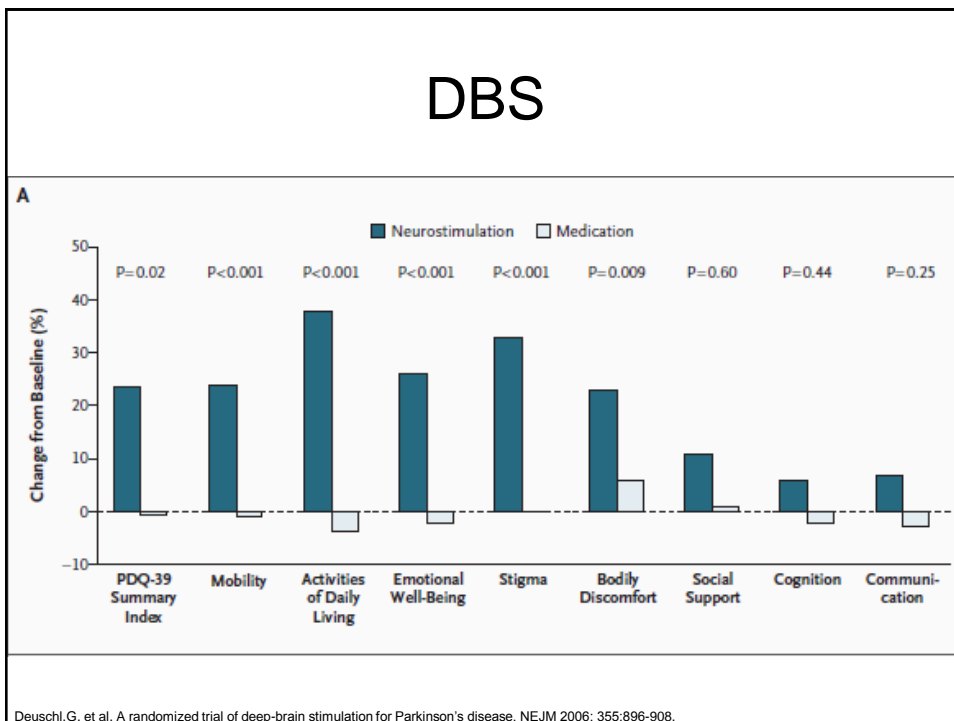
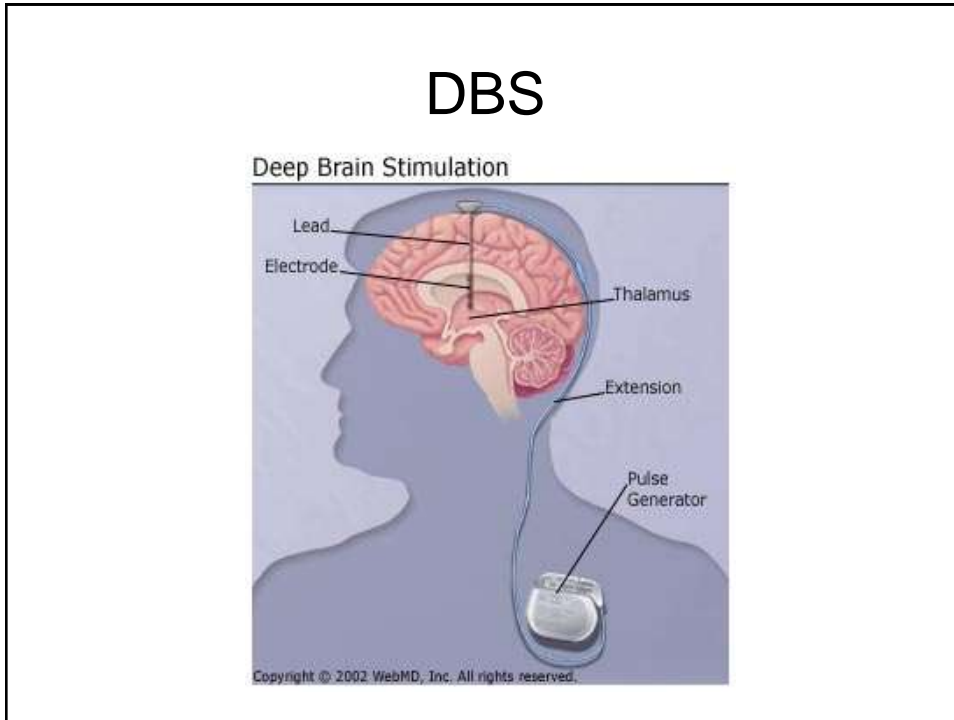
Inclusion criteria

1. Clinically definite Parkinson's disease
2. Hoehn and Yahr stage 2–4 (moderate to severe bilateral disease, but still ambulatory when on)
3. L-dopa responsive with clearly defined off and on periods
4. Persistent disabling motor fluctuations despite best drug treatment with some combination of
 - At least 3 h of off period daily
 - Unpredictable off periods
 - Disabling dyskinesia
5. Intact cognition as measured by neuropsychological testing and no active psychiatric disturbances
6. Strong social support system and commitment from patient and family members to keep follow-up appointments

Exclusion criteria

1. Parkinson-plus syndromes
2. Atypical parkinsonism—eg, vascular parkinsonism
3. Drug-induced parkinsonism
4. Medical contraindications to surgery or stimulation (serious comorbid medical disorders, chronic anticoagulation with warfarin, cardiac pacemakers, etc)
5. Dementia or psychiatric issues (untreated depression, psychosis, etc)
6. Intracranial abnormalities that would contraindicate surgery—eg, stroke, tumour, vascular abnormality affecting the target area
7. Severe brain atrophy on imaging (makes target localisation difficult)
8. Serious doubt about patient's commitment to return for follow-up visits (several no-shows in the past, poor compliance record, etc)

Sámi A, Nutt J, et al. *Lancet*. 363. 1783-93. 2004



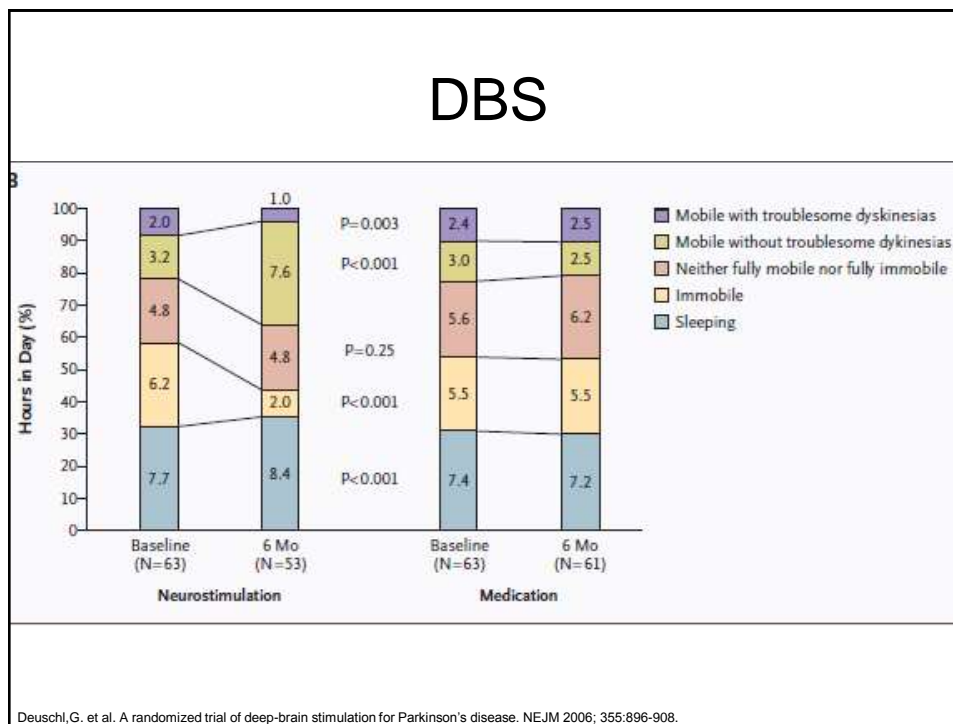


Table 4. Frequent Moderate and Severe Adverse Events for Best Medical Therapy and Deep Brain Stimulation Groups^a

Adverse Events ^b	Adverse Events From Randomization to 3 Months					Adverse Events From 4 to 6 Months				
	Best Medical Therapy		Deep Brain Stimulation		P Value ^c	Best Medical Therapy		Deep Brain Stimulation		P Value ^c
	No. of Patients	No. of Events	No. of Patients	No. of Events		No. of Patients	No. of Events	No. of Patients	No. of Events	
Fall	6	6	16	17	.02	5	5	14	14	.03
Gait disturbance	9	9	15	16	.14	4	4	10	10	.10
Dyskinesia	11	11	9	9	>.99	5	5	12	12	.08
Motor dysfunction	9	9	13	13	.27	6	6	3	3	.51
Balance disorder	6	6	12	13	.14	4	4	6	6	.53
Pain	3	3	10	13	.04	3	3	8	9	.12
Speech disorder	2	2	12	13	.004	3	3	7	7	.20
Dystonia	5	5	10	11	.18	1	1	8	8	.02
Headache	1	1	20	22	<.001	0	0	1	1	.48
Bradykinesia	4	4	12	13	.04	3	3	4	4	.71
Confusional state	1	1	13	16	<.001	3	3	3	3	>.99
Freezing phenomena	6	6	5	5	>.99	3	3	7	7	.20

^aAdverse events exclude those that were rated as mild and those with low total frequency (<10 events); also note that adverse events include severe adverse events by definition.
^bThe total number of moderate and severe adverse events were 236 for the best medical therapy group and 659 for the deep brain stimulation group.
^cBased on the number of unique patients.

In DBS more **falls**, speech problems, **dystonia**, confusion, headache.

Case continued

- JH does well on testing and well with surgical implantation of bilateral Gpi electrodes. You see her back for programming which goes well. She asked you if she can stop her medications.

Her doctor tells her...

- To either gradually decrease the amantadine as you suspect the dyskinesias will not be as problematic o
- Gradually decrease the ropinirole because you think it is making her a little confused and sleepy and
- **Continue her exercise program**

Case continued

JH has now had Parkinson's for over 20 years. Since her DBS surgery she only has rare "off times" and her dyskinesias are generally manageable but she is noticing more problems with her gait (especially her feet getting stuck) and losing her balance.

Her doctor discusses

- Increasing her carbidopa/levodopa if it seems to help with the freezing
- And refers her to PT to learn some "tricks" to reduce freezing and
- **The PT tells her to continue her exercise program**

Case con't

- At 30 years into her disease. JH has severe problems with ambulation. She cannot get up from a chair without assistance and even with a walker tends to fall back and lose her balance. She has moved into a nursing facility. She frequently hallucinates, usually seeing small children, but recently seeing adults who frighten her.

Her doctor does the following

- Makes sure she is no longer on medications that can worsen her thinking:
 - Ropinirole, Amantadine, selegiline, rasagiline, or trihexyphenidyl.
- Considers decreasing her carbidopa/levodopa gradually
- Considers start her on quetiapine (Seroquel)
- Considers starting her on a donepezil (Aricept) and
- **Continue her exercise program**

Medications for thinking problems in Parkinson's

- If is poor memory often prescribe cholinesterase inhibitors
 - Donepezil (Aricept)
 - Tacrine (Cognex)
 - Rivastigmine (Exelon)
 - Galantamine (Razadyne)
- If there are hallucinations also consider adding quetiapine (Seroquel)*

* black box warning for increased death in elderly

Medications to Avoid in PD

- Neuroleptics: Haldol, Thorazine, Abilify...
- Anti- nausea: Promethazine, prochlorperazine, metoclopramide
- Anti-histamine/anti-anxiety: hydroxyzine

Sámi A, Nutt J, et al. *Lancet*. 363. 1783-93. 2004

One last word on exercise



Thank you

