Parkinson's Disease: Advances in Treatment Strategies

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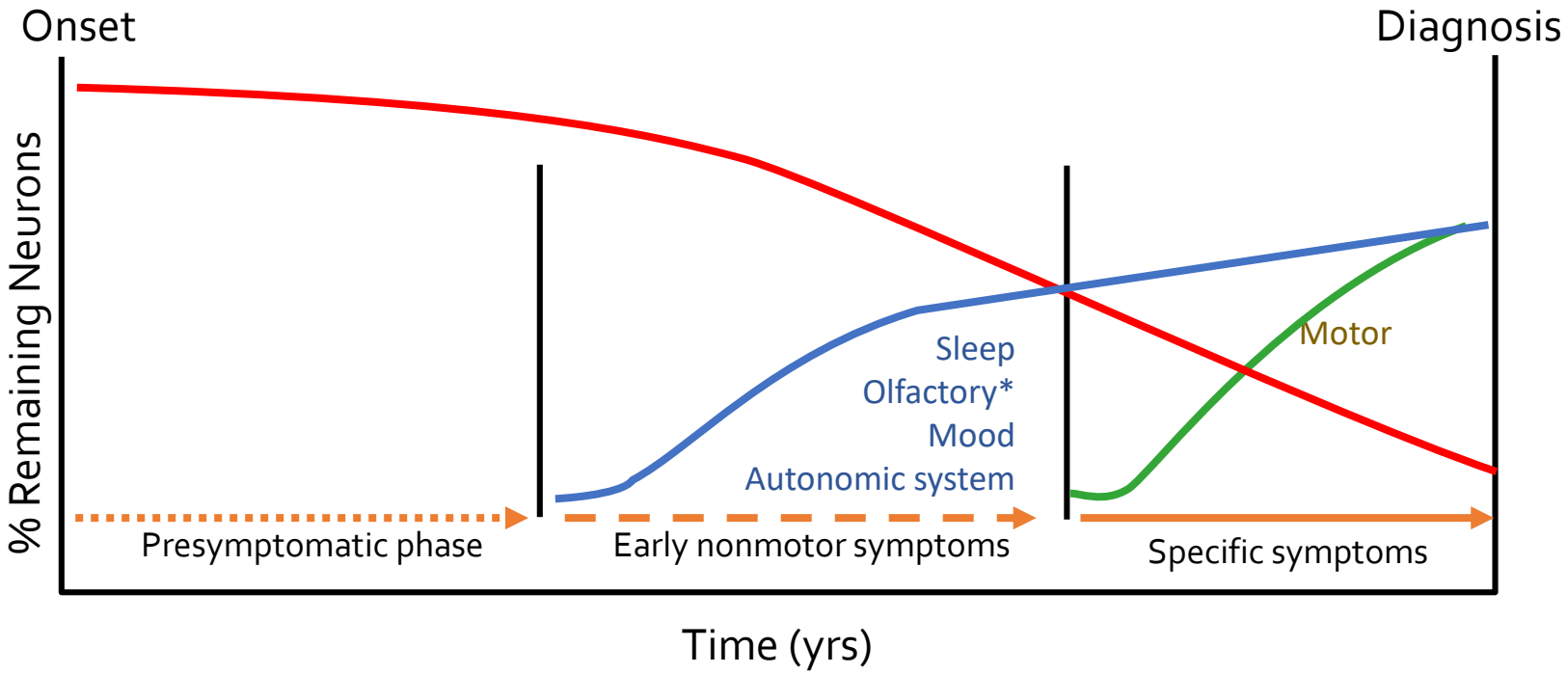
Motor Features of Parkinson’s Disease

Sir William Richard Gowers:
Parkinson’s Disease sketch (1886)

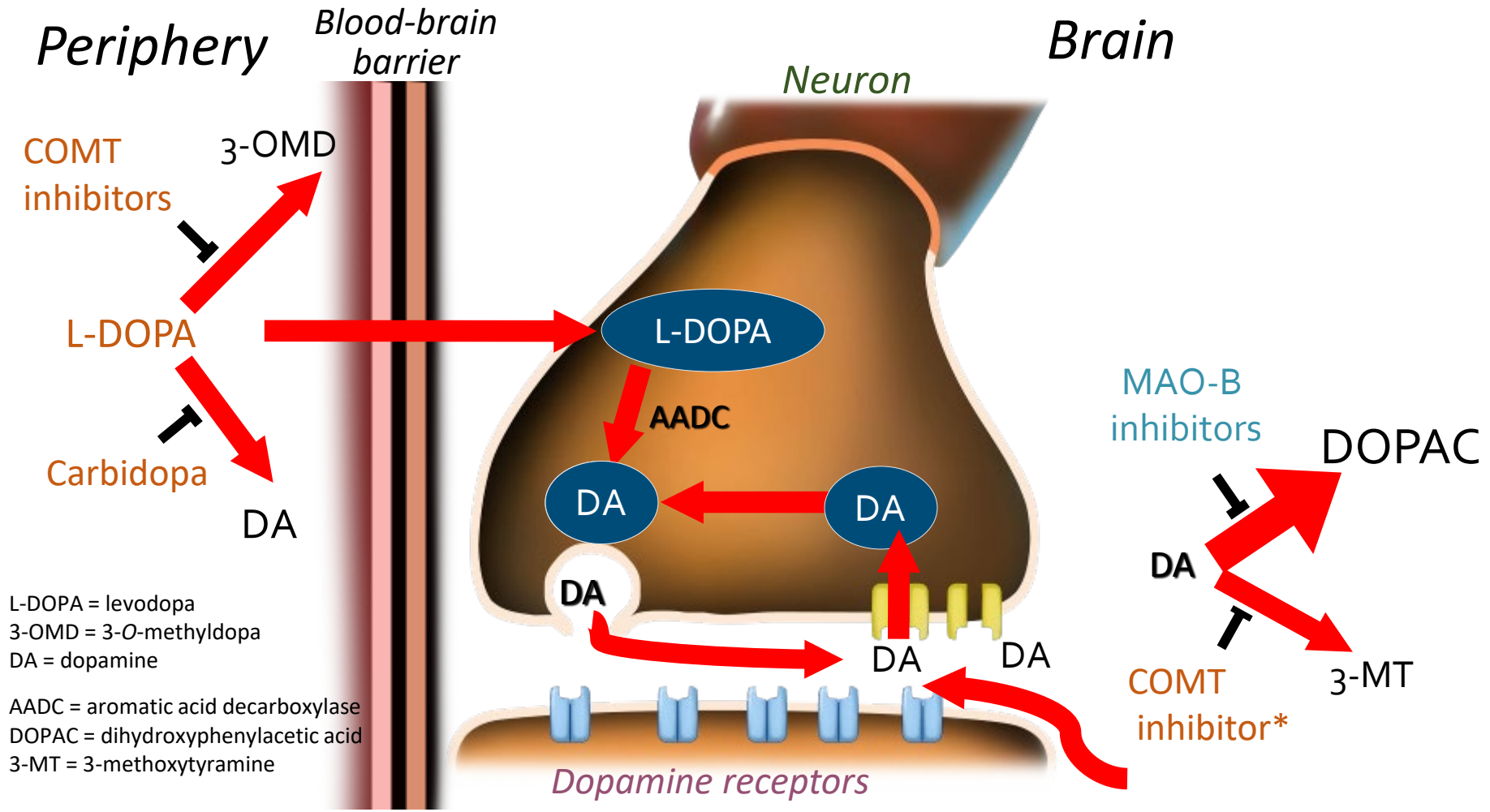
Progression of PD



*Olfactory dysfunction may predate clinical PD by at least 4 years

Image adapted from Halperin et al. *Neurotherapeutics* 2009.

Current Oral Therapies for Parkinson's Disease



Pearls in the Treatment of Early PD

- Sleep does not fix everything, but it helps almost everything… treat the RBD, RLS, sleep apnea
- Undertreated depression and anxiety will make motor symptoms look and feel worse
- Autonomic symptoms (constipation, low BP) have a significant impact on quality of life
- The symptom that bothers the patient the most is the one they will track when relating response to medication
- Patients almost always get used to side effects of PD drugs. Sometimes the longer acting drugs are associated with fewer side effects than the corresponding IR formulation. However, early patients do not wear off much, so it is expensive and not clearly beneficial to start with the longer acting medication

Non Motor Features of PD

- **Mood disorders** such as depression, anxiety and irritability
- **Sleep disorders** such as insomnia, excessive daytime sleepiness (EDS),RBD, RLS
- **Orthostatic hypotension**
- **Constipation and early satiety**
- **Excessive sweating**, especially of hands and feet, with no or little exercise
- **Fatigue/Pain**
- **Sexual problems/ Urinary urgency, frequency and incontinence**
- **Vision problems**
- **Seborrhea dermatitis or oily skin**
- **Loss of sense of smell**
- **Weight loss or weight gain**
- **Impulsive control disorders** such as binge eating, excessive shopping or gambling, usually a side effect of medications
- **Cognitive changes** such as problems with focused attention and planning, slowing of thought, language and memory difficulties, personality changes
- **Hallucinations and delusions**

Motor Complications Occur in Up to 80% patients

End-of-dose “wearing-off”

- 1 to 3 years post-initiation of levodopa
- Response duration (~4 hours) becomes shorter
- Symptoms may re-emerge 1–3 hours after each dose (“off” state)

Dyskinesias

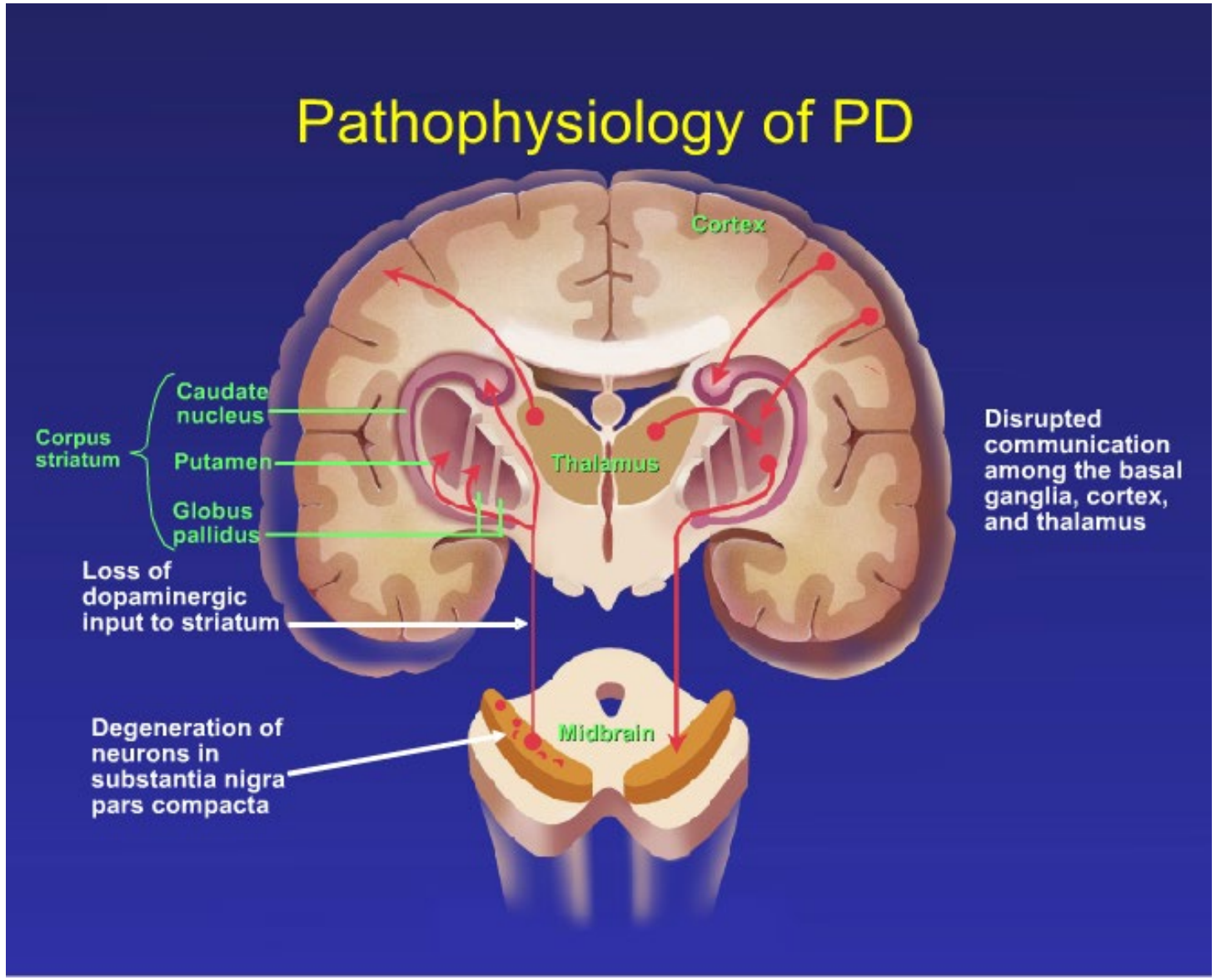
- Usually take the form of abnormal involuntary choreoathetoid movements
- Usually appear in middle of “on” period
- Occur months to years post-initiation of levodopa

Effect of levodopa

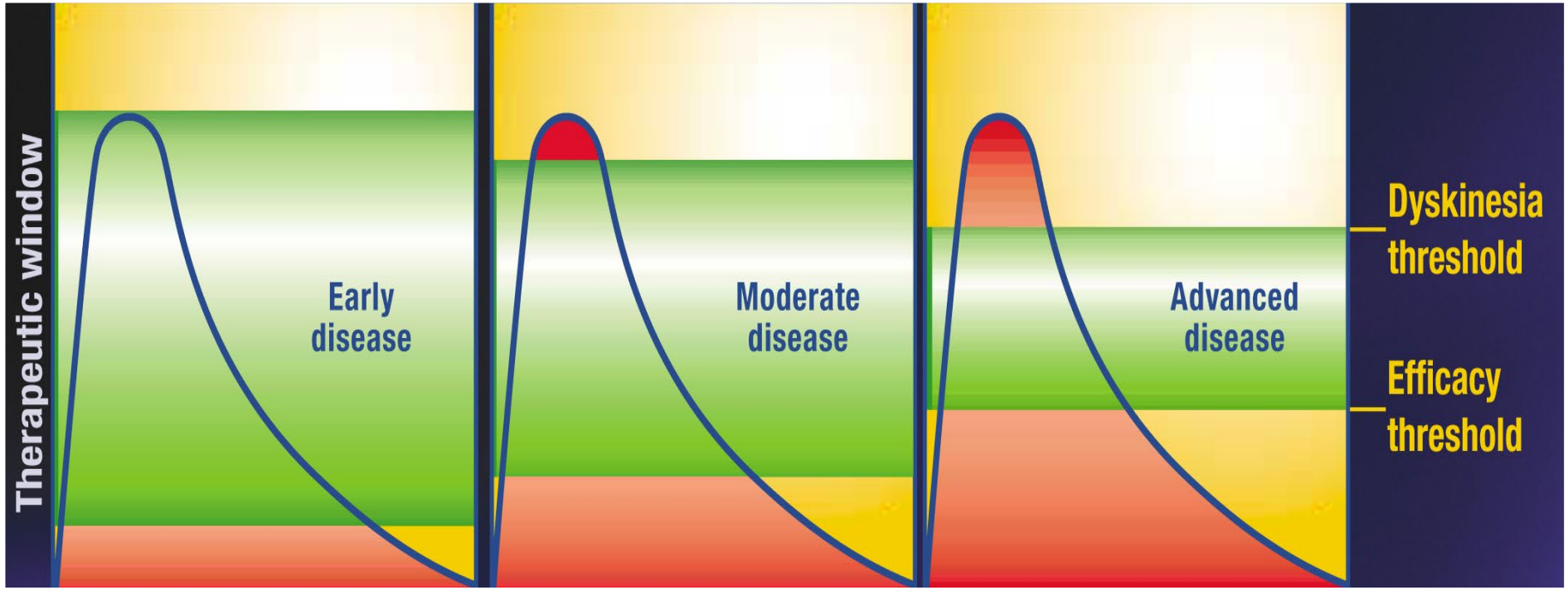
End of Dose Wearing Off

Tremor Predominant PD

- Tremor-predominant Parkinson's disease is characterized by prominent tremor of one or more limbs with a relative lack of significant rigidity and bradykinesia.
- Despite the lack of other disabling motor symptoms, the tremor of tremor-predominant Parkinson's disease can be very disabling, especially if a postural and kinetic component exists.
- First line medications (levodopa, dopamine agonists, anticholinergics) can be very effective in controlling tremor.
- However, some patients with Parkinson's disease tremors are unresponsive to first line drugs and treatment with second line medications (clozapine, amantadine, clonazepam, propranolol, gabapentin) should be attempted.
- In the small number of patients with disabling tremor that is refractory to all medications, neurosurgical intervention should be considered.


Pathophysiology of PD
Cortex
Caudate nucleus
Corpus striatum
Putamen
Globus pallidus
Thalamus
Loss of dopaminergic input to striatum
Disrupted communication among the basal ganglia, cortex, and thalamus
Degeneration of neurons in substantia nigra pars compacta
Midbrain

Symptoms and side effects occur as the levodopa therapeutic window diminishes*



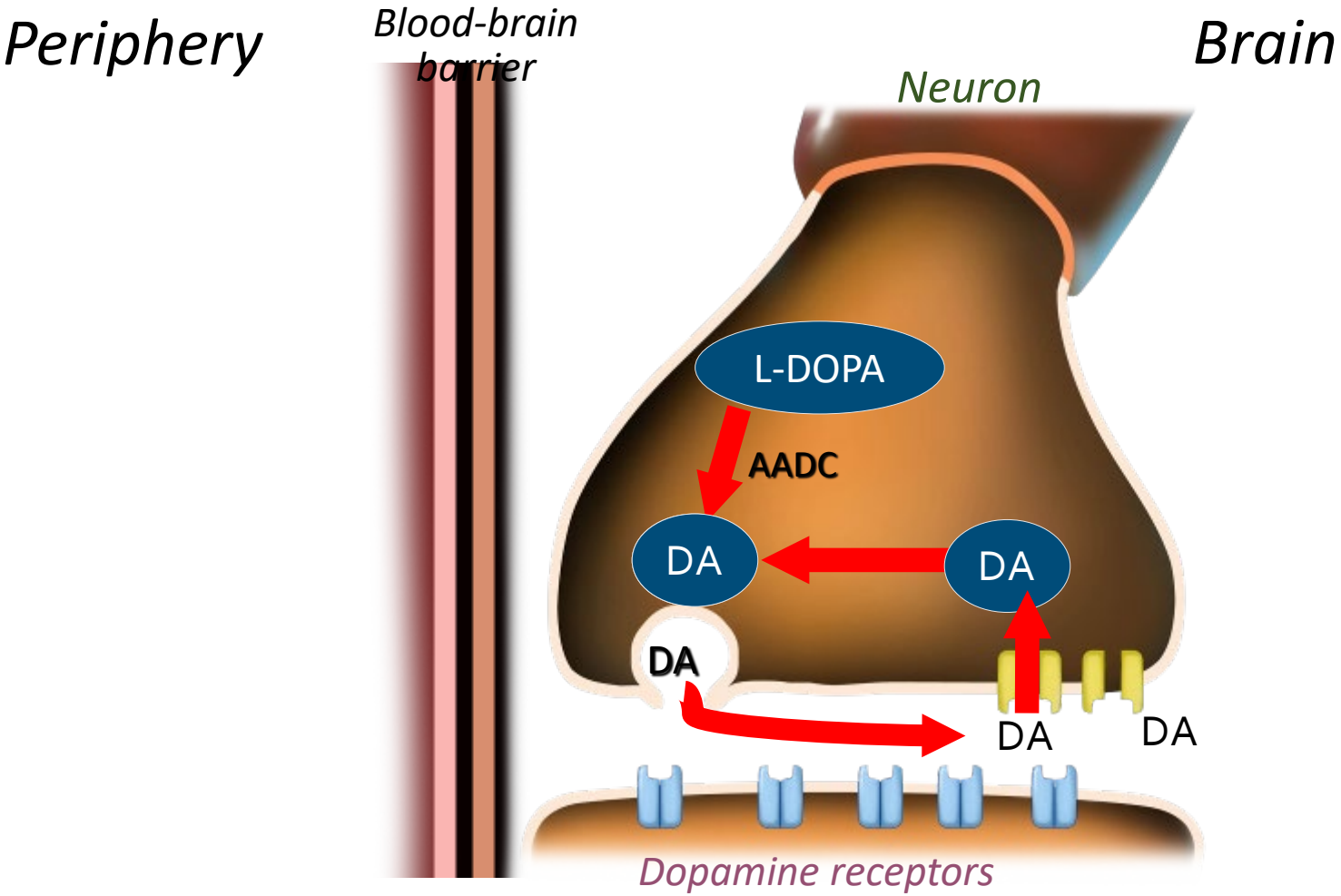
- Smooth, extended response
- Absent or infrequent dyskinesia

- Diminished duration
- Increased incidence of dyskinesia

- Shorter, unpredictable response
- "On" time with increased dyskinesia

*Artist's interpretation of plasma pharmacokinetic curves and the narrowing therapeutic window Adapted from: Stocchi F, et al. *Eur Neurol*, 1996.

Neuronal loss in Parkinson's Disease



Why Use Extended Release Formulations?

- If immediate release ropinirole is given with meals, the 12-hour gap between last evening dose and breakfast dosing, the differences between peak and trough levels for immediate release ropinirole may be as much as 5-fold, compared with the 2-fold change seen with ropinirole 24-hour (Shill and Stacey, Neuropsychiatr Dis Treat. 2009; 5: 33-36.)
- Clinically, this translates to significantly improved PD symptoms in the am for patients with "off" symptoms such as am painful "off" dystonia

Early AM “off” dystonia

End of Dose “off” Dystonia

Levodopa- related dyskinesias may be classified into three main categories:

- On dyskinesias coincide with the time of clinical improvement ("on“ period) and may occur when motor capacity is greatest ("peak of dose") or be present throughout the whole "on" time. The movements are almost always choreic in nature but can also consist of dystonic movements or action dystonia of the limbs, blepharospasm, and cranial dystonia.
- Diphasic dyskinesias in which the involuntary movements start at the end of the "On" period. Diphasic dyskinesias usually consist of rapid movements affecting the lower limbs, dystonic postures of the limbs or rarely blepharospasm.
- Off-period dyskinesia which takes the form of dystonic postures, during periods of decreased mobility, more often in the morning before taking the first levodopa dose. Off-period dystonia is characterized by a high prevalence of foot dystonia.

Severe Dyskinesia

On Dystonia and Dyskinesia

Dyskinesia Impacting Gait

Gait Freezing

Extended Release Formulations of LD

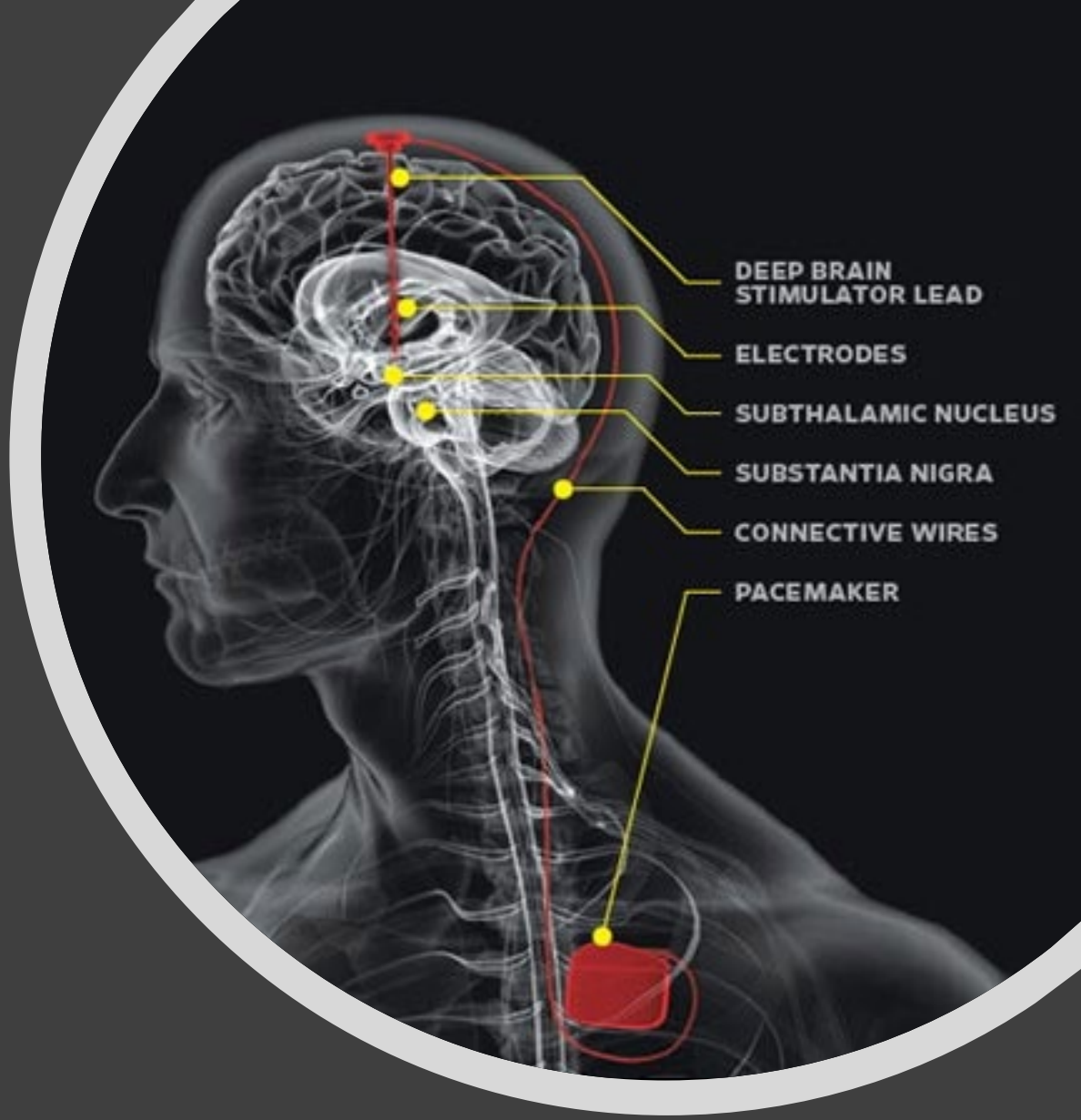
- CR levodopa is sometimes referred to as “crummy release” levodopa. Absorption of the CR formulation can vary significantly from dose to dose (not a protein effect)
- The formulation of carbidopa/levodopa extended release (IPX066/Rytary) contains special beads designed to dissolve at different rates within the stomach and the intestines. The medication capsule was designed to provide longer lasting benefit for patients with Parkinson’s disease.
  - Rytary in early PD. Patients enrolled in Study 1 (n=381) were Hoehn and Yahr Stage I–III with a median disease duration of 1 year, and had limited or no prior exposure to levodopa and dopamine agonists. Patients continued taking concomitant selective monoamine oxidase B (MAO-B) inhibitors, amantadine, and anticholinergics provided the doses were stable for at least 4 weeks before screening. Eligible patients were randomized (1:1:1:1) to placebo or one of three fixed doses of RYTARY (carbidopa/levodopa doses of 36.25 mg / 145 mg, 61.25 mg / 245 mg, or 97.5 mg / 390 mg, three times a day)
  - Rytary in late PD. The randomized study that led to FDA approval included 393 Parkinson’s disease patients who reported at least of 2.5 hours of “off time,” defined as periods when they felt the medication was not working. The results revealed that the group on extended release formulations took less overall medication dosages (3.6 vs. 5 doses per day); however they also took more total pills. The daily “off-time” improved by over an hour each day in the extended-release formulation.

Deep Brain Stimulator Surgery: indicated for adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease not adequately controlled with medication

Challenges Associated with DBS

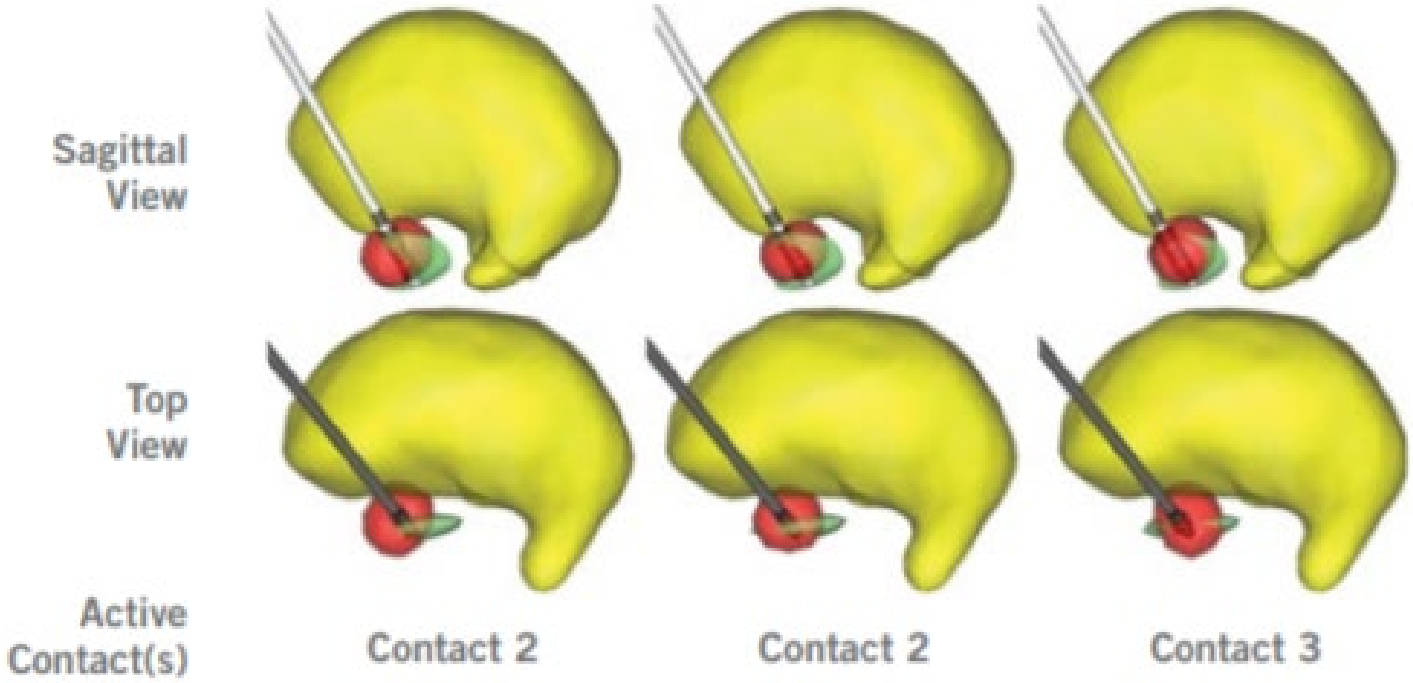
- Death (0-4.4%)
- Intracranial bleeding (<2% for most centers)
- Infection around brain leads or around wires/battery in chest (0-15%)
- Lead erosion (1-2.5%), lead fracture (0-15%) or lead migration (0-19%)
- Psychiatric/behavioral complications: worsening cognitive function, depression/apathy, mania, change in verbal fluency
- Patients still require pharmacotherapy
- Patients with cognitive impairment are not candidates for DBS

-Bronstein et al. Deep Brain Stimulation for Parkinson's Disease: An Expert Consensus and Review of Key Issues. Arch Neurol. 2011 Feb;68(2):165.



Ability to Steer Current Towards a Target

Figure 4. VTAs (red) are shown relative to the thalamus (yellow) and subthalamic nucleus (green) as directional contacts are selectively activated. Changing active contacts can preferentially steer activation around the directional DBS lead.



St. Jude Medical Infinity™ Deep Brain Stimulation System

The Right Candidate for DBS

- Intact intellectual function and memory.
- History of significant benefit from taking levodopa (Sinemet). Good mobility, with the ability to walk, in the best "on-medication" state is important for a good outcome. In general, surgery makes the "off" medication state more like the "on" state but rarely does better than the best "on" state,
- Certainty of diagnosis.
- Lack of other untreated or inadequately treated illnesses. Serious cardiac disease, uncontrolled hypertension, or any major other chronic systemic illness increases the risk and decreases the benefit of surgery.
- Realistic expectations. People who expect a sudden miracle are disappointed with the results, and they may have difficulty with the complexity of the therapy.
- Patient age. The benefits of DBS for PD decline with advancing age, and the risks go up. We rarely offer surgery to a person over 80 and would only consider it if they are in otherwise excellent health, are cognitively intact, and have good function in the on state. For patients over 75, the benefits are likely to be modest.
- MRI of the brain should be free of severe vascular disease, extensive atrophy, or signs of atypical parkinsonism.
- Degree of disability.
- Ability to remain calm and cooperative during an awake neurosurgical procedure lasting 2-3 hours per brain side.

DBS Patient Flow at IM Prior to Neurosurgery Consult

- Neuropsychological testing to assess mood and cognition. Neuropsychological tests evaluate functioning in a number of areas including: intelligence, executive functions (such as planning, abstraction, conceptualization), attention, memory, language, perception, sensorimotor functions, motivation, mood state and emotion, quality of life, and personality styles. Neuropsychological tests are standardized, meaning that they are given in the same manner to all patients and scored in a similar manner time after time. An individual's scores on tests are interpreted by comparing their score to that of healthy individuals of a similar demographic background (i.e., of similar age, education, gender, and/or ethnic background) and to expected levels of functioning.

  The testing helps with the evaluation as to whether deep brain stimulation is appropriate for a particular person and provides a baseline against which subsequent evaluations can be compared. For example, this test can be repeated down the road to help us decide whether your functioning has declined because of the disease process or whether your functioning has worsened or improved as a result of treatment (e.g. medications or DBS). PLEASE MAKE SURE THAT YOU HAVE TAKEN ALL OF YOUR MEDICATIONS AS PRESCRIBED FOR THE NEUROPSYCHOLOGICAL TESTING.

- On/Off testing with a physical therapist followed by an appointment with me to review the results of the On/Off testing and neuropsychological testing.

Neuropsych Tests

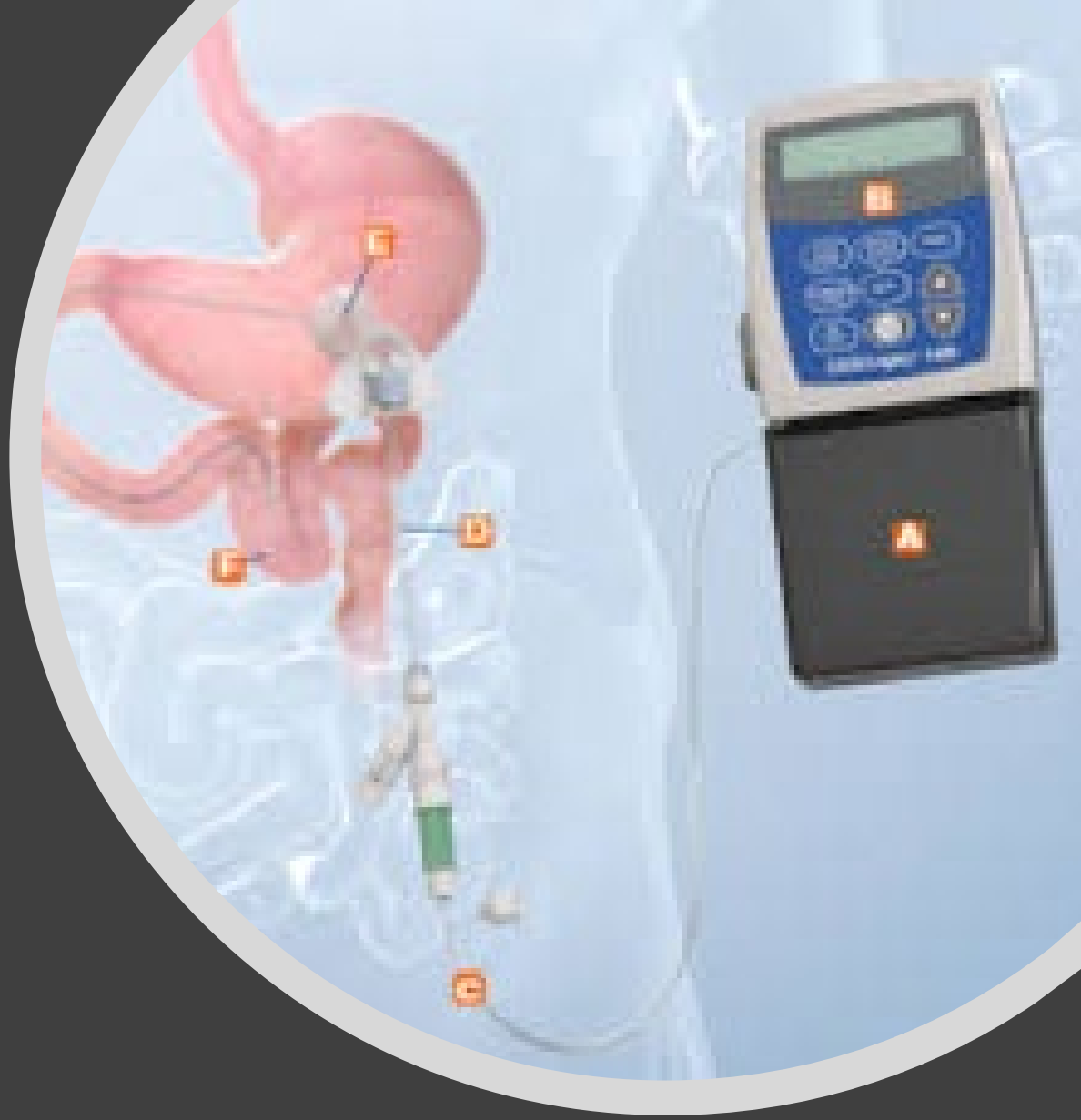
- Goal is to understand how PD impacts the following cognitive domains:
  - Attention
  - Processing Speed
  - Learning and Memory
  - Visuospatial
  - Language
  - Executive function

On-Off Testing Examples

- 74 yo woman with PD (left sided tremor and rigidity) for 8 years. MDS-UPDRS motor subscore in the "off" state (last meds at 8pm the night before) was 35; MDS-UPDRS motor subscore in the "on" state (after 2x carbidopa/levodopa 25/100mg and 1.5mg pramipexole) was 19. In the "on" state, no dyskinesia was observed.
  - This represents a 46% improvement in motor symptoms.
  - The patient had significant improvements in bradykinesia, rigidity, tremor but no improvement in posture scores, ability to write or facial masking (the issues that bothered her the most)
- 52 yo woman with PD (left bradykinesia, severe dyskinesias, gait freezing) for 6 years. MDS-UPDRS motor subscore in the "off" state (last meds at 5pm the night before) was 43; MDS-UPDRS motor subscore in the "on" state (after 3 tabs of carbidopa/levodopa 25/100mg) was 18. In the "on" state, dyskinesia was observed (mild)
  - This represents a 58% improvement in motor symptoms.
  - The patient had no improvement in postural instability and while gait freezing improved during testing, there was a history of “on” gait freezing.
  - No cognitive issues but history of alcohol use, TBI and cosmetic concerns about DBS
- 62 yo man with PD (tremor, off dystonic cramping, “off” anxiety, “on” mania, ICD on dopamine agonists,) for 11 years. MDS-UPDRS motor subscore in the "off" state (last meds at 7pm the night before) was 32; MDS-UPDRS motor subscore in the "on" state (after 4 tabs of carbidopa/levodopa 25/100mg) was 0. In the "on" state, moderate dyskinesia was observed.

Duopa

- DUOPA (carbidopa and levodopa) enteral suspension is used to treat motor fluctuations in advanced Parkinson's disease.
- Duopa is delivered continuously by a pump through a tube into the intestine for up to 16 hours.
- The improvement in On time with Duopa is as good as that seen following DBS.
- The side effect profile is different (and largely related to having the procedure needed to insert the indwelling tube or to complications involving the tubing system).



The Burden of Advanced PD

- Narrowing of the PD Therapeutic Window
  - Patients routinely take a complex regimen of oral medication every 3 hours; many patients with advanced PD take oral medication every 1 to 2 hours
- Medication Side-effects
  - Limit ability to increase oral PD medications enough to adequately treat motor symptoms
- Limited/No autonomy
  - High dependence on other people for daily tasks of dressing, bathing, eating, getting out of the house
- Complications of decreased mobility
  - Urinary tract infections, bed sores, pneumonia, blood clots
- Negative impact on health related quality of life
  - Survey of VA patients (n=887,775) found that patients with PD (n=14,530) had lower self-reported physical and mental health than patients with coronary artery disease, congestive heart failure, diabetes, chronic back pain and stroke (Gage H, Hendricks A, Zhang S and Kazis L. The relative health related quality of life of veterans with Parkinson's Disease. J Neurol Neurosurg Psychiatry 2003; 74: 163-169)

Neuroprotection Studies

- Prasinezumab (PRX002/RG7935) is an investigational monoclonal antibody that targets α-synuclein, a protein that is believed to misfold and aggregate to form the protein structures that are highly implicated in Parkinson's disease pathology. (Prothena/Roche collaboration)
- Phase 1 data: A total of 40 healthy volunteers were enrolled in the study. The participants received either an escalating dose of PRX002 or a placebo. Although some mild adverse side effects, including headache, nausea, pain on the site of injection, viral infection, and viral upper respiratory tract infection, were observed, the drug candidate was deemed generally safe and well-tolerated. No antibodies against the drug were detected in the blood of the participants. Results showed that PRX002 reduced the levels of free alpha-synuclein in the blood by up to 96.5 percent within one hour of treatment administration.
- Similar results observed in patients with mild to moderate Parkinson's disease, according to a phase 1b study, published online on June 18 in JAMA Neurology.
- There is an ongoing phase 2 study,

Studies with an Interesting MoA

- Under normal conditions, serotonergic and dopaminergic cells run side by side without interfering with each other. In the more complex stages of Parkinson's, when fewer dopamine-producing brain cells are left, the levodopa drugs can end up being taken up by the serotonin-producing brain cells, turned into dopamine and packaged with serotonin.
- Once packaged the dopamine and serotonin mix is released into the synapse, but these serotonin-producing cells have no feedback system to monitor the amount of dopamine they are releasing.
- The dopamine that is stowing away inside serotonin packages can quickly start to build up inside the synapse.
- Eltoprazine is a small molecule 5HT1A/1B partial agonist in clinical development for the treatment of Parkinson's disease levodopa-induced dyskinesia (PD-LID) and adult attention deficit hyperactivity disorder (ADHD). Eltoprazine has been evaluated in over 680 human subjects to date, and has a well-established safety profile. Eltoprazine was originally developed by Solvay Pharmaceuticals for the treatment of aggression. Upon Solvay's merger with Abbott Pharmaceuticals, the eltoprazine program was out-licensed to PsychoGenics. PsychoGenics licensed eltoprazine to Amarantus following successful proof-of-concept trials in PD-LID and adult ADHD.
- Elto Pharma expects to initiate the phase IIb trial for Parkinson's disease levadopa-induced dyskinesia in the first half of 2019

Me Too Drugs (or Drug Studies)

- Gocovri (Amantadine extended release)
- Xadago® (safinamide) with selective MAO-B-inhibition. Results from two double-blind, placebo-controlled, multinational, 6 month studies with over 1,100 patients revealed that safinamide provides statistically significant increases in ON-time without troublesome dyskinesia, as well as a decrease in OFF-time. Safinamide requires a once-daily dose and has no diet restrictions due to its high MAO-B versus MAO-A selectivity.
- P2B001 is a low dose, sustained release combination of pramipexole and rasagiline. P2B001 is dosed once daily with no titration. Data from P2B001 phase II clinical trial implies that it may provide significant therapeutic effects comparable to those published for higher doses of the individual components, with favorable safety profile.

You Tube Drugs

- Studies have not clearly supported the use of marijuana for PD. The clinical studies of cannabis as a PD treatment that have been conducted did not use the clinical trial gold standard of a double blind, placebo controlled trial design. Some studies had as few as five subjects.
- In 2017, the National Academies of Science, Engineering and Medicine released a report based on a review of 10,000 scientific abstracts concerning research into marijuana's effects on all aspects of health and disease. They concluded that there was not enough evidence in the literature to currently support the use of medical marijuana in PD
- A Study is ongoing at U. Colorado on effect of GWP42003-P (purified cannabidiol) on PD tremor

Exercise and PD

- Forty newly diagnosed patients with PD were treated with rasagiline and randomly assigned to 2 groups (Neurorehabilitation Neural Repair, 2015)
  - One group went through a 28-day intensive rehabilitation treatment that was repeated one year later. The other group only received rasagiline. Both groups were examined every 6 months, up to two years after the study start.
  - In the group that received intensive rehabilitation, all of the measurements to assess Parkinson's disease were better than the initial scores before treatment. The group that received intensive rehabilitation also added fewer medications over the two year period to treat the Parkinson's disease than the group that only received rasagiline at the start of the study.
- The effect of treadmill training with body weight support on patients with moderate to severe Parkinson's disease has been evaluated (Archives of Physical Medicine Rehabilitation, 2000)
  - Patients were assigned to undergo 4 weeks of physical therapy or weight-supported treadmill training for 45 minutes, 3 times per week, followed by cross-over to the other treatment.
  - Each treadmill session consisted of 12 minutes of walking with support of 20% body weight, followed by 10% support, and then 0%, interspersed with rest.
  - Both groups improved, but at the end of the 4 week treatment, all of the measurements to assess Parkinson's disease improved more with treadmill training than physical therapy.