

# Treatment of Parkinson's Disease and Movement Disorders

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# Movement Disorders

- **Parkinson's Disease**
- **Tremor**
- **Chorea**
- **Ballism**
- **Dystonia**
- **Tic Disorders**

# Parkinson's disease

AN  
ESSAY

ON THE  
SHAKING PALSY.

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CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

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SHAKING PALSY. (*Paralysis Agitans.*)

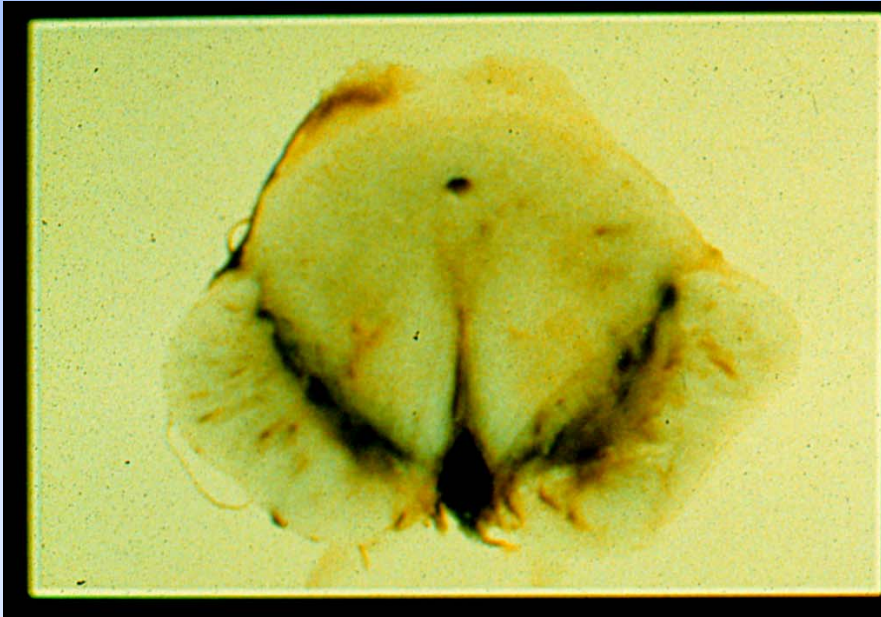
Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported ; with a propensity to bend the trunk forward, and to pass from a walking to a running pace : the senses and intellects being uninjured.

- ◆ Described by James Parkinson, 1817
- ◆ Most common disorder of movement
- ◆ Affects 3% of the population over the age of 65 years
- ◆ About 500,000 patients in the US

# “Cardinal Features” of Parkinson’s Disease

- **Tremor**
- **Rigidity**
- **Bradykinesia**
- **Postural Instability**

Normal



Parkinson's



- ◆ Loss of dopamine neurons from the *substantia nigra pars compacta*
- ◆ Leads to deficiency of dopamine in the caudate and putamen (“striatum”).

# Human basal ganglia

Caudate ●

Putamen ●

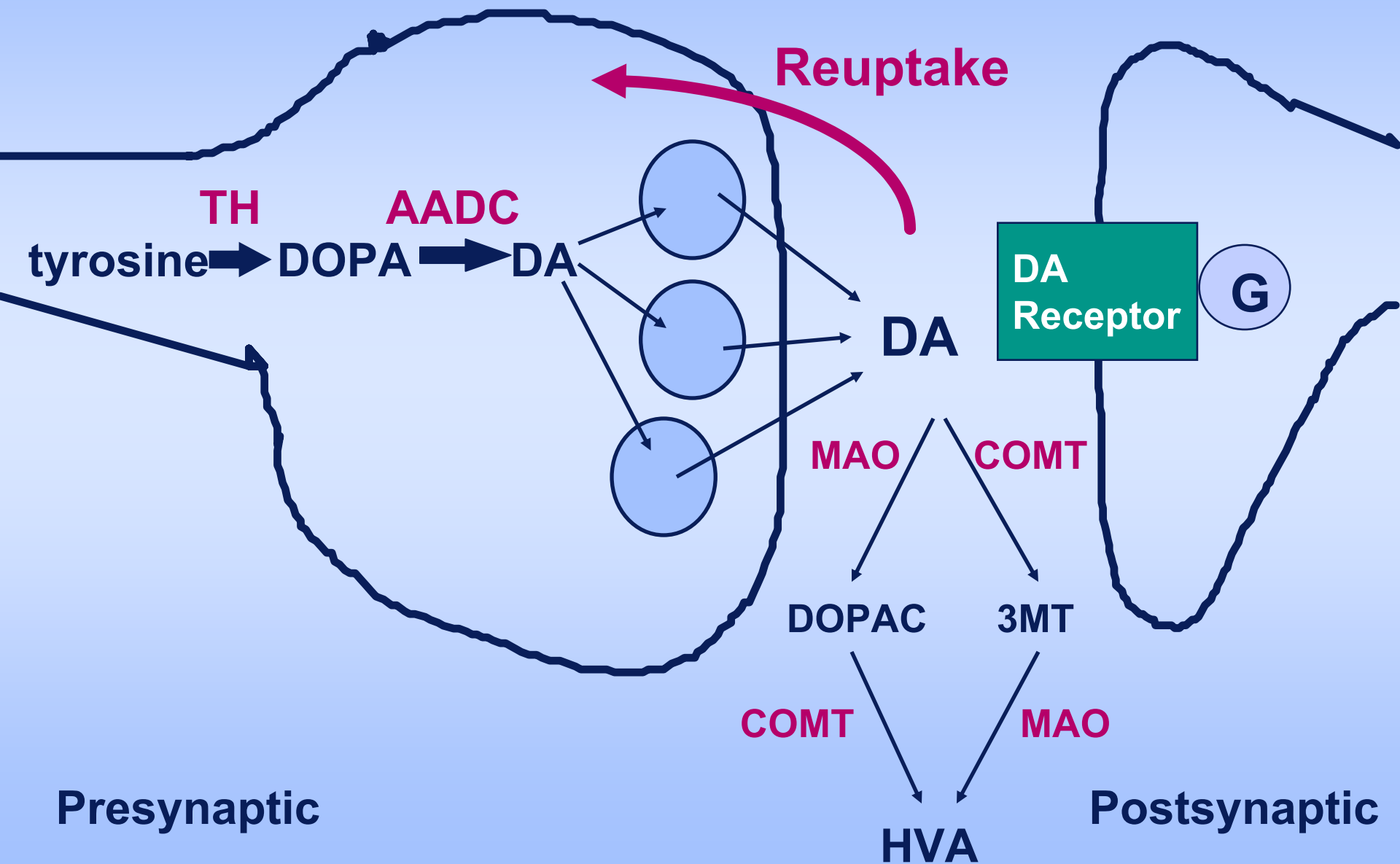
Globus pallidus ●

Subthalamic nucleus ●

Substantia nigra ●



# The Dopaminergic Synapse



# Dopamine Receptors

- **Classical Pharmacology:**
  - D1 - stimulates cAMP formation
  - D2 - inhibits cAMP formation
- **Molecular Pharmacology:**
  - Family of at least 5 receptor proteins
  - All have 7 transmembrane regions, typical of G-protein coupled receptors
  - d1 and d2 are abundant in striatum, correspond to classically identified sites
  - Others primarily extrastriatal, likely account for many of the side effects of dopaminergic drugs



# Pharmacological Approaches to Treatment of Parkinson's Disease

- **Symptomatic treatments**
  - most are based on dopamine augmentation
- **“Neuroprotective” treatments**
  - none presently proven
  - most current studies are based on “oxidative stress hypothesis”

# The “Oxidative Stress” hypothesis



- Proposes that dopamine cell death is caused by the reactive free radicals produced by the catabolism of dopamine
- suggests that treatments which reduce catabolism of dopamine should slow the progress of the disease

# Levodopa therapy

- ◆ also called L-DOPA, L-dihydroxyphenylalanine
- ◆ Works by replacing biosynthetic precursor:



- ◆ Usually given with carbidopa, an inhibitor of peripheral AADC - prevents nausea.
- ◆ Adverse effects: peripheral, central
- ◆ Most important limitation of treatment is the development of “complications of levodopa therapy” - wearing off and dyskinesias

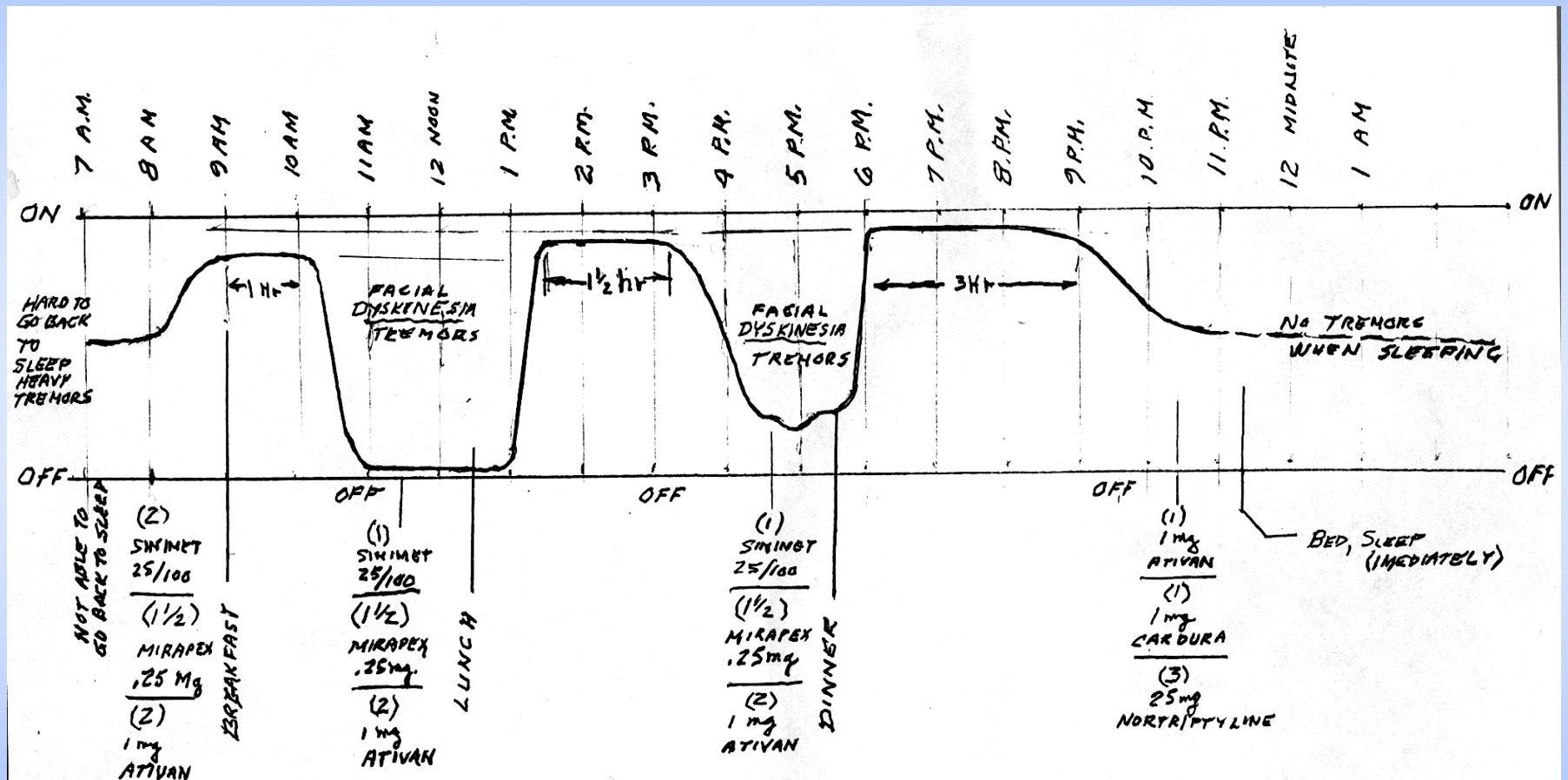
# Levodopa Therapy of Parkinson's Disease

- ◆ **1950's:** Arvid Carlsson discovers that dopamine is a neurotransmitter, reserpine replicates features of Parkinson's
- ◆ **1960:** Deficiency of dopamine in postmortem PD described by Enringer and Hornykeiwicz
- ◆ **1961:** Effect of levodopa in PD reported by Birkmayer and Hornykeiwicz
- ◆ **1967:** Long term treatment of PD with levodopa described by Cotzias et al.
- ◆ **2000:** Carlsson, Kandel and Greengard awarded Nobel prize

# Motor complications of levodopa therapy

- ◆ **Fluctuations:** variations in mobility related to medication dose and interval.
- ◆ **Wearing-off:** loss of efficacy at the end of a dosing interval
- ◆ **Dyskinesias:** excessive, involuntary movements

# Motor complications - a patient's view



# What causes fluctuations, wearing off, and dyskinesias?

- ◆ Not explained by simple DA receptor upregulation
- ◆ Loss of “buffering capacity” is an important factor
- ◆ Clinical and experimental data suggests that variations in plasma levodopa levels have an important “inductive” effect
- ◆ Role of NMDA glutamate receptors

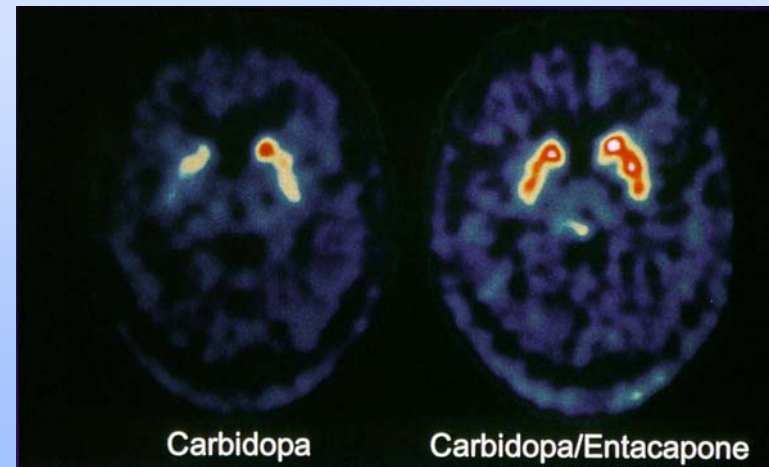
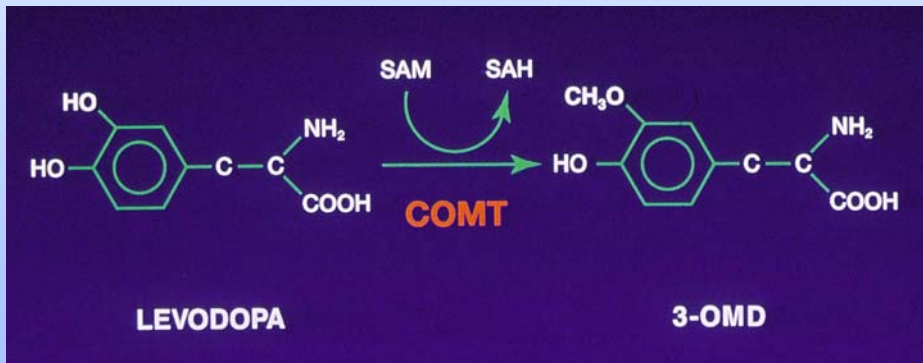
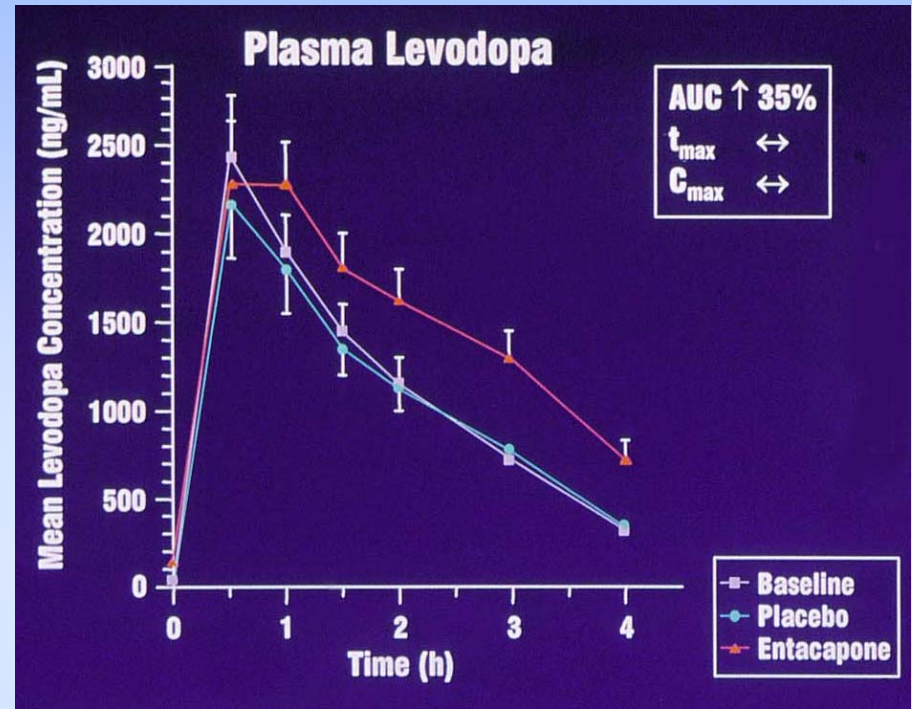
# Dopamine Agonists

- ◆ Act directly at postsynaptic DA receptors
- ◆ Longer half life - less wearing off
- ◆ Older Agents:
  - **bromocriptine** - d2 agonist, partial d1 antagonist
  - **pergolide** - d1 and d2 agonist
- ◆ Newer Agents - d2/d3 agonists
  - **pramipexole** (Mirapex<sup>®</sup>)
  - **ropinirole** (Requip<sup>®</sup>)



# COMT Inhibitors

- ◆ Entacapone, tolcapone
- ◆ Inhibitors of the enzyme *catechol-O-methyl transferase*
- ◆ Slow breakdown of levodopa and dopamine

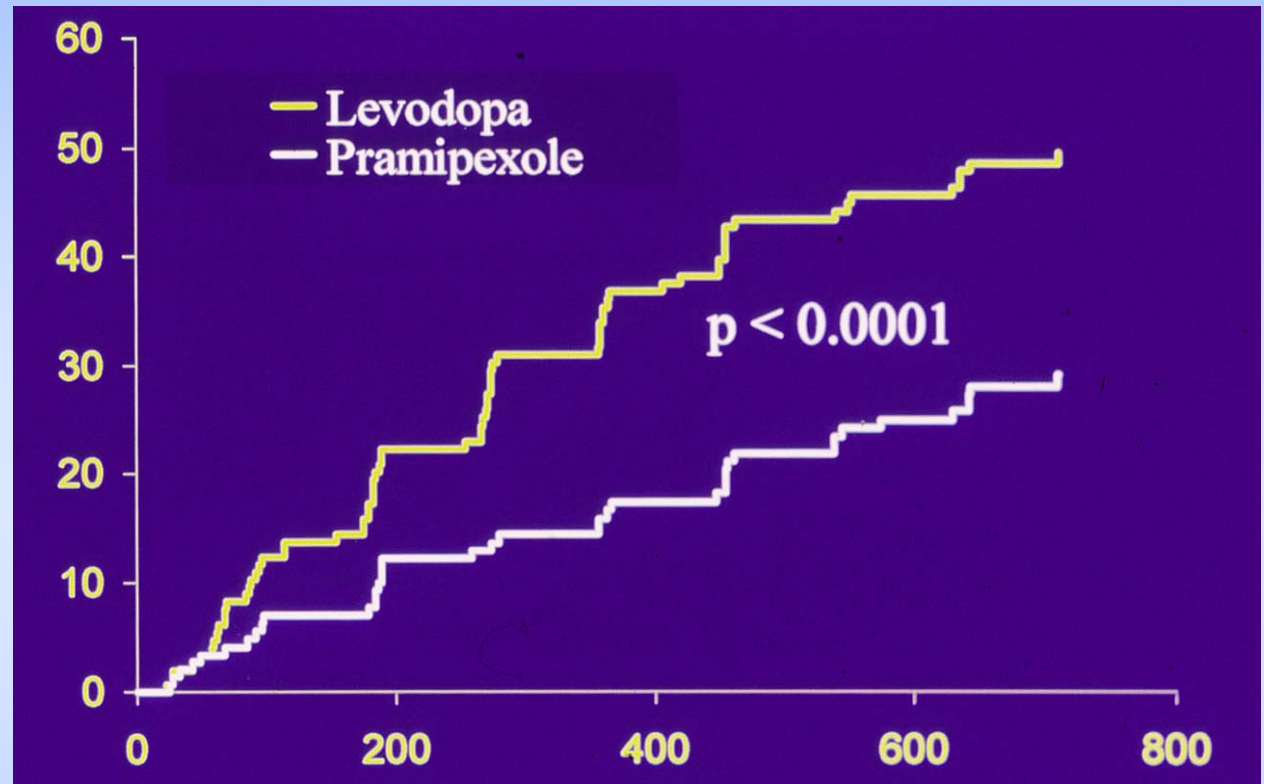


# Motor complications of levodopa: prevention?

- ◆ Hypothesis: “non-physiologic” replacement of dopamine by oral levodopa underlies the development of motor complications
- ◆ Dopamine agonists: a “more physiologic” replacement ?

# CALM-PD: Wearing Off or Dyskinesias

- ◆ Randomized trial comparing levodopa to pramipexole as initial treatment for PD
- ◆ 301 patients, followed for 2 years

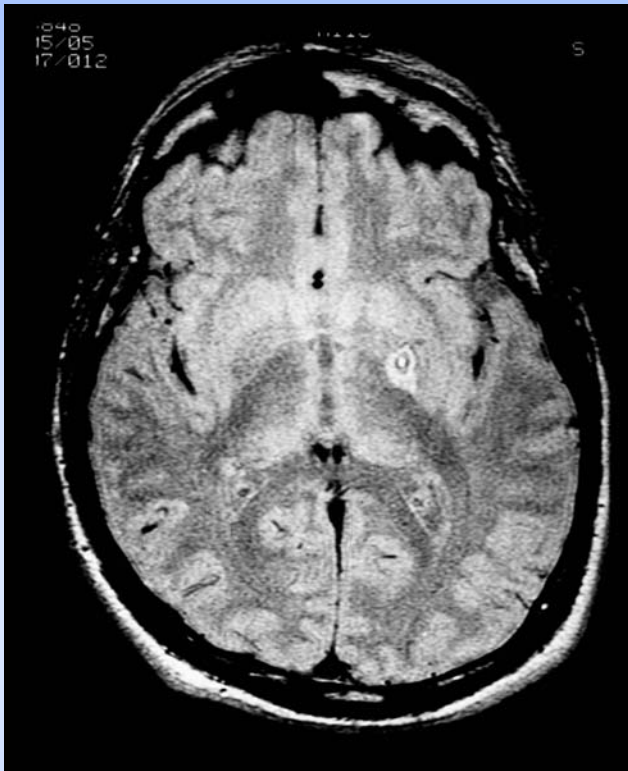


- ◆ Less wearing off and dyskinesias in patients treated with a dopamine agonist instead of levodopa/carbidopa

# Dopamine agonists as initial therapy

- ◆ Initial treatment with pramipexole or ropinirole instead of levodopa reduces development of wearing off or dyskinesias.
- ◆ But this comes at a price:
  - Increased fatigue and somnolence
  - Increased hallucinations in the elderly
  - ? Reduced efficacy
  - Increased cost

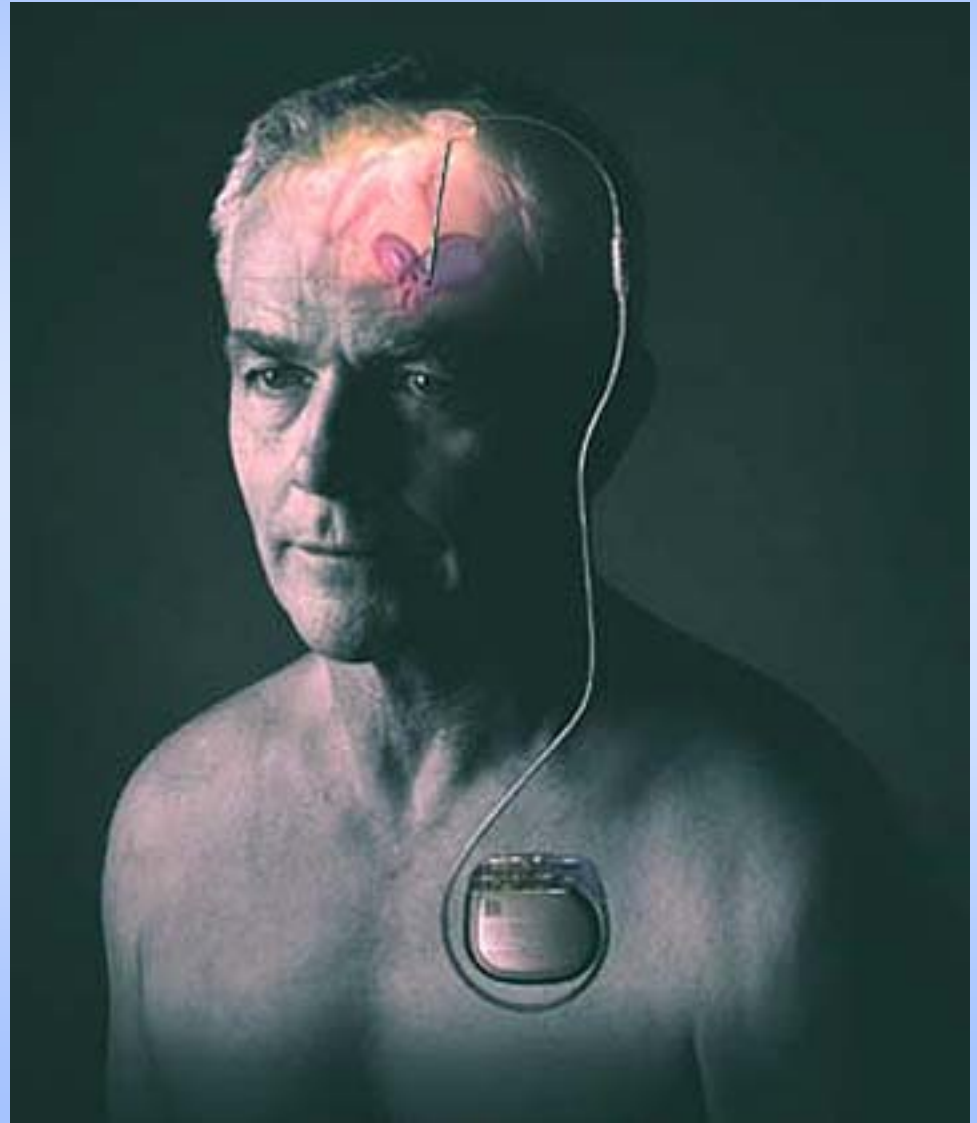
# Pallidotomy



- ◆ Surgical lesion of the globus pallidus
- ◆ Effect can be long-lasting (>3 years), but underlying disease continues to progress

# Deep Brain Stimulation

- ◆ Recently FDA-approved
- ◆ Implanted into subthalamic nucleus, to control all symptoms of PD
- ◆ Require periodic adjustment, battery changes, carry risk of infection, surgical complications



# Dopamine receptor antagonists

- Principal application is treatment of psychosis
- Also used as antiemetics
- “Typical” antipsychotics
  - Distinguished by potency at D2 receptors and degree of sedation
  - May cause movement disorders -
    - » Akathisia
    - » Dystonia
    - » Tardive Dyskinesia
    - » “Neuroleptic Malignant Syndrome”
- “Atypical” antipsychotics
  - clozapine - d4 antagonist. Effective in refractory psychosis, but causes seizures, neutropenia
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