The rationale behind use of medications for Parkinson's Diseases

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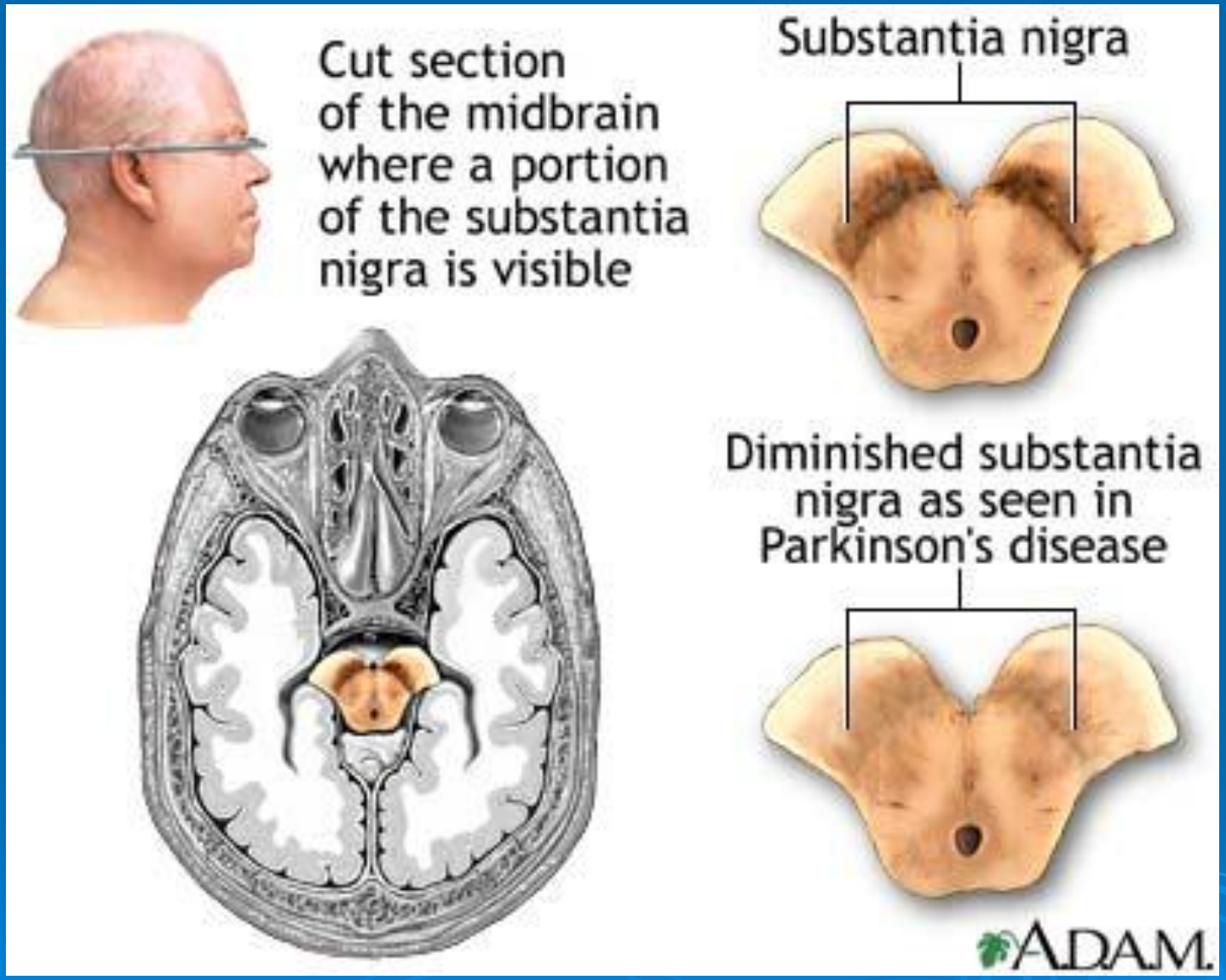
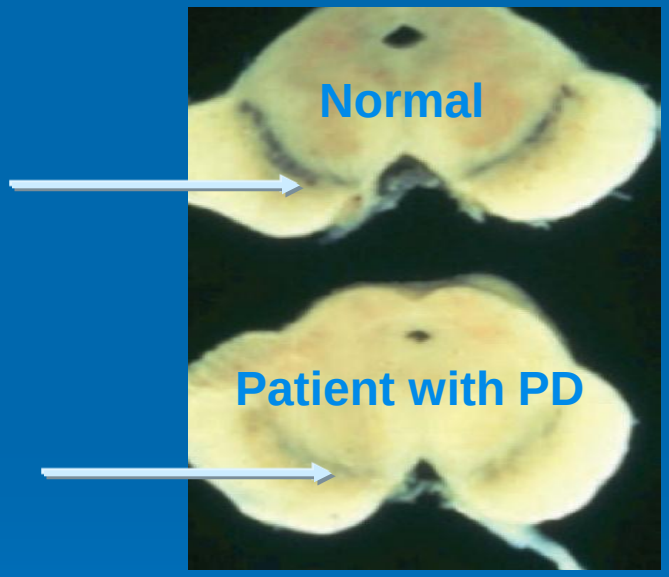
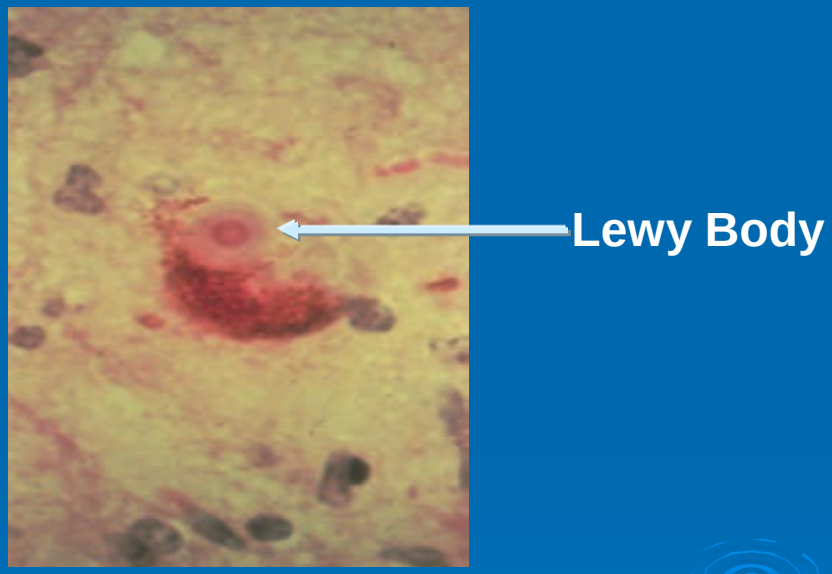

Cut section of the midbrain where a portion of the substantia nigra is visible
Substantia nigra
Diminished substantia nigra as seen in Parkinson's disease
A.D.A.M.

Neuronal Pathology of PD

Pathological hallmark of PD is nigrostriatal degeneration, occurring primarily in the substantia nigra pars compacta (SNpc) and striatum

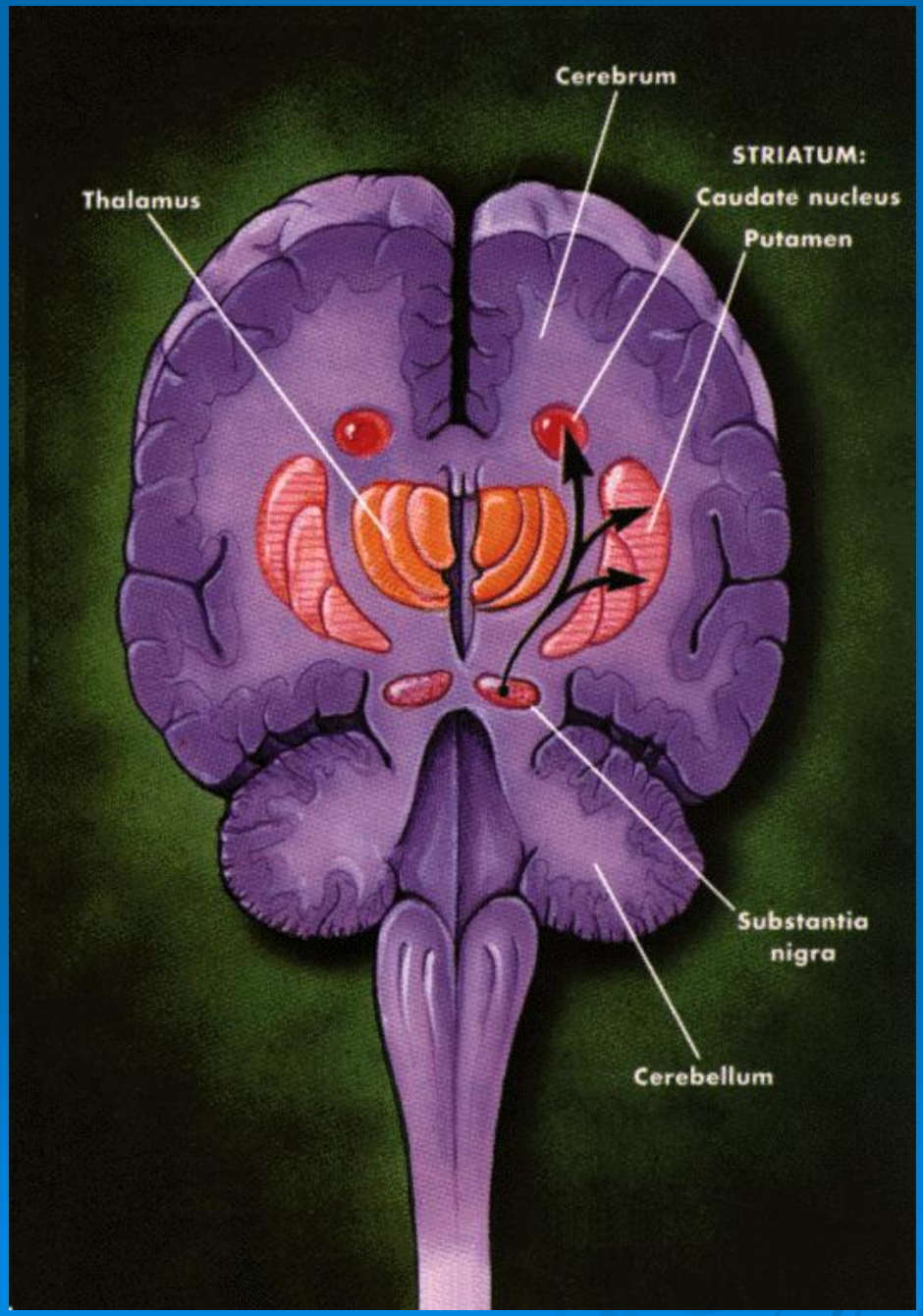


Significant nigral dopaminergic neuronal loss is marked by a reduction in neuromelanin pigment in the SNpc



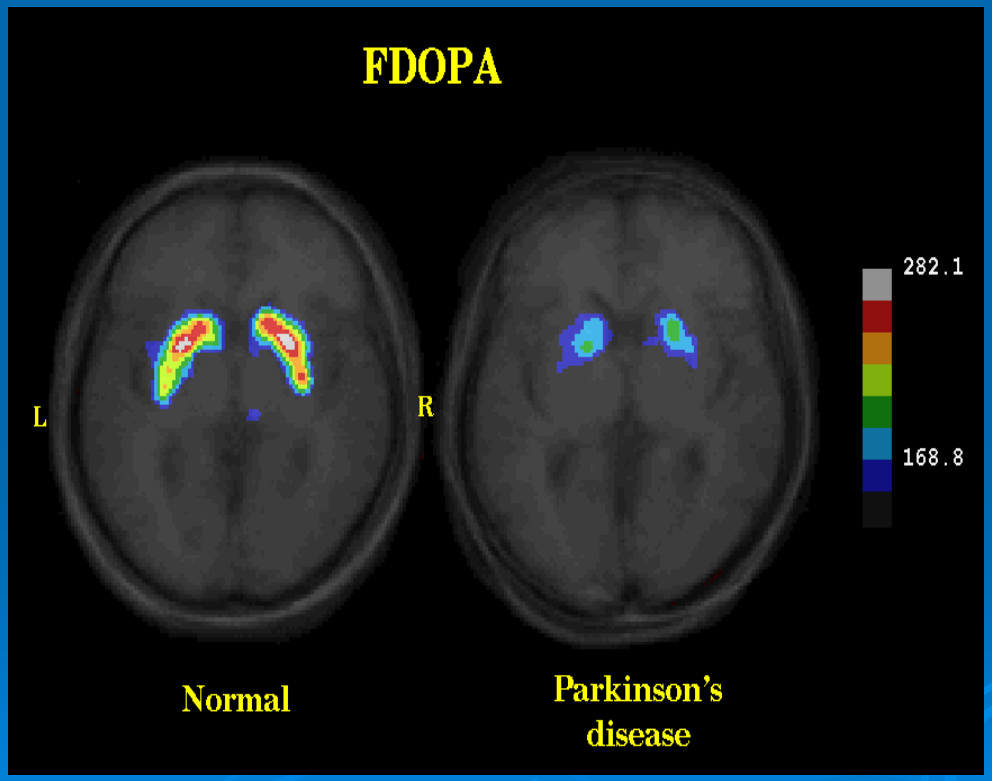
Intraneuronal cytoplasmic inclusions, or "Lewy Bodies"

Boska et al. *J Neurosci*. 2005;25:1691-1700.
Olanow et al. *Neurology*. 2009;72(21 suppl 4):S1-S136.



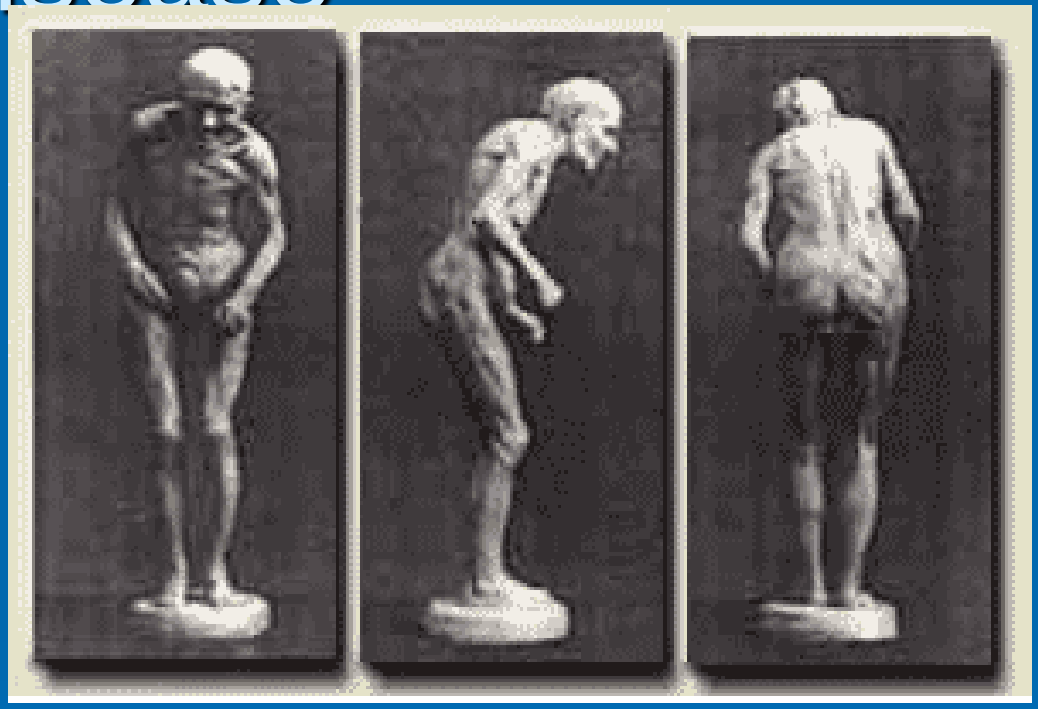
Substantia nigra connects to the basal ganglia

Substantia Nigra cell loss & loss of dopamine in brain



Hallmark of Parkinson's Disease

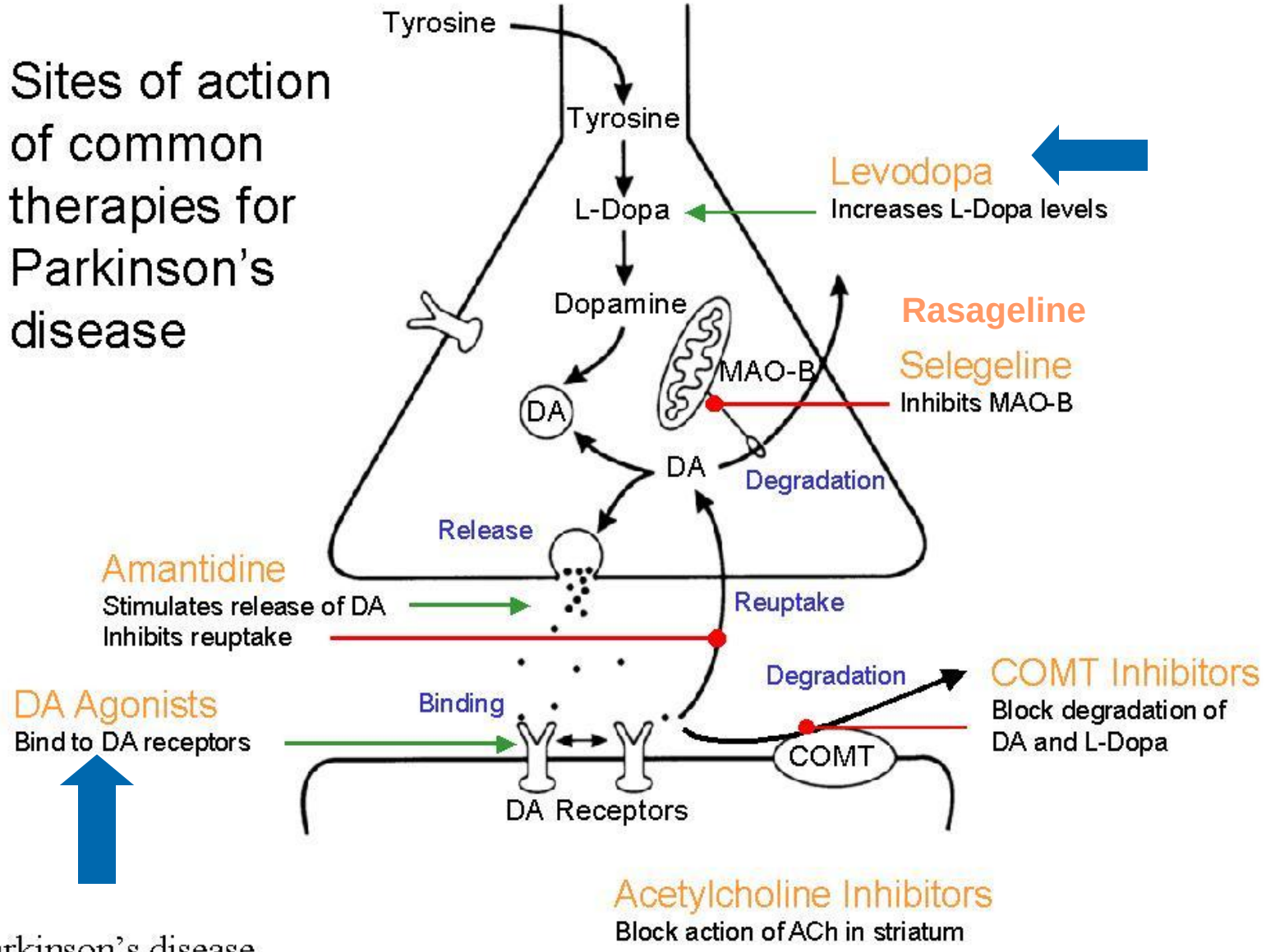
- Cogwheel rigidity
- Bradykinesia
- Abnormality of posture and gait
- Tremor



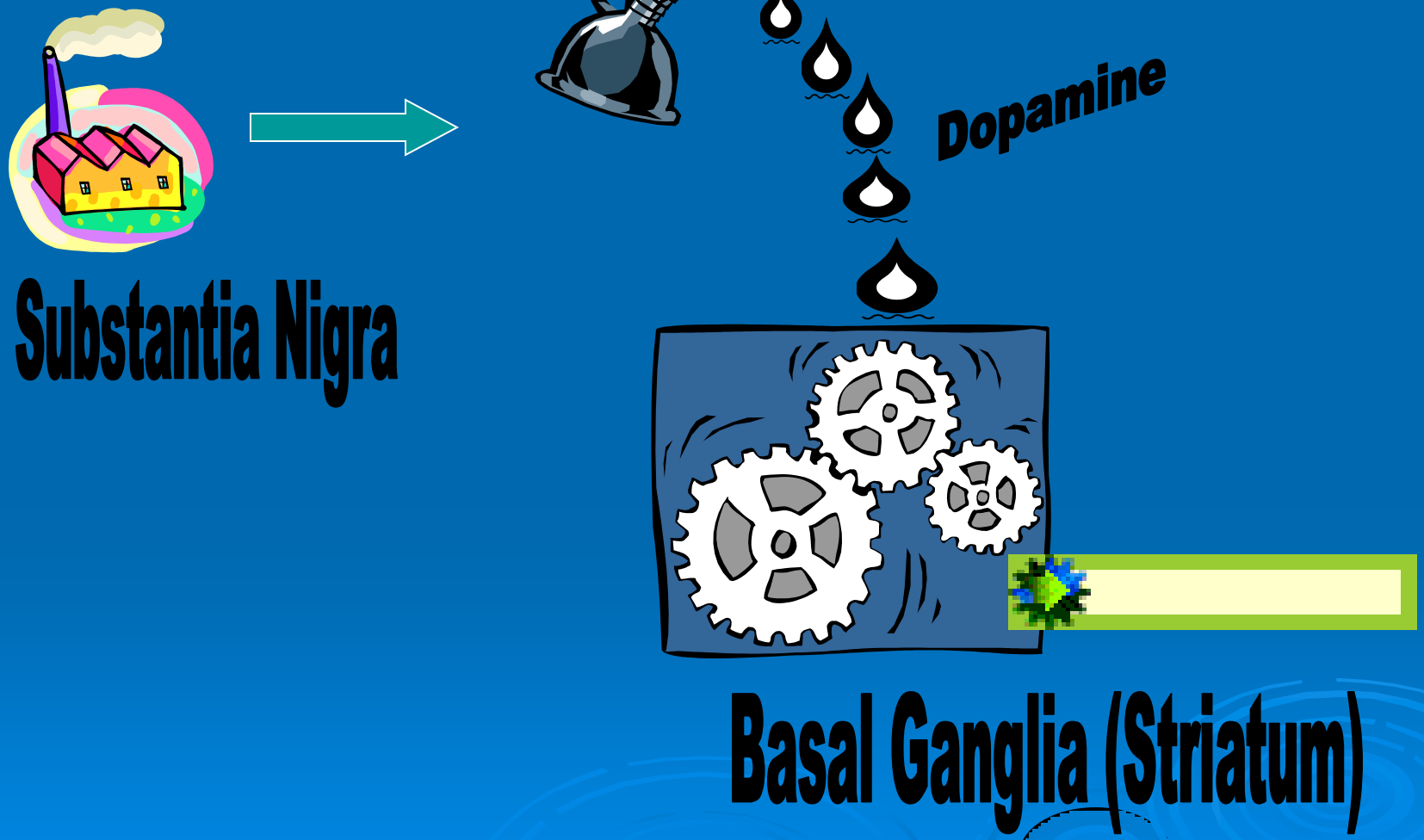
Woman with Paralysis Agitans

Statuette by Paul Richer

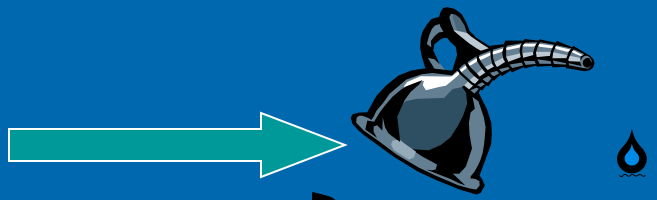
Treatment of Parkinson's



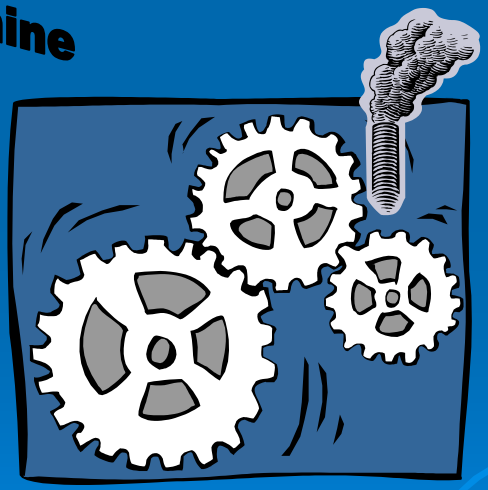
Dopamine & Substantia Nigra



Dopamine & Parkinson's Disease



Dopamine



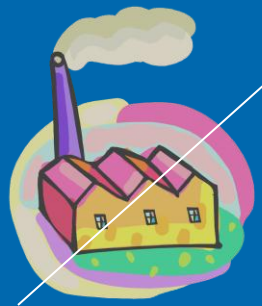
Substantia Nigra

Basal Ganglia (Striatum)

L dopa Rx for PD

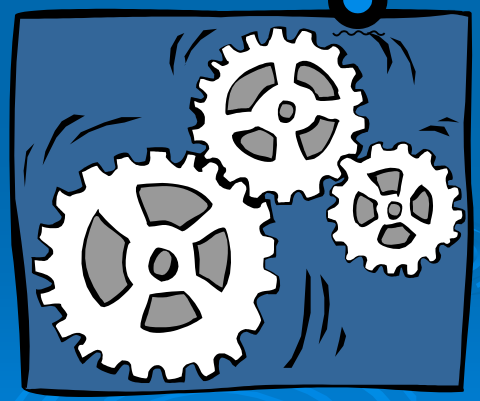
L dopa

Dopa decarboxilase



Substantia Nigra

Dopamine

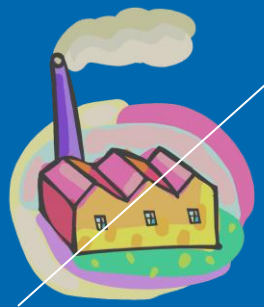


Basal Ganglia (Striatum)

L dopa Rx for PD
Carbidopa levodopa

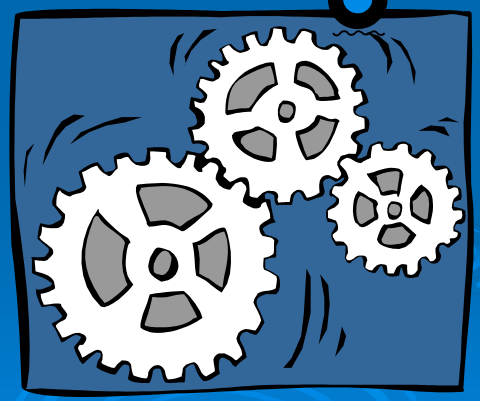
L dopa

Dopa decarboxilase



Substantia Nigra

Dopamine



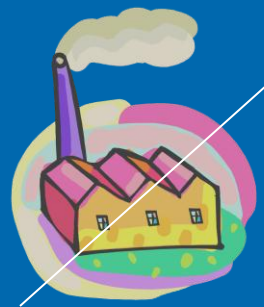
Basal Ganglia (Striatum)

carbidopa

L dopa Rx for PD
Sinemet

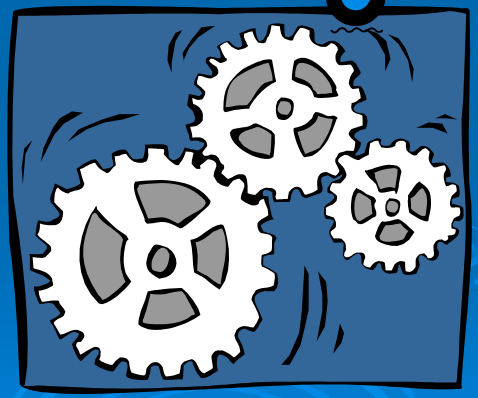
Ldopa

Dopa decarboxilase



Substantia Nigra

Dopamine

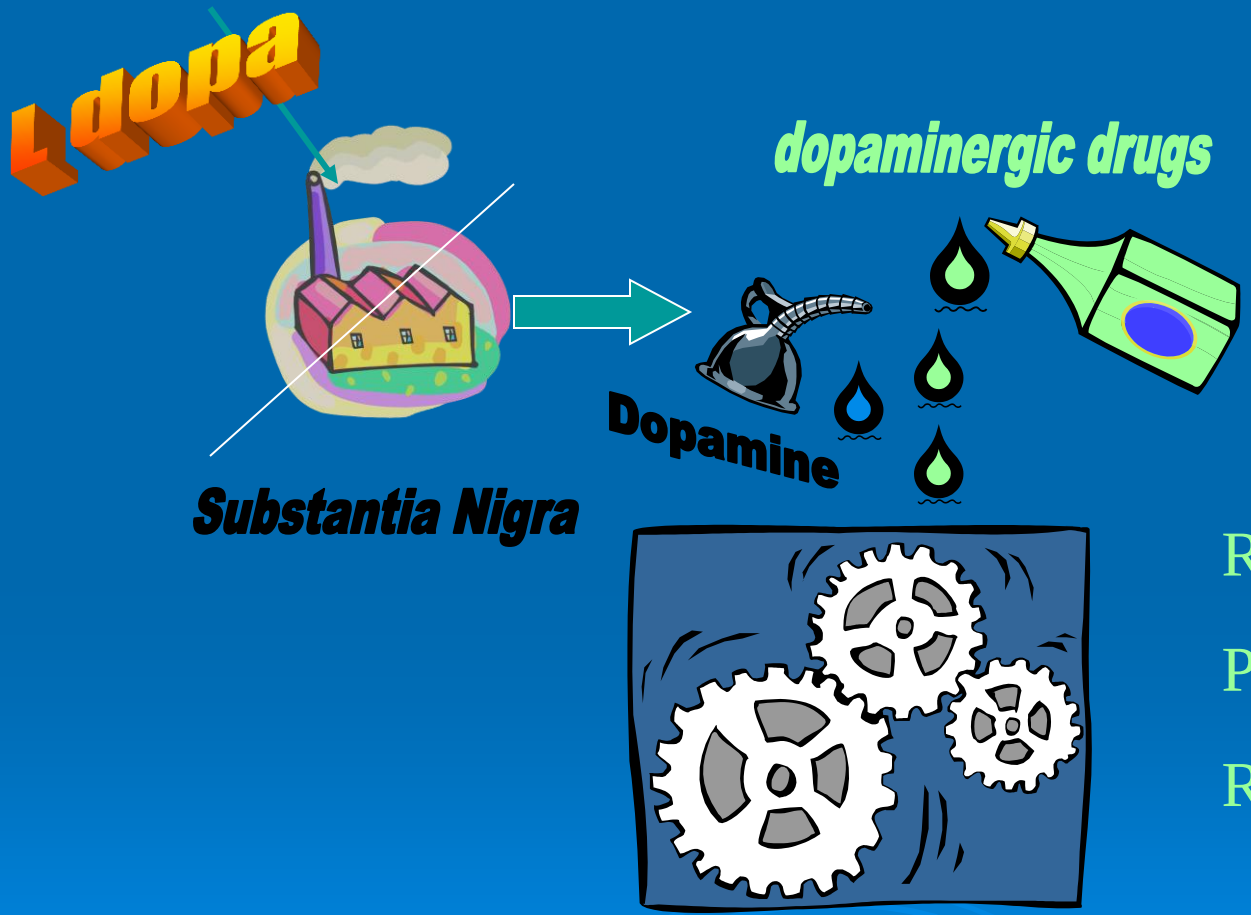


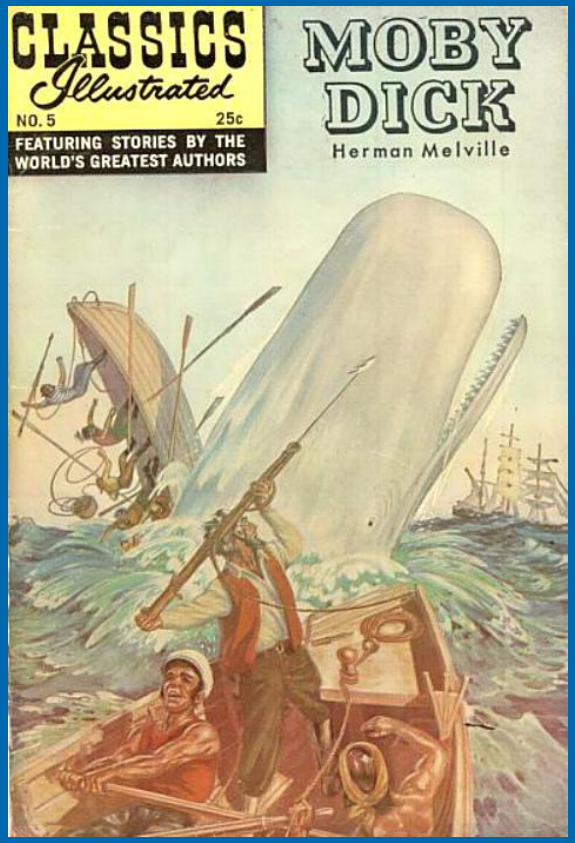
Basal Ganglia (Striatum)

carbidopa

Lodosyn

Dopaminergic Rx





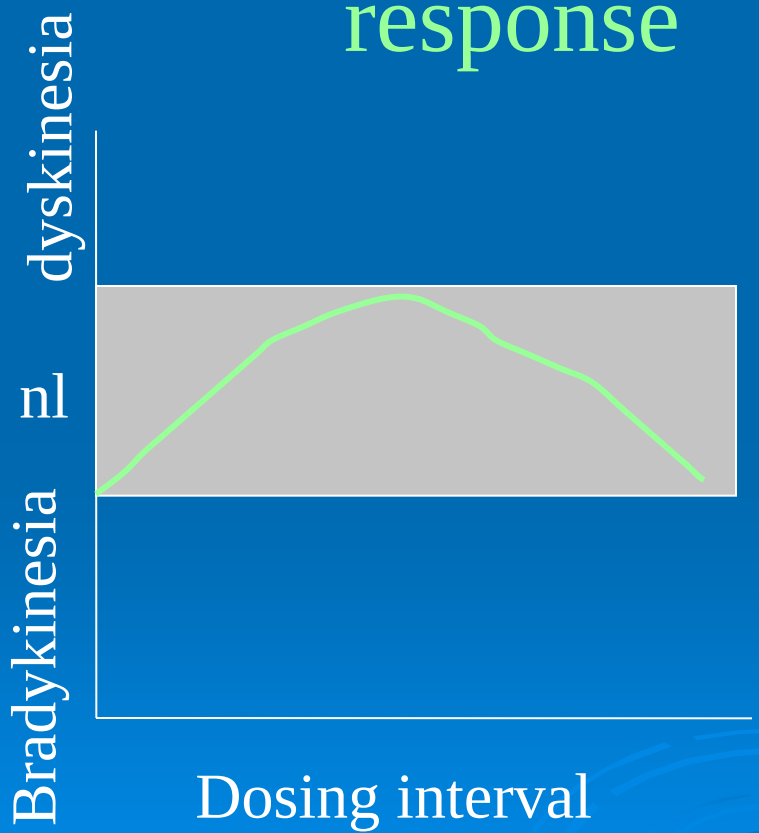
Ropinerole(Requip)

Pramipexole(mirapex)

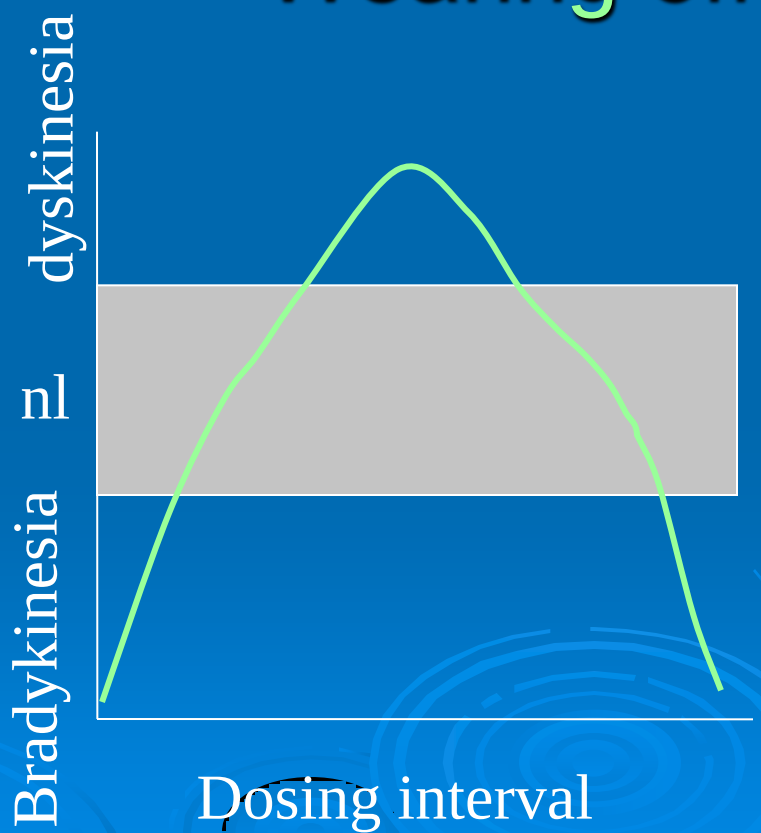
Rotigotene (Neupro)

Motor complications of advanced Parkinson's Disease

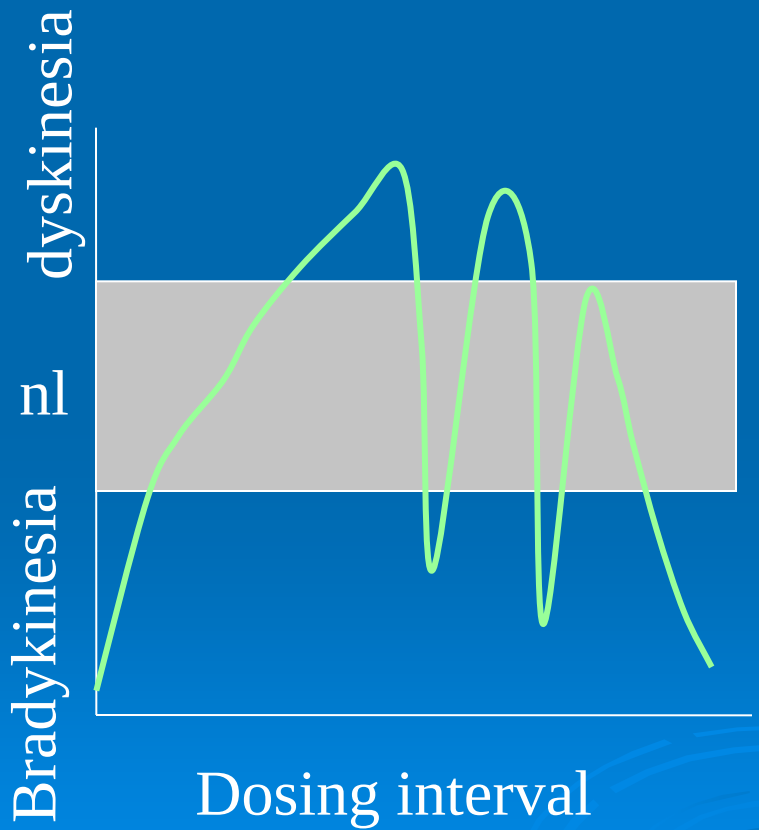
Normal L-dopa response



Wearing off



On-off



Dyskinesia and the narrowing of the therapeutic window

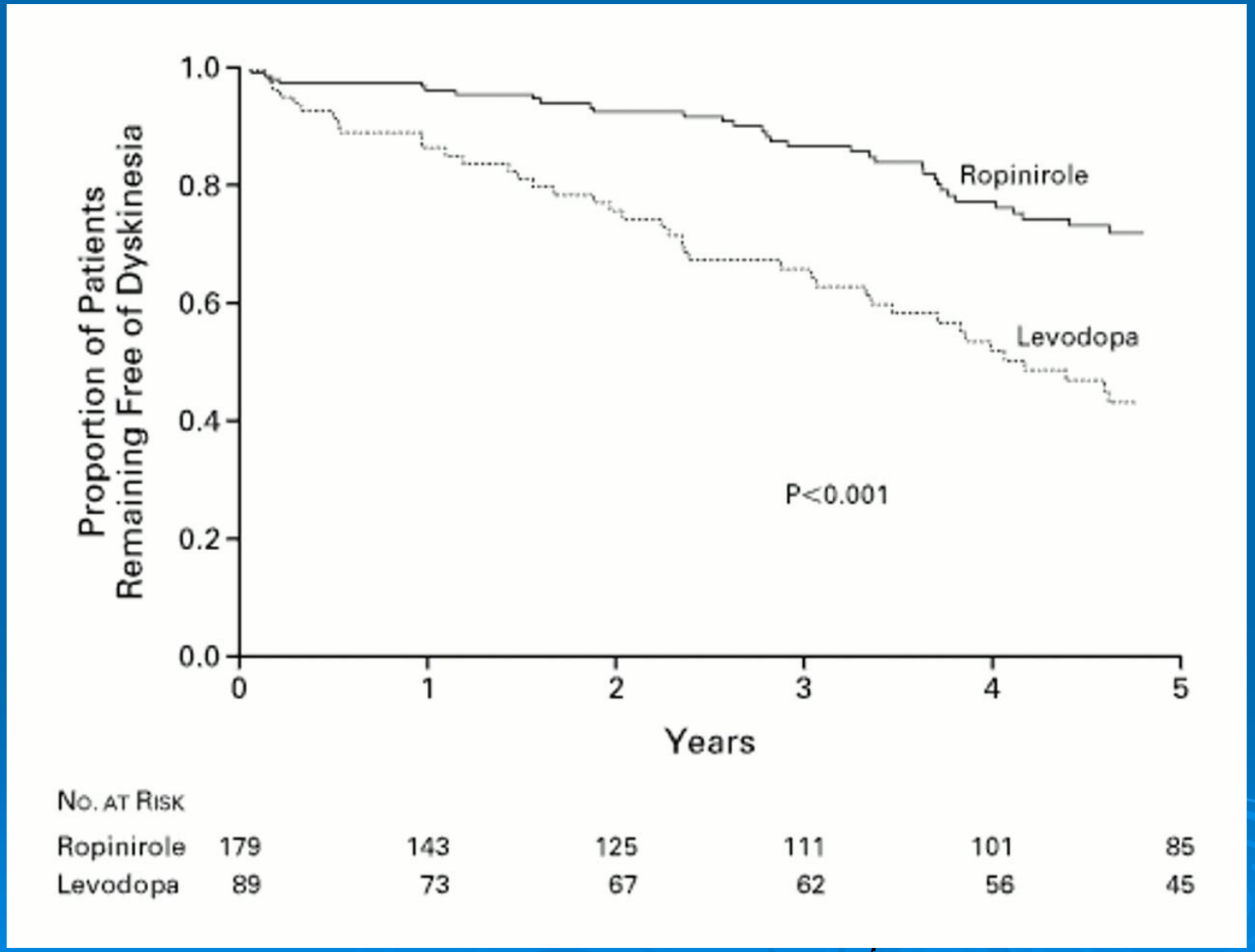
Progression of PD over time

Patient “on”

Patient “off”

Patient “on” with dyskinesia

Proportions of Patients Remaining Free of Dyskinesia in the Ropinirole and Levodopa Groups

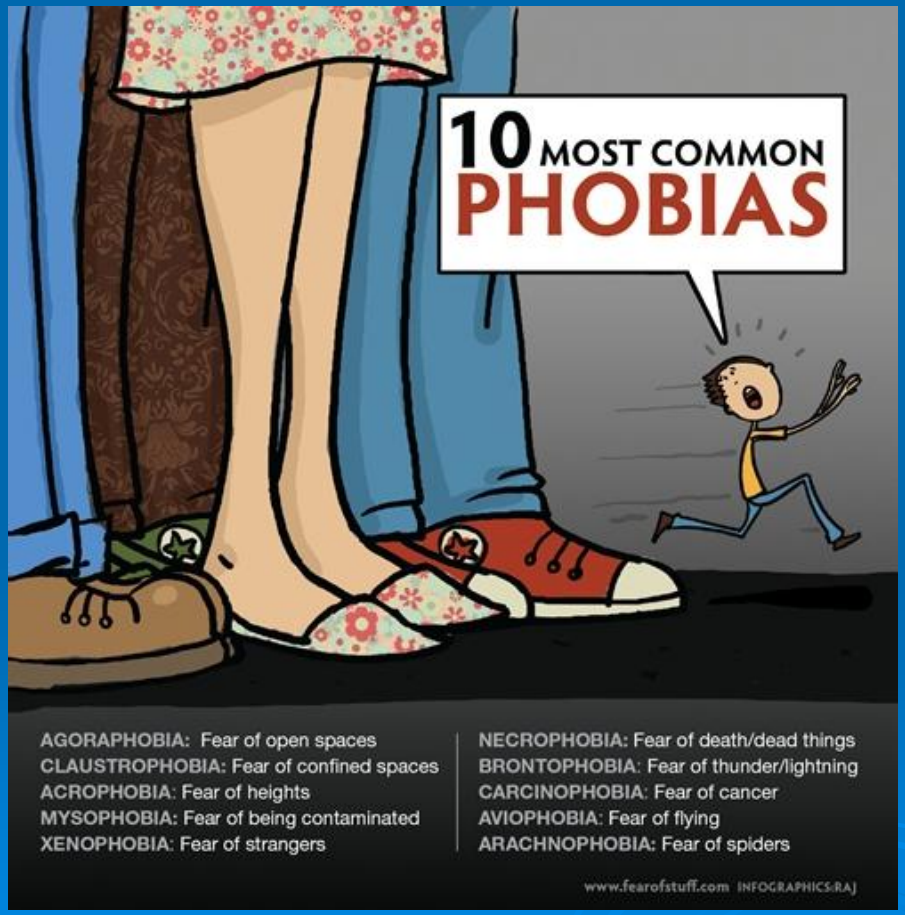


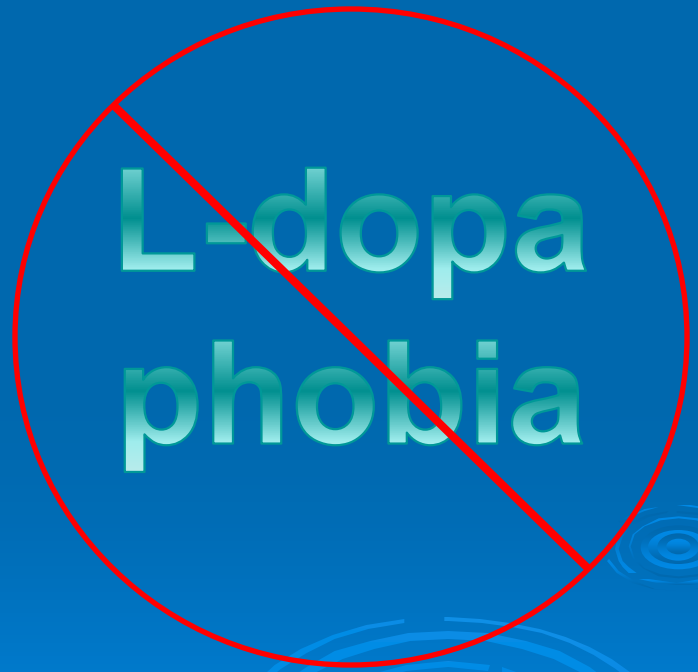
Rascol, O. et al. N Engl J Med 2000;342:1484-1491

- **L-dopa**
- Earlier motor fluctuations
- Less cognitive side effect
- Eventually everyone is placed on it

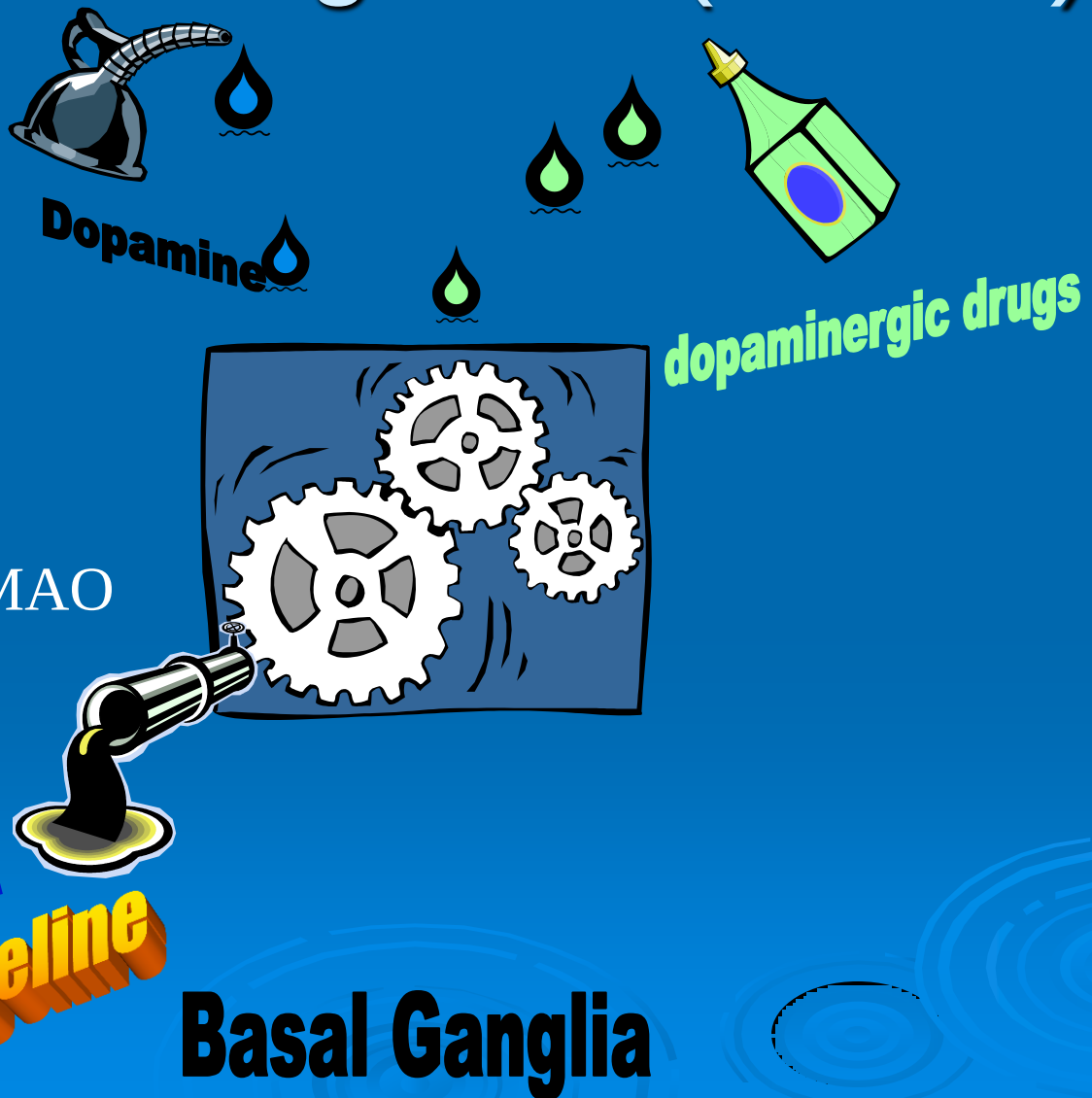
- **Dopaminergic drugs**
- Less late motor consequences
- Increased cognitive side effects (confusion sleepiness, paranoia, hallucinations)

No L–dopa phobia!!!!

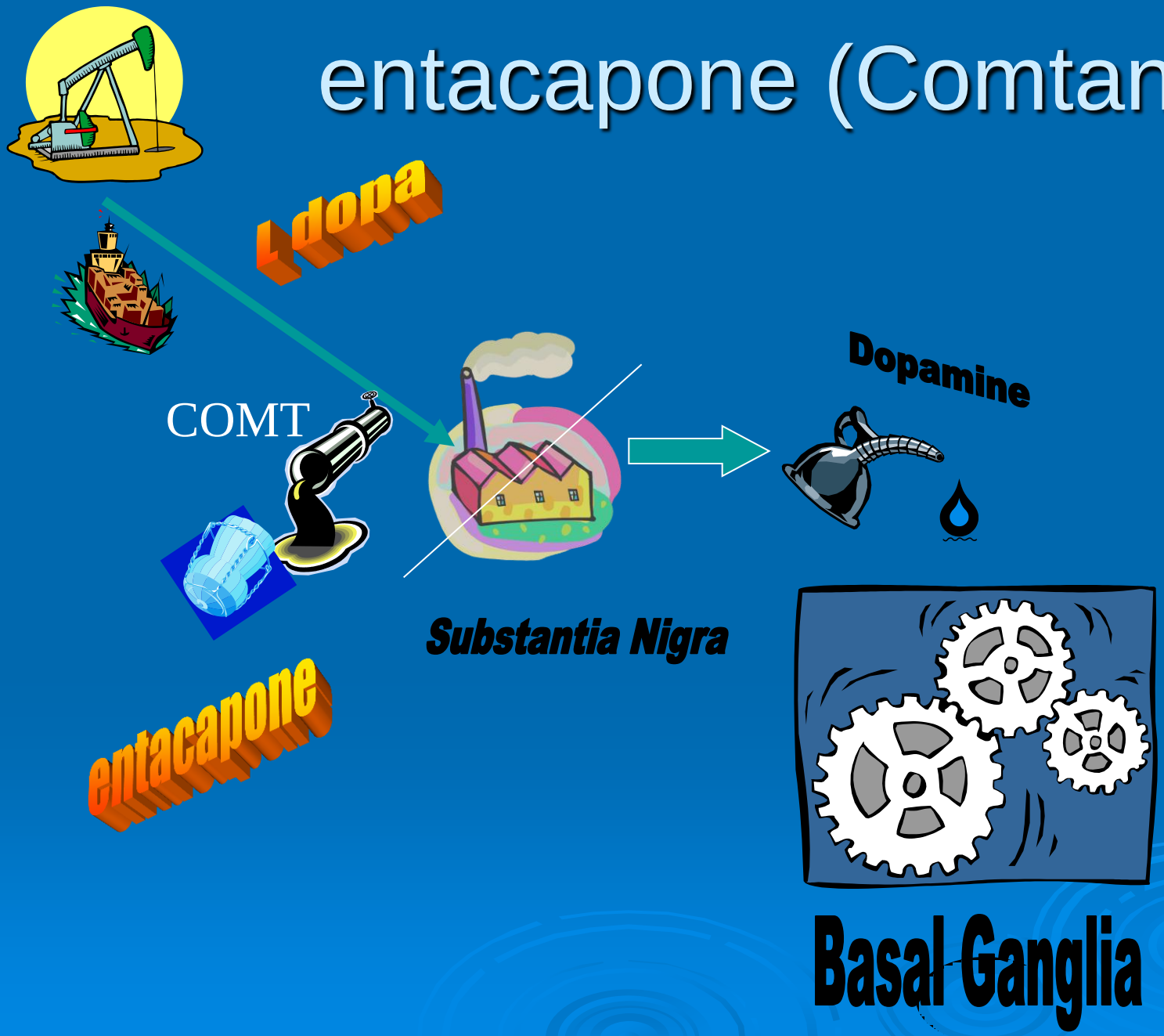




selegeline (Eldepryl)
Rasageline (Azilect)

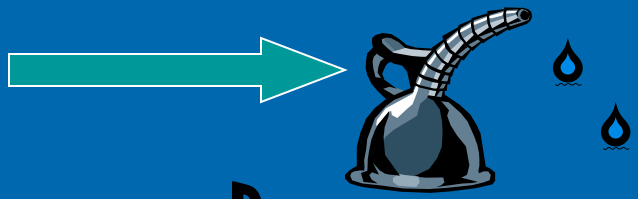


entacapone (Comtan)



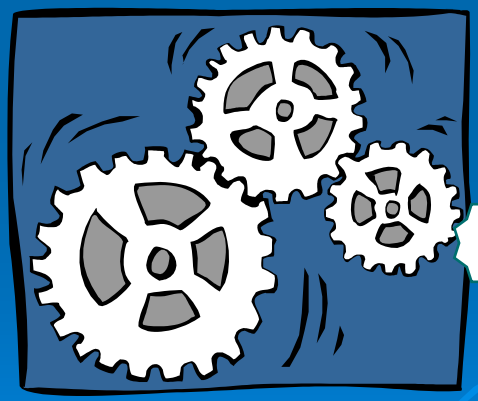
Anticholinergics: Trihexiphenidyl (Artane) or benztropine (cogentin)

Substantia Nigra



Dopamine

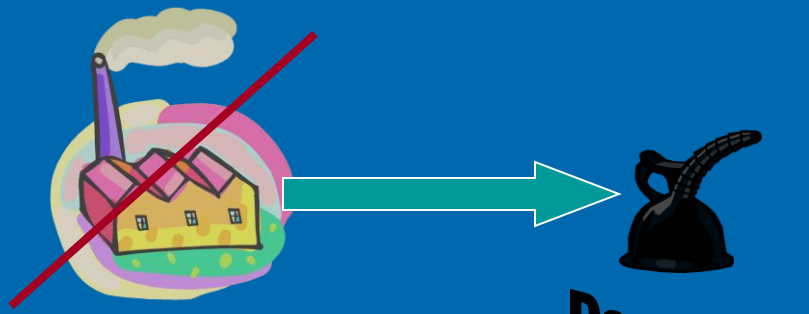
anticholinergics
artane/cogentin



Basal Ganglia (Striatum)

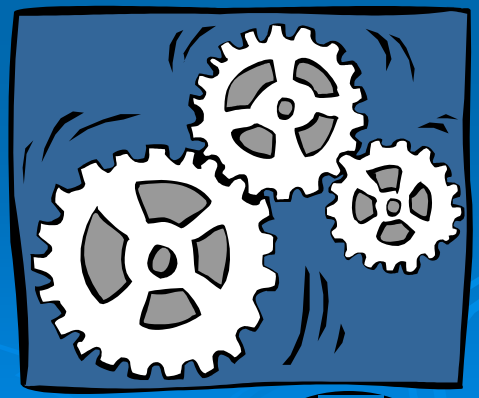
Amantadine squeezes more dopamine from the brain

amantadine



Substantia Nigra

Dopamine



Basal Ganglia

Stalevo

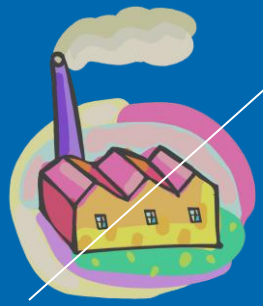
L dopa

Dopa decarboxilase

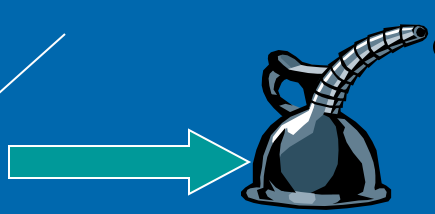
carbidopa

COMT

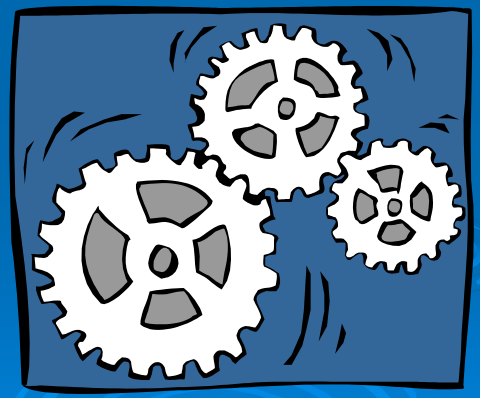
entacapone



Substantia Nigra

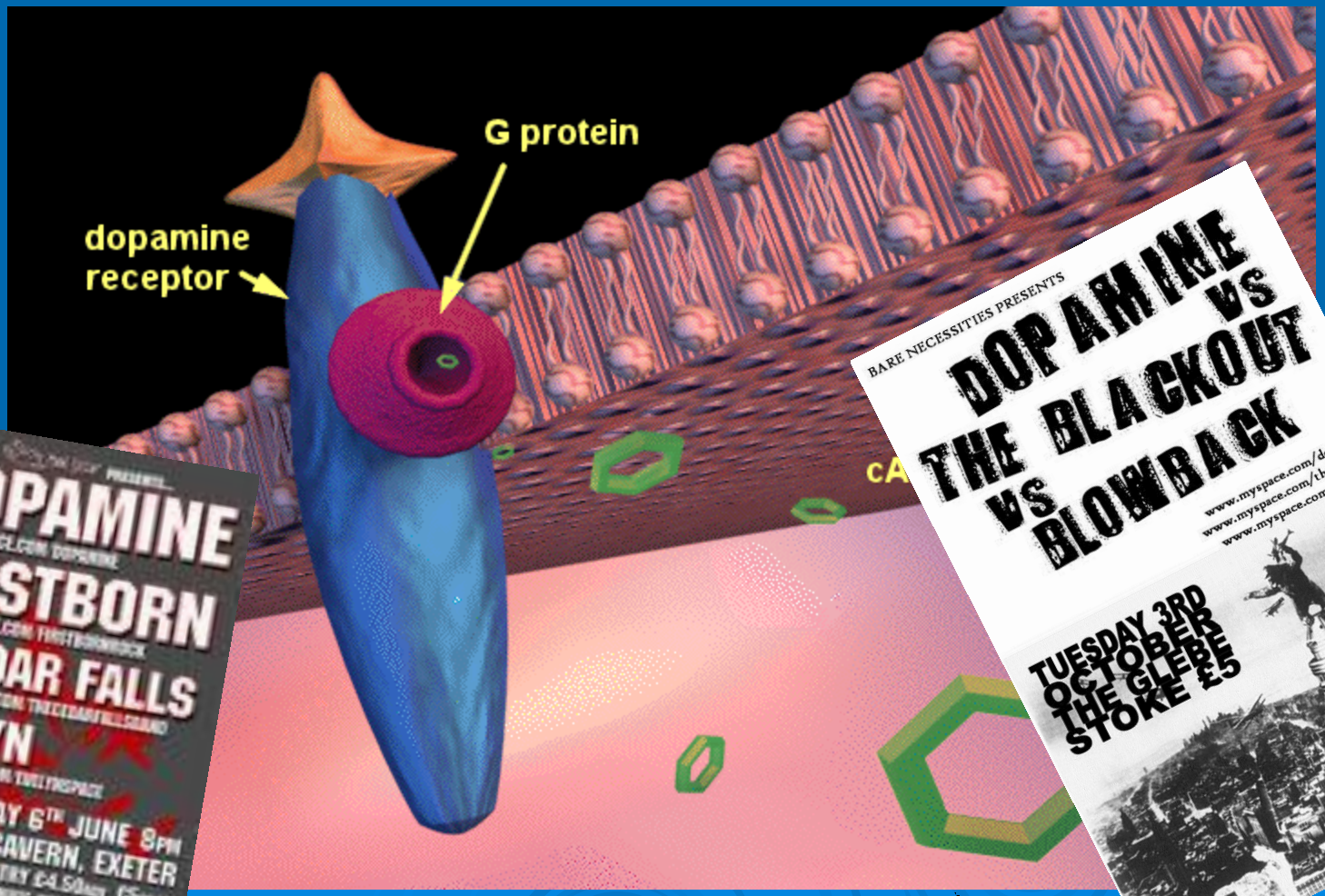


Dopamine



Basal Ganglia

Providing dopamine is not the total solution for Parkinson's Disease



Non motor complications of Parkinson's Disease

- Higher Cortical Function
  - Dementia
  - Depression
  - Dellusions/hallucination psychosis
- Sleep disturbance
  - Insomnia
  - REM sleep abn
  - Restless leg
- Leg edema
- Sensory abnormality
  - Paresthesias
  - Loss of smell
- Kyphoscoliosis
- Autonomic dysfunciton
  - Bladder dysfunction
  - Orthostatic hypotension
  - Constipation
  - Abn sweating
- Seborrheic dermatitis
- Fatigue

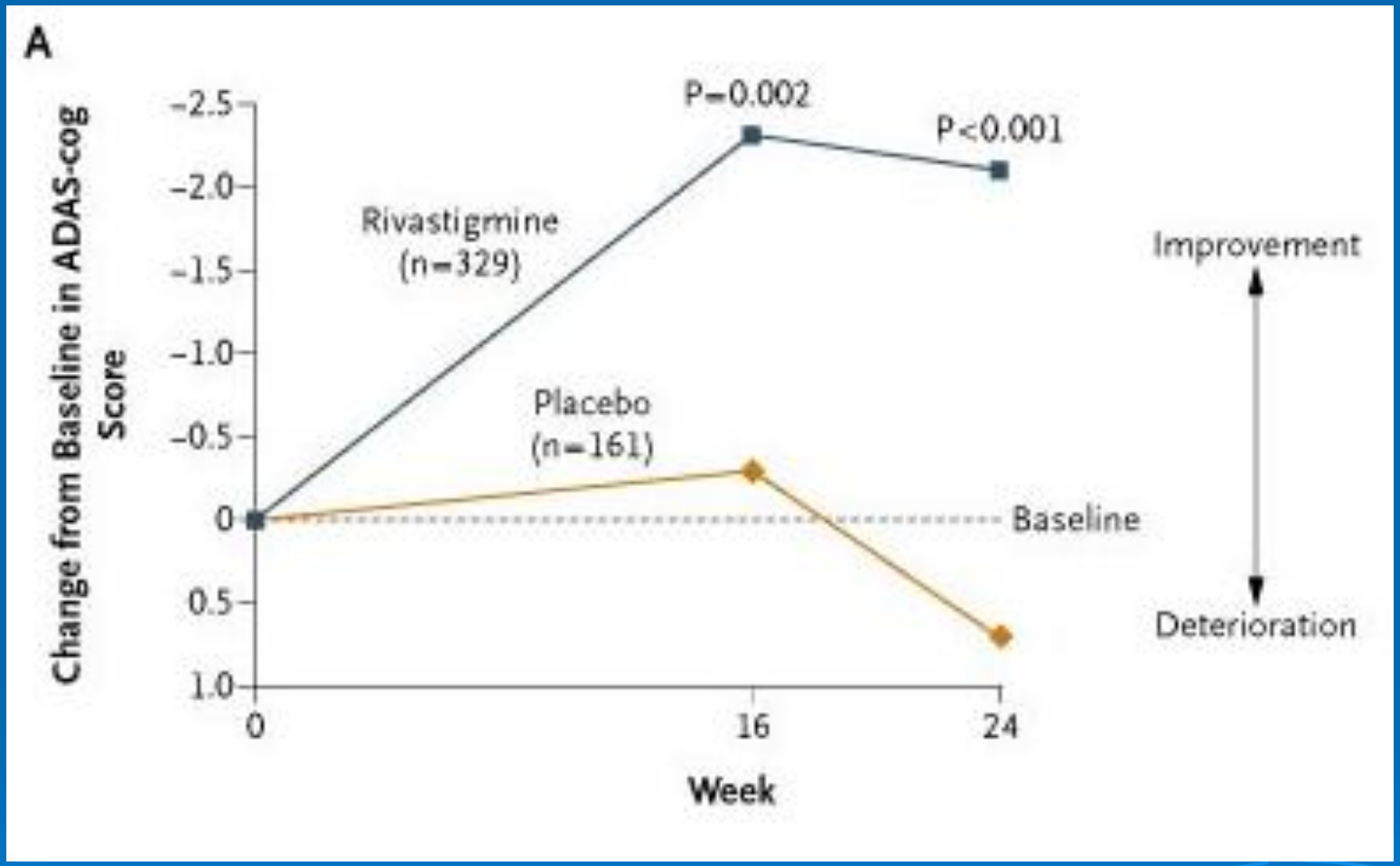
Depression in Parkinson's

- Most common neuro-behavioral problem in PD
- effects 40-50% of PD patients
- Depression is more than reaction to chronic disease

Dementia in Parkinsons Disease

- 65% pt with PD over age 85 are demented, There was a steep increase risk for dementia between ages 65 to 75

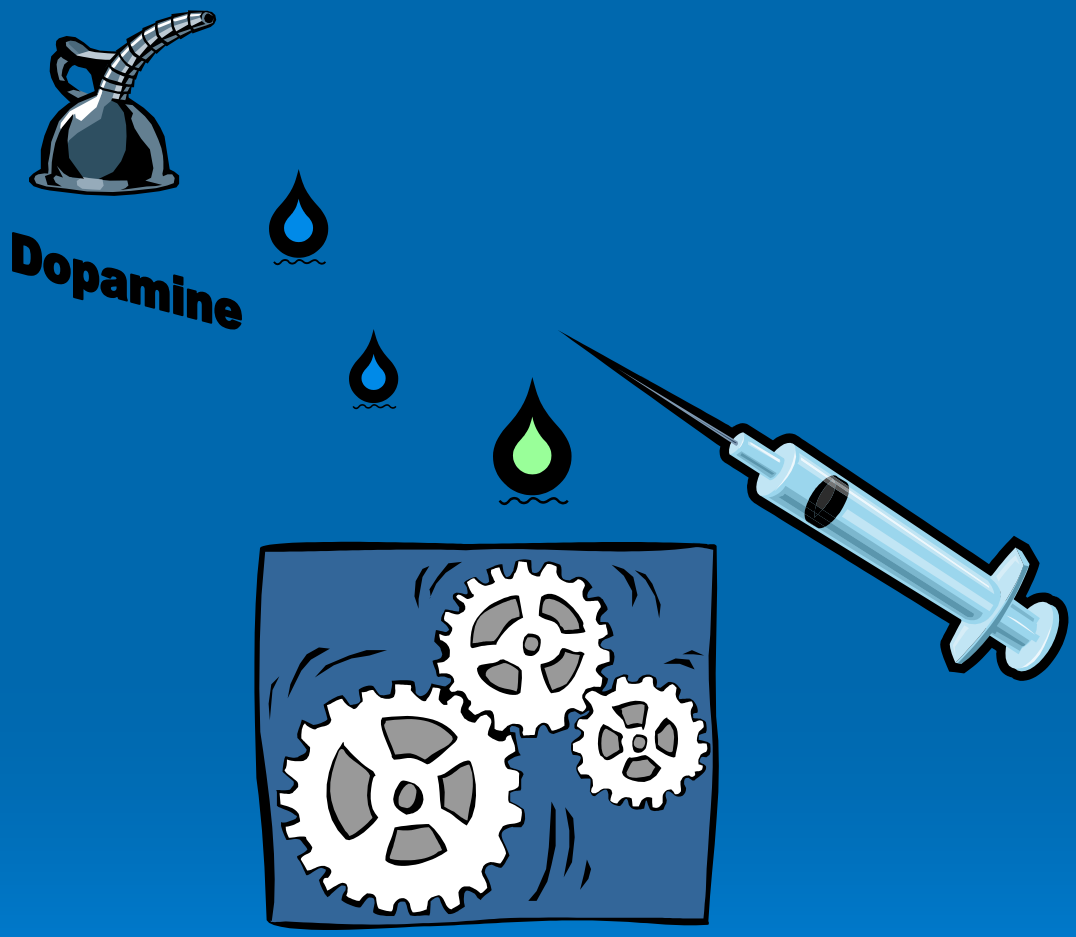
J. Neural Transm 2004;1303-1315



Results of the Primary Efficacy Analysis in the Efficacy Population

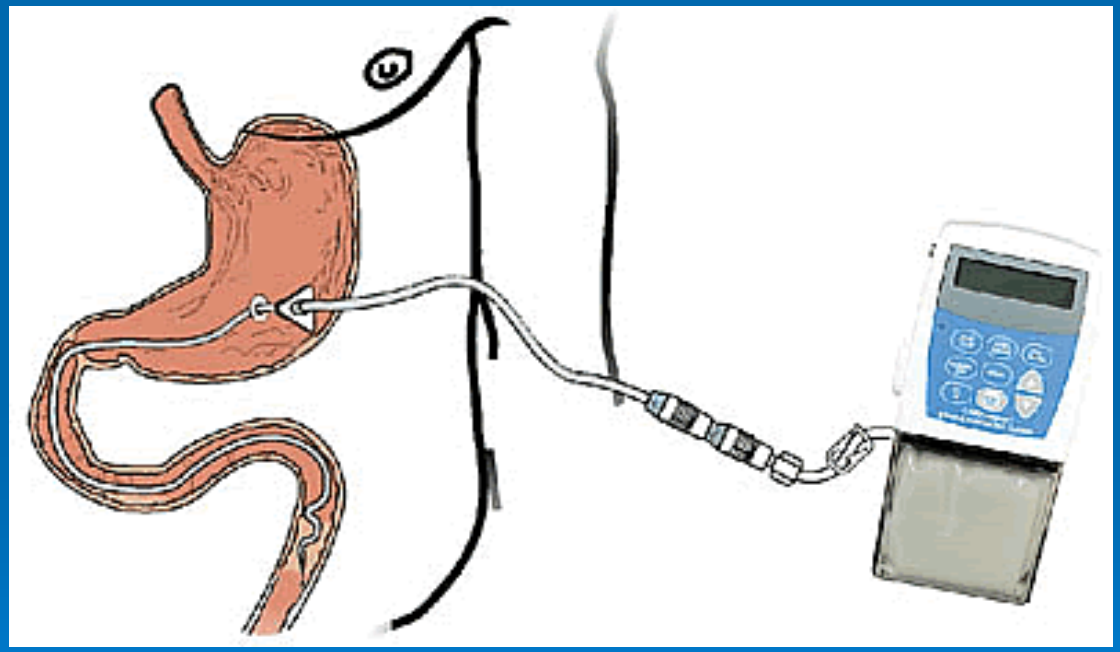
Emre, M. et al. N Engl J Med 2004;351:2509-2518

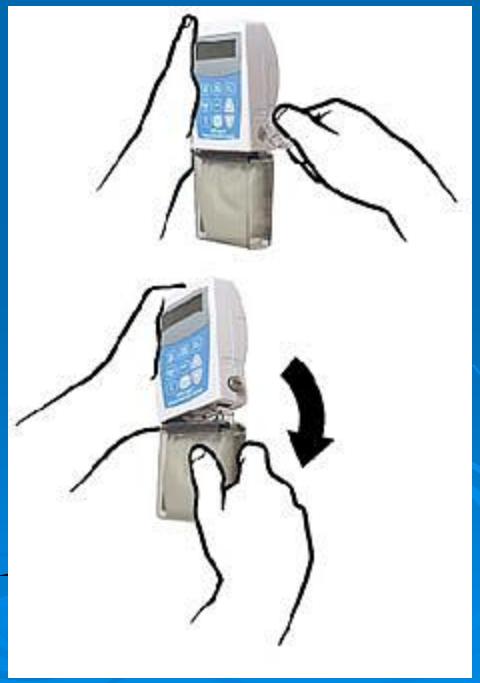
Apomorphine (apokyn)



- Apomorphine Injectable fast acting dopaminergic drug
- Onset of action within 10 minutes
- May have to premedicate with antiemetic
- Helpful for on-off
- May become available as continuous subq infusion

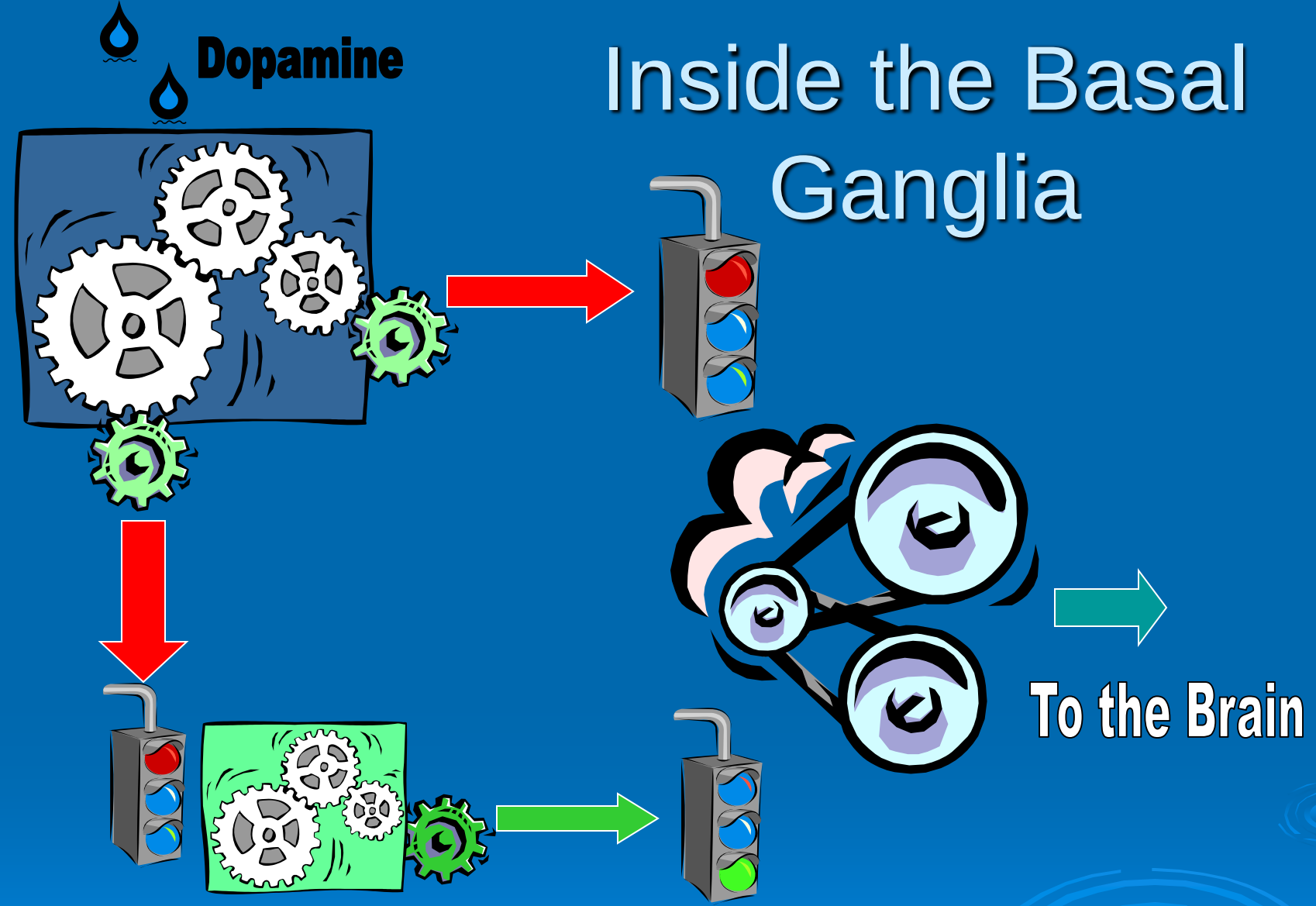
Continuous L dopa infusion



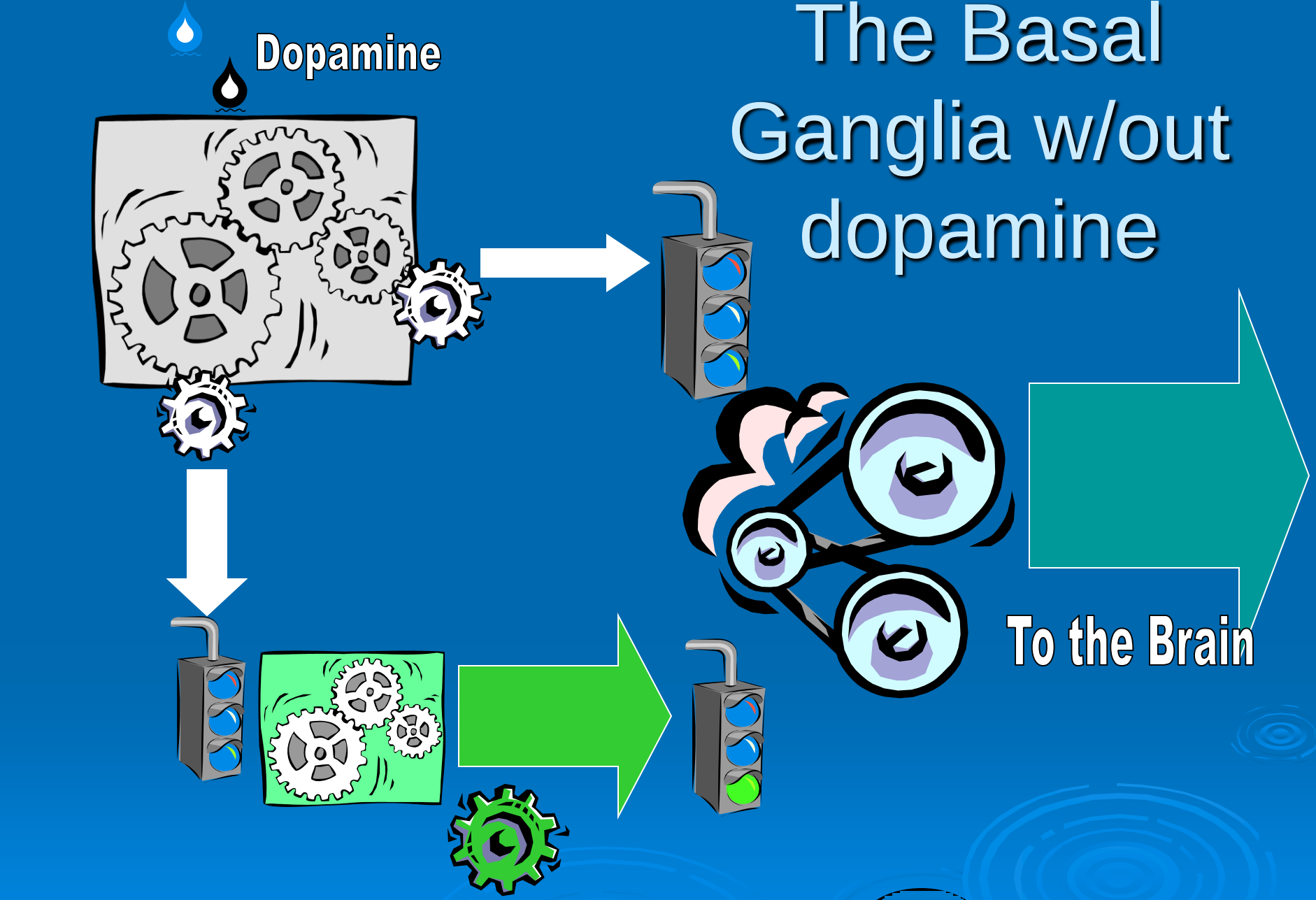


Thank you

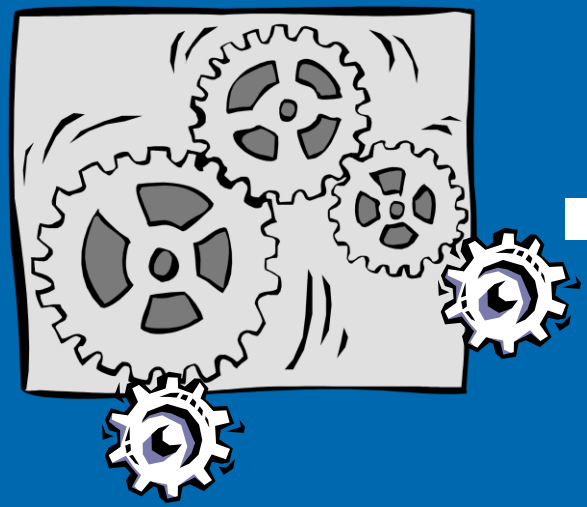
Inside the Basal Ganglia

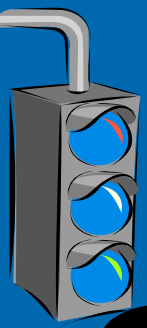


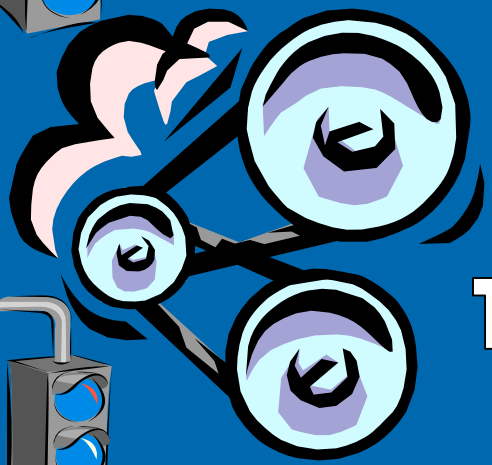
The Basal Ganglia w/out dopamine



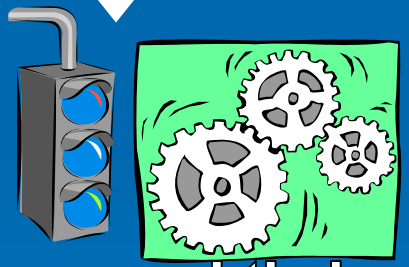
The Basal Ganglia w/ Deep Brain Stimulator



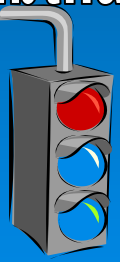




To the Brain



subthalamic nucleus



Deep Brain Stimulator