Anti-Parkinson Drugs

Prevalence

- 1.5 million in USA and 120,000 in the UK – accounts for about 10% of all acute hospital admissions
- Effects 2 in 1,000 people; aged 80+ incidence is 1 in 50.
- Mainly affects adults in later life
- Slightly more common in men, Afro-Caribbean's and people from the Indian subcontinent
- Affects the quality of life of about 500,000 (family, carers etc)
- Manifests when 60-70% of the dopaminergic neurons are even lost!

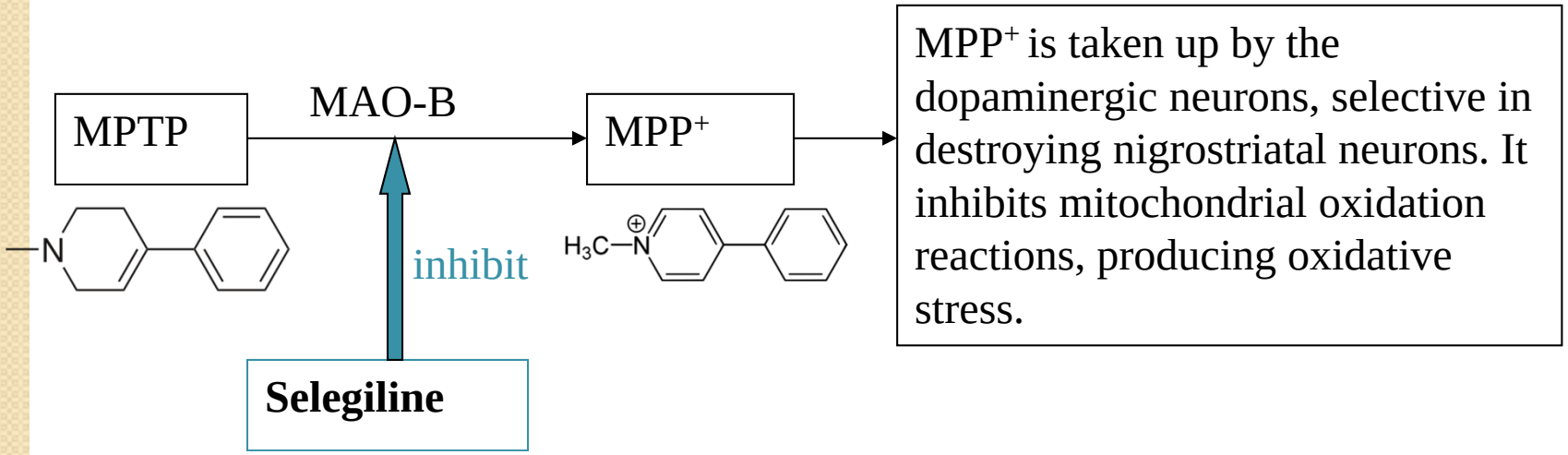
Causes

- Unclear, but is a number of factors:
  - Environmental – toxins (MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
  - Free Radicals – there is an increase in post-mortem brain sections
  - Aging – age related decline in dopamine production
  - Genetic: Gene mutations (alpha-synuclein, parkin (early onset, A.R.), LRRK2, UCHL2)
  - Drug induced (e.g. chlorpromazine, reserpine)
  - Cerebral ischaemia
  - Viral encephalitis

Action of MPTP

Meperidine byproduct

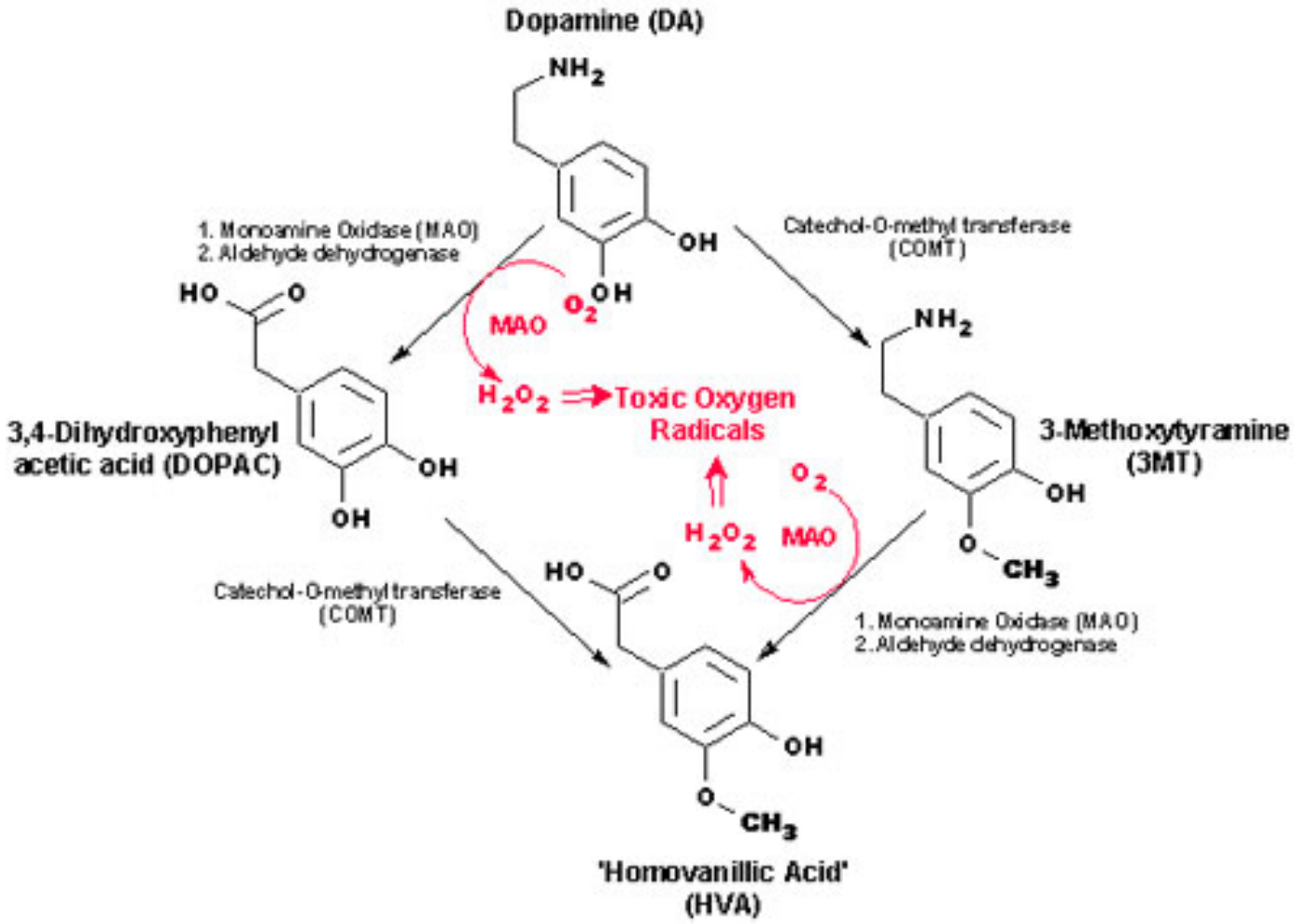
- 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) causes irreversible destruction of nigrostriatal dopaminergic neurons in various species, and produces a PD-like state in primates.



Parkinson's Disease

- A degenerative and progressive disorder
- Associated with neurological consequences of decreased dopamine levels produced by the basal ganglia (substantia nigra)
- Dopamine is a neurotransmitter found in the neural synapses in the brain
- Normally, neurones from the SN supply dopamine to the corpus striatum (controls unconscious muscle control)
- Initiates movement, speech and self-expression

Metabolism of Dopamine by MAO and COMT[22]



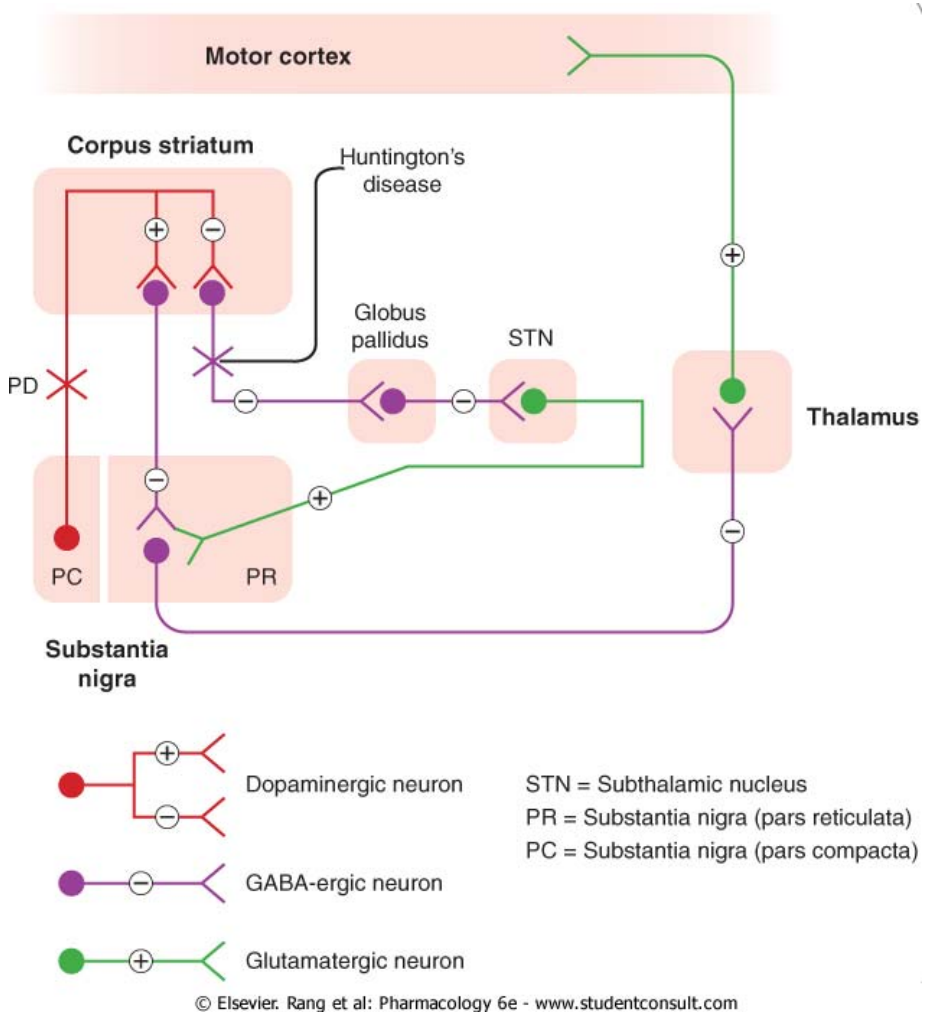
DA is a double edged sword

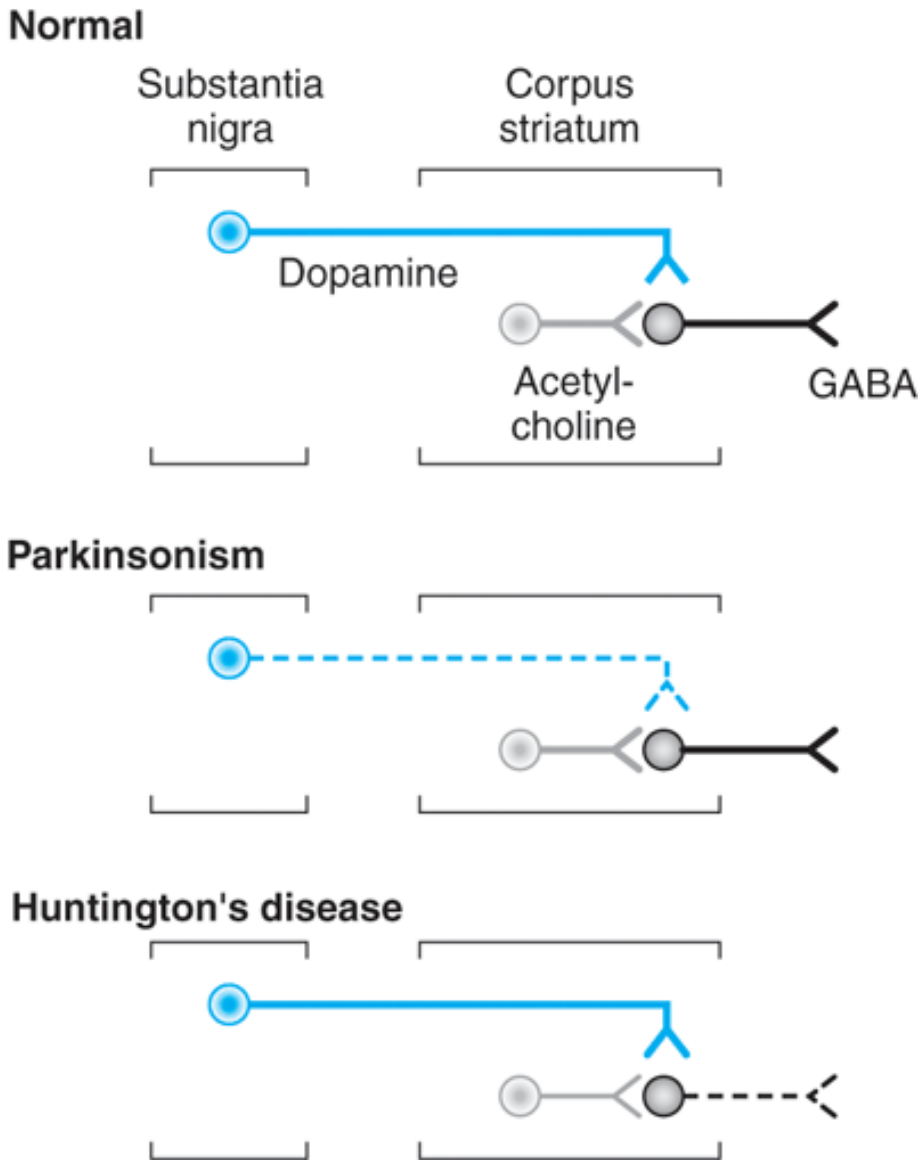
- DA has been shown to be a double-edged sword, because it displays antioxidant properties in relation to both the Fenton reaction and lipid peroxidation and exhibits pro-oxidant properties by causing both generation *OH and oxidation of mitochondrial proteins.
- H.J.H Fenton discovered in 1894 that several metals have a special oxygen transfer properties which improve the use of hydrogen peroxide. Actually, some metals have a strong catalytic power to generate highly reactive hydroxyl radicals (.OH). Since this discovery, the iron catalyzed hydrogen peroxide has been called Fenton's reaction. Nowadays, the Fenton's reaction is used to treat a large variety of water pollution such as phenols, formaldehyde, BTEX, pesticides, rubber chemicals and so on.

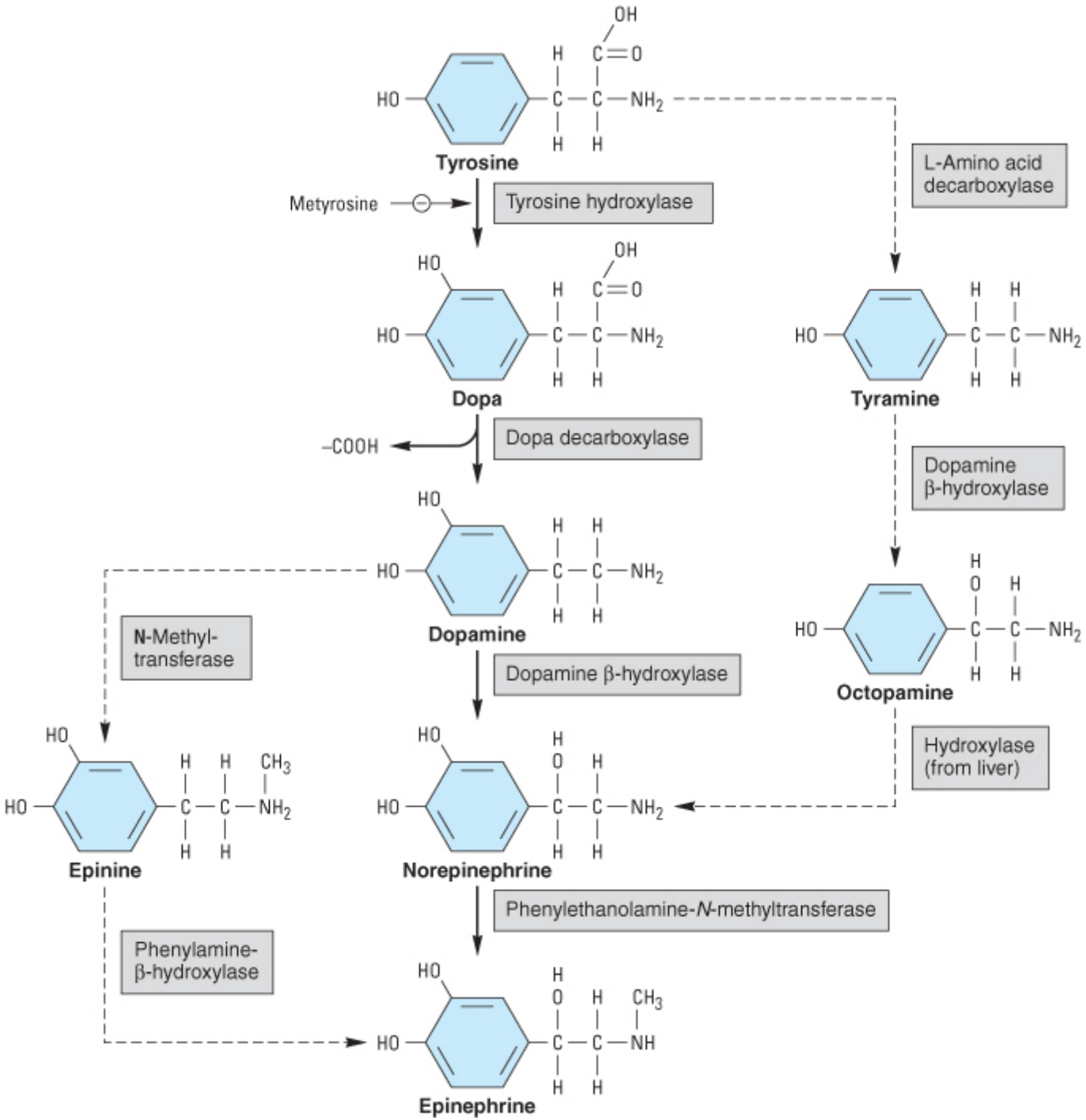
- Balance, posture, muscle tone and involuntary movement depends on the roles of dopamine (inhibitory) and acetylcholine (Ach: excitatory)
- If dopamine missing, Ach produces more of an effect on muscles

- Basis to exploit by drugs:
  - Restore dopamine function
  - Inhibit Ach within corpus striatum

Simplified diagram of the organisation of the extrapyramidal motor system and the defects that occur in Parkinson's disease (PD) and Huntington's disease.




Normal
Substantia nigra
Corpus striatum
Dopamine
Acetyl-choline
GABA
Parkinsonism
Huntington's disease


Tyrosine
Metyrosine
Tyrosine hydroxylase
L-Amino acid decarboxylase
Dopa
Tyramine
–COOH
Dopa decarboxylase
Dopamine β-hydroxylase
Dopamine
N-Methyl-transferase
Dopamine β-hydroxylase
Octopamine
Hydroxylase (from liver)
Epinine
Norepinephrine
Phenylethanolamine-N-methyltransferase
Phenylamine-β-hydroxylase
Epinephrine

Consequences of dopamine reductions

- **Tremors** – hands and head develop involuntary movements when at rest; pin-rolling sign (finger and thumb)
- **Muscle rigidity** – arthritis-like stiffness, difficulty in bending or moving limbs; poker face
- **Brandykinesia** – problems chewing, swallowing or speaking; difficulty in initiating movements and controlling fine movements; walking becomes difficult (shuffle feet)
- **Postural instability** – humped over appearance, prone to falls

Additional symptomology

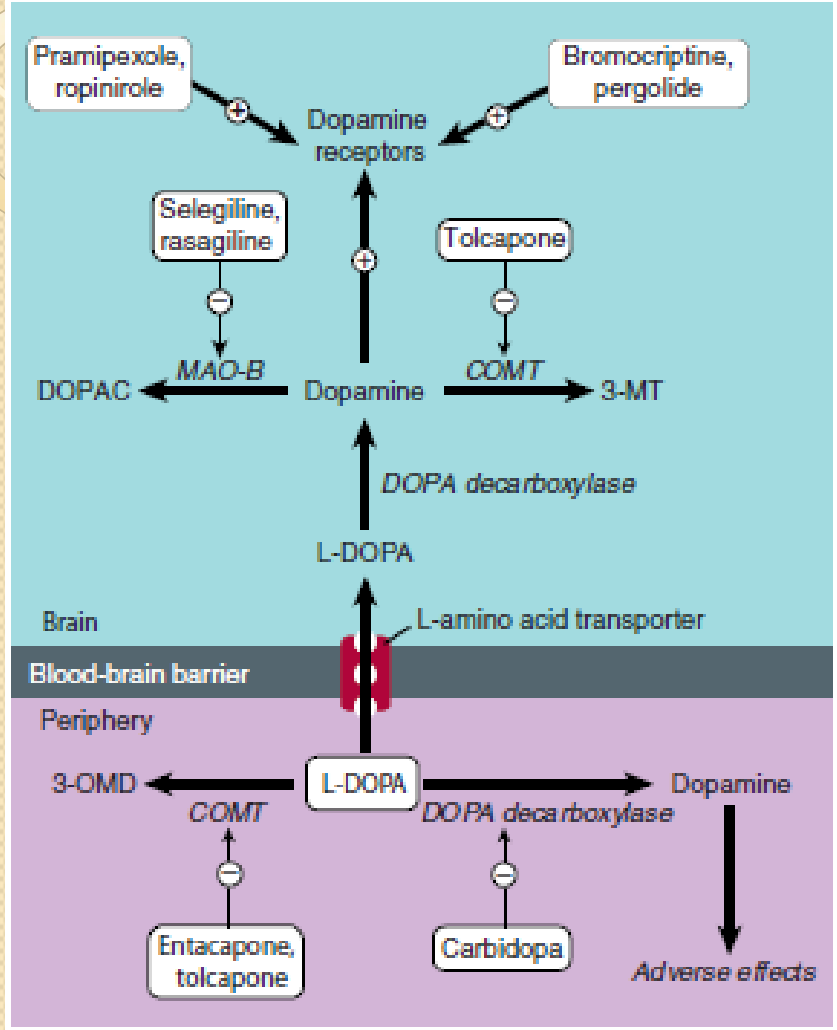
- Anxiety
- Depression
- Sleep disturbance
- Dementia
- Disturbance of ANS (difficulty in urinating)

Clinical Presentation

- Altered body image (depression)
- Poor balance
- Bradykinesia (slow movement)
- Bradyphrenia (slowness of thought)
- Constipation
- Dribbling/drooling
- Dyskinesias (involuntary movements)
- Dysphagia (difficulty swallowing
- Dystonia (pain spasms)
- Excessive sweating (impaired thermoregulation)
- Festinating gait
- Hallucinations (visual)
- Postural hypotension
- Restless leg syndrome (leg aches, tingle, or burn)
- Rigidity
- Sleep disturbance
- Slurring/slowing of speech
- Tremor (resting)

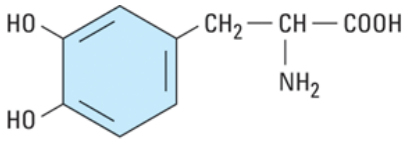
Medication Rational

- Replace depleted levels of dopamine
- Stimulate the nerve receptors enabling neurotransmission
- Increase the effect of dopamine on nerve receptors (agonist)
- Counteract the imbalance of Ach and Dopamine

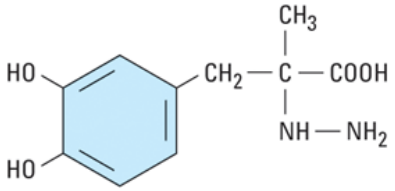


- Pharmacologic strategies for dopaminergic therapy of Parkinson's disease.
- MAO, monoamine oxidase; COMT, catechol- O -methyltransferase; DOPAC, dihydroxyphenylacetic acid; L-DOPA, levodopa; 3-OMD, 3- O -methyldopa; 3-MT, 3-methoxytyramine.

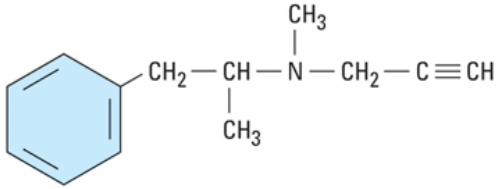
- The Drugs:
  - Dopaminergic drugs (improving dopamine functioning)
    - Levodopa
    - Dopamine receptor agonists
    - Amantadine
    - Selective monoamine oxidase B inhibitors
    - Catechol-O-methyltransferase inhibitors
  - Antimuscarinic drugs (Ach inhibitors)



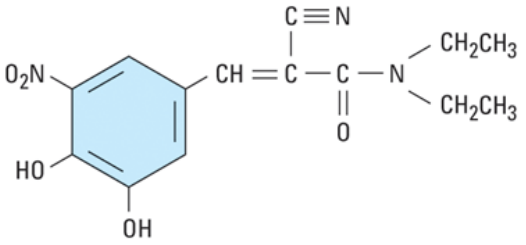
Dihydroxyphenylalanine (dopa)



Carbidopa



Selegiline

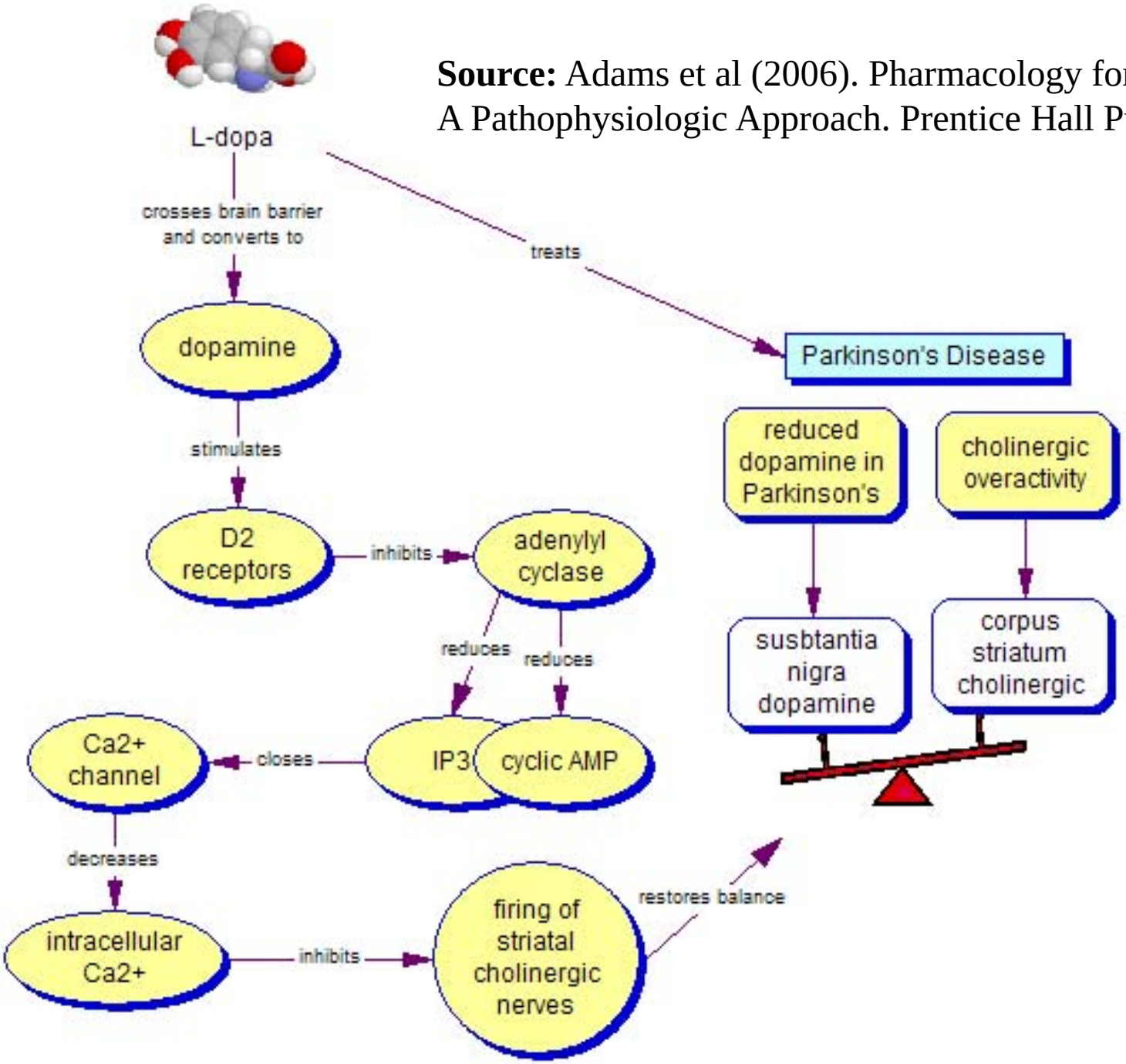


Entacapone

Levodopa (Madopar & Sinemet)

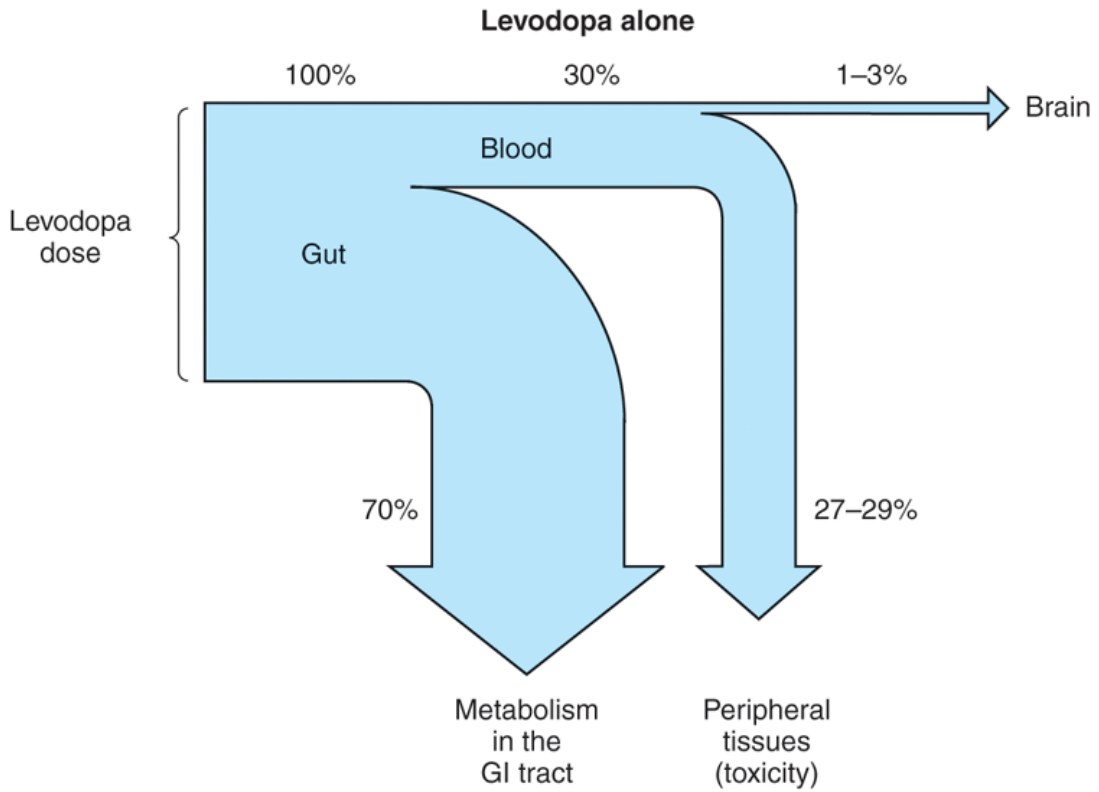
- Can not administer dopamine directly, as it does not cross the blood brain barrier
- A natural amino acid that the brain converts into dopamine (replacement therapy) used since the 1960's
- To make it slow release, combined with benserazide (an enzyme inhibitor) to create co-beneldopa or co-careldopa (Sinemet)
- Dose = 50, 100 or 200mg (12.5, 25 or 50mg)

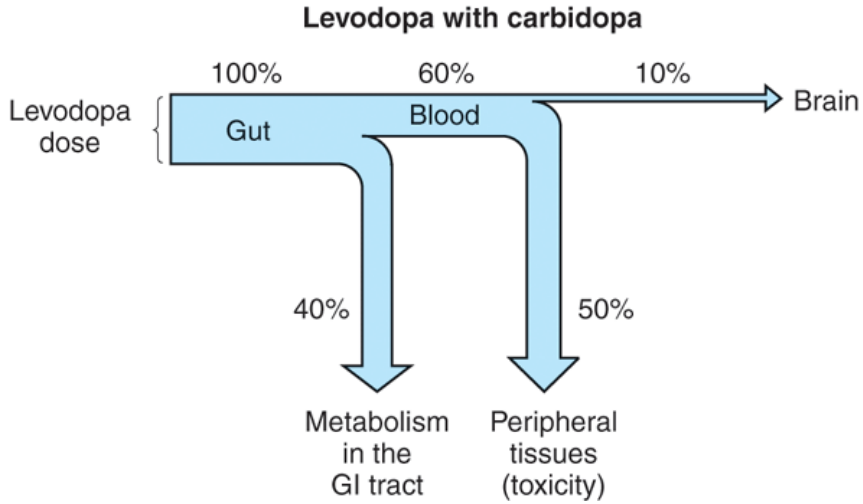
Source: Adams et al (2006). Pharmacology for Nurses – A Pathophysiologic Approach. Prentice Hall Publishers



Levodopa PK

- Pharmacokinetics:
  - Absorbed in the proximal duodenum like large neutral amino acids. High-protein food diet disturbs absorption.
  - Decarboxylation occurs in peripheral tissues (gut wall, liver and kidney)
    - L-amino acid decarboxilase (cofactor Vitamin B6) (carbidopa, benserazid)
    - COMT (entacapone, tolcapone)
      - decrease amount available for distribution
      - Extracerebral dopamine amounts causing unwanted effects (benserazide)
  - Large first pass effect (gut wall and liver 95% digested) – 1% of an oral dose
  - Short half-life


Levodopa alone
100%
30%
1–3%
Brain
Blood
Levodopa dose
Gut
70%
27–29%
Metabolism in the GI tract
Peripheral tissues (toxicity)


Levodopa with carbidopa
100%
60%
10%
Brain
Levodopa dose
Gut
Blood
40%
50%
Metabolism in the GI tract
Peripheral tissues (toxicity)

Levodopa

- Pharmacologic effects:

(1) The effects on bradykinesia and rigidity are more rapid and complete than the effects on tremor. Other motor defects in PD improve. The psychological well-being of patient is also improved.

Levodopa

- Pharmacologic effects:

  (2) Tolerance to both beneficial and adverse effects occurs with time. Levodopa is most effective in the first 2-5 years of treatment. After 5 years of therapy, patients have dose-related dyskinesia, inadequate response, or toxicity.

Levodopa

- Adverse effect:

Principal adverse effects include:

(1) Anorexia, nausea, and vomiting (80%) upon initial administration, which often limit the initial dosage.

(2) Cardiovascular effects, including tachycardia, arrhythmias (10%), and orthostatic hypotension (25%).

Levodopa

- Adverse effect:

(3) Mental disturbances, including vivid dreams, delusions, and hallucination.

(4) Hyperkinesia, dyskinesia (30%) (peak-dose dyskinesia)

(5) On-off phenomen

(6) End-of-Dose (wearing off) phenomen

Levodopa

- Adverse effect:

Sudden discontinuation can result in fever, rigidity, and confusion. The drug should be withdrawn gradually over 4 days.

Levodopa

Drug interactions:

- **Vit B6 (co-factor of decarboxilase) reduces the beneficial effects of Levodopa by enhancing its extracerebral metabolism.**
- **Therapy with MAO inhibitors must be stopped 14 days prior to the initiation of levodopa therapy. Antidepressant Phenelzine!**
- **Phenothiazines, reserpine, and butyrophenones antagonize the effects of levodopa because they lead to a junctional blockade of dopamine action.**
- **Antipsychotic drugs (clozapine is the best in this regard)**

Carbidopa

- Carbidopa is an inhibitor of dopa decarboxylase. Because it is unable to penetrate (polarized in physiologic pH) the blood-brain barrier, it acts to reduce the peripheral conversion of levodopa to dopamine. As a result, when carbidopa and levodopa are given concomitantly.

Carbidopa

Virtue:

a. It can decrease the dosage of levodopa.

b. It can reduce toxic side effects of levodopa.

c. A shorter latency period precedes the occurrence of beneficial effects.

Dopamine receptor agonists

- They don't require living dopaminergic neurons! Helpful in advanced PD.
- Act mainly on the D2 receptors
- Apopmorphine (APO-go):
  - SC administration
  - Rescue therapy – rapid onset with a short duration of action (~50mins)
- Ergot alkaloids:
  - Bromocriptine (Parlodel)
  - Pergolide (Celance, Permax) (withdrawn because it damaged the heart valves)
- Non-ergot D agonists (activates D2 receptors)
  - They can delay of the need of L-DOPA!
  - Ind: Early stage PD! In advanced stage can reduce the „off" period. Can be used in the treatment of restless leg syndrome!
  - Side effects: Dizziness, hallucinations, insomnia, nausea, vomiting, sedation

Bromocriptine (BROMOCRIPTIN-RICHTER)

- Ergot derivative
- D2 agonist, D1 antagonist
- Good in combination with L-DOPA in case of End-of-dose and on-off phenomena treatment
- Side effects: confusion, dyskinesias, sedation, vivid dreams, hallucinations
- Dose: 7.5-30 mg/d
- Dose is build up slowly over 2-3 months

Non-ergot D agonists

- activates D2 receptors
- They can delay of the need of L-DOPA!
- Ind: Early stage PD! In advanced stage can reduce the „off” period. Can be used in the treatment of restless leg syndrome!
- Side effects: Dizziness, hallucinations, insomnia, nausea, vomiting, sedation

Pramipexol (MIRAPEXIN, OPRYMEA, PRAMITENORM)

- Not ergot derivative
- D3 agonist as well
- In mild PD effective alone
- Scavenges H_2O_2 -> neuroprotection
- PK: A: rapid (peak 2 h) E: unchanged (kidney)
- Start dose: 0.125 mg 3x/d (XR tablets exist)

Ropinirole (REQUIP, AROPILO, RALNEA, ROMYL)

- Non-ergot derivative
- D2 agonist
- In mild PD effective alone
- Dose: 0.25 mg 3x/d

Rotigotine (NEUPRO)

- TTS
- Activates D3 receptors
- In early disease
- Available in EU

Apomorphine

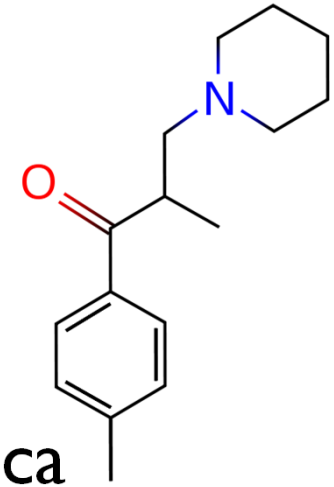
- Does not bind to opioid receptors
- D agonist
- Obsolete drug but used in acute, intermittent hypomobility (freezing episodes) in advanced PD.
- Inj only. 5-10 min for reversal of hypomobility.

Adverse effects of DA

- GI: anorexia, nausea, vomiting, constipation, dyspepsia, GERD
- CV: postural hypotension, painless digital vasospasm, cardiac arrythmias, edema
- Dykinesias: abnormal movements
- Mental dysturbances: confusion, hallocinations, delusions
- Misc: headache, nasal congestion, increased arousal, pulmonary infiltration, pleural/retroperitoneal fibrosis, erythromelalgia (Mitchell's disease)

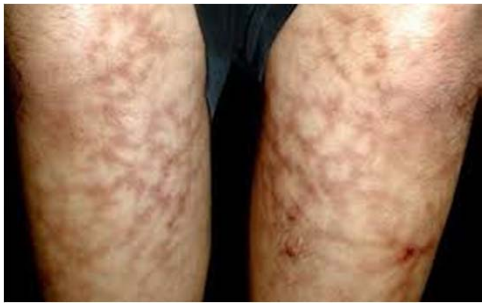
Centrally acting muscle relaxants

- Tolperison (Mydocalm, Mydeton)
  - Treats muscle rigidity
  - Spondylosis, spondyloarthrosis
  - Acrocyanosis, dysbasia angioneurotica intermittens
  - Little-disease
  - Encephalopathies with distonias
- carisoprodol

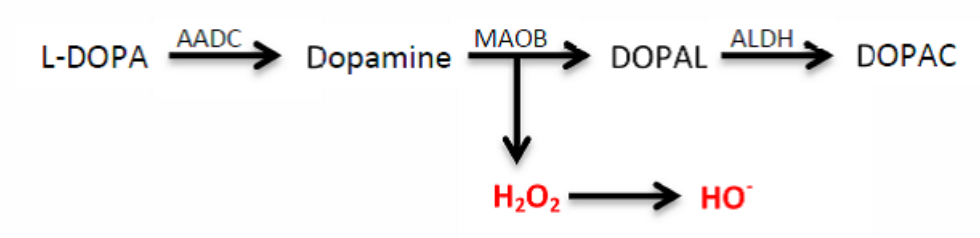


Amantadine (VIREGYT, PK-MERZ)

- Originally an antiviral drug, now used as conjunctive therapy for dyskinesis effects produced by Levodopa
- MoA:
  - stimulates/promotes the release of dopamine stored in the synaptic terminals
  - Reduces reuptake of released dopamine by pre-synaptic neuron
- Pharmacokinetics:
  - Well absorbed, long half-life, excreted unchanged by the kidney
- Adverse effects:
  - CNS: restlessness, depression, insomnia, agitation, hallucinations
  - Ankle oedema, postural hypotension, livedo reticularis
- Ind: Early and mild PD.
- Side eff: sedation, restlessness, vivid dreams, nausea, dry mouth, hypotension, leg swelling livedo reticularis reddish-blue mottling on the skin

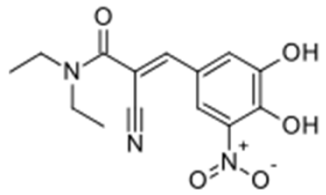


MAO-I



- Selective monoamine oxidase B inhibitors (selegiline – Trade name: Eldepryl/Zelapar/Jumex):
  - MoA: prolongs the effects of levodopa as MAO-B degrades dopamine, reduce free radical formation, slows down the PD progression
  - Pharmacokinetics: completely absorption, short half-life, partially metabolized to amphetamine
  - Adverse effects: Constipation; dry mouth, sore throat; transient dizziness; insomnia, confusion and hallucinations
  - Drug-drug interaction: meperidine, fluoxetine
  - Early stage – prescribed on it is own to delay need for levodopa and there is good evidence for its slowing down of PD progression
  - Rasagiline (AZILECT)
  - Safinamide (inhibits MAO-B and dopamine reuptake)

COMT-I



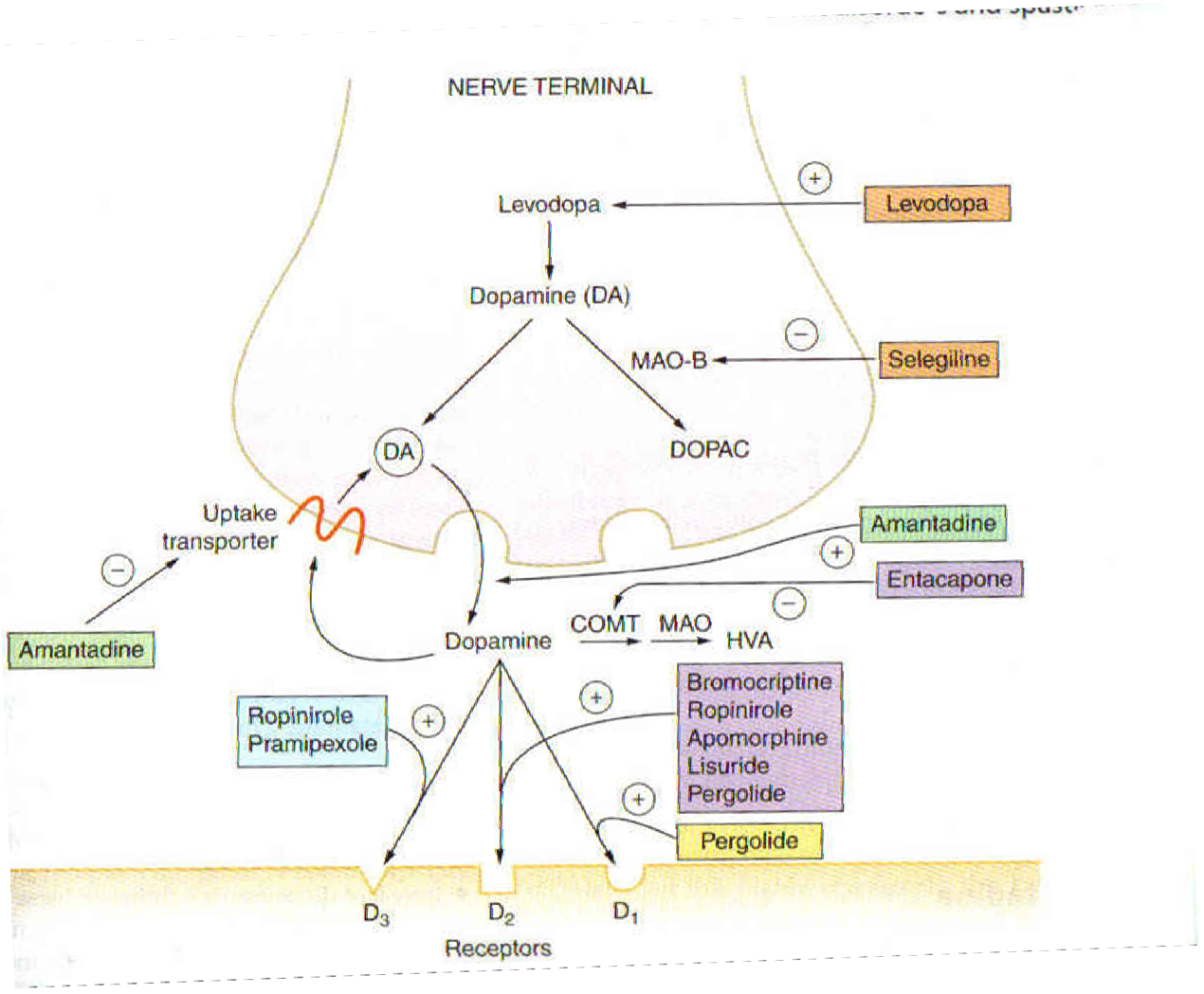
- Catechol-O-methltransferase inhibitors - COMT (entacapone, COMTAN, STALEVO)
  - MoA: inhibits the breakdown of levodopa
  - Pharmacokinetics: variability of absorption, extensive first-pass metabolism, short half-life
  - Adverse effects: dyskinesias, hallucinations; abdominal pain
  - New combination – Levodopa/carbidopa/entacapone (Stalevo) as 1 tablet (50, 100, 150mg)

Centrally acting cholinolytics

- Antimuscarinic/Anticholinergic Drugs:
  - Trihexyphenidyl (Broflex, Artane, Agitane); Benztropine (Cogentin); Orphanadrine (Disipal); Procycline (Kemadrin, Arpicolin)
  - Ind: treatment of tremor
  - Less common drugs but they affect Ach based interactions
  - MoA: blocking cholingeric (Ach) receptors to restore balance
  - Pharmacokinetics: fairly well absorbed, extensive hepatic metabolism, intermediate to long half-lifes
  - Adverse effects: dry mouth and confusion

Drug	Usual Daily Dose (mg)
Benztropine mesylate	1–6
Biperiden	2–12
Orphenadrine	150–400
Procyclidine	7.5–30
Trihexyphenidyl	6–20

Disease Modifying Drugs Overview



Symptom Management Drugs

- PD is multidimensional, therefore there are a number of clinical presentations that require supplementary agents
  - Drug-Drug reactions is the problem
  - Major area is depression

Antidepressants

- Amitriptyline (Tryptizol), imipramine (Tofranil), Nortriptyline (Allegron), Iofepramine (Gamanil)
- MoA: block re-uptake of noradrenaline and serotonin => Sedative actions, can help with drooling and loss of appetite
- Adverse effects: sleepiness, dry mouth, increased hunger, cardiac arrhythmias and changes in BP
- Can interfere with the effects of levodopa!

Other Drugs to Avoid

Generic Name	Brand Name	Prescribed for
Prochlorperazine	Stemetil	N +V, Dizziness
Prephenazine	Triptafen	Depression
Flupentixol	Fluanxol/Depixol	Confusion, Hallucinations
Chlorpromazine	Largactil	“
Pimozide	Orap	“
Sulpiride	Dolmatil	“

Treatment (early stage)

- Clinical judgements based upon level of disability, age, cognitive status, concurrent medial problems
- Initial pharmacological therapies are titrated to determine optimal dose per person
  - Agent used: Levodopa
- Social support and health education vital
- Referrals to other professional groups

Treatment (maintenance stage)

- Speech therapist is prophylactic and deals with swallowing problems (recommend exercises etc)
- Impaired thermoregulation – use beta-blockers
- Disturbance in sleep – can be side effects of medication; change time of intake or use a controlled release drug delivery system
- Continued health education and liaison with other professionals

Treatment (complex stage)

- Function has deteriorates to such a level a combination of drugs are prescribed
- Dyskinesias and Dystonia – can be associated with long-term Levodopa use and it can be difficult to manage these effects – co-agent is co-beneldopa
- Restless-leg – dopamine agonists
- Anxiety – relaxation, distraction, CBT
- Depression – alterations in dose of anti-parkinson's drugs

- Cognitive problems – referral to clinical psychologist and prescription of anti-dementia agents
- Hallucinations - ?anti-psychotics

Essentially, a multidimensional approach to pharmacological treatment combined with a multidisciplinary approach