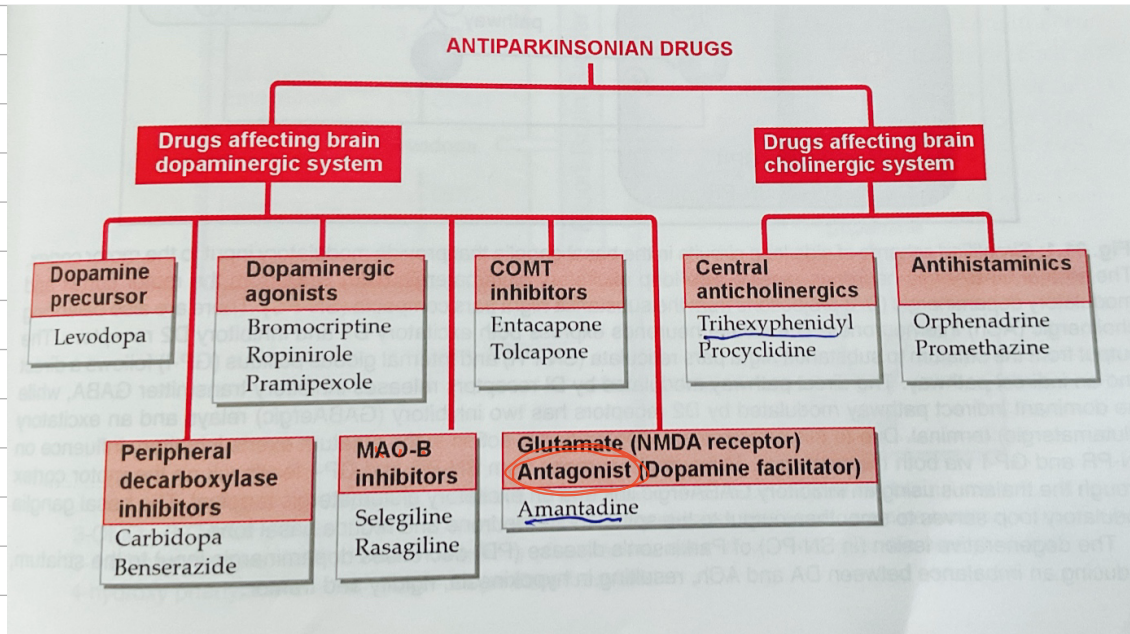


CNS



LEVODOPA

- Precursor of the transmitter DA
- About 1-2% of the administered levodopa crosses the brain

ACTIONS

- CNS - Hypokinesia & rigidity resolve first, later tremor
 - 2^o symptoms of posture, gait, handwriting, speech, mood are gradually normalized
- CVS - tachycardia & arrhythmia
 - Postural hypotension is quite common
- CTZ - elicits nausea & vomiting
- Endocrine - Acts on pituitary mammotropes to inhibit prolactin release & on somatotrophs to increase GH release

PK

- orally
- Bioavailability of levodopa affected by
 - ↳ gastric emptying
 - amino acids present on food competes for the same carrier for absorption

ADR

At the initiation of therapy:

- Nausea & vomiting
- Postural hypotension
- Cardiac arrhythmias
- Exacerbation of angina

After prolonged therapy :

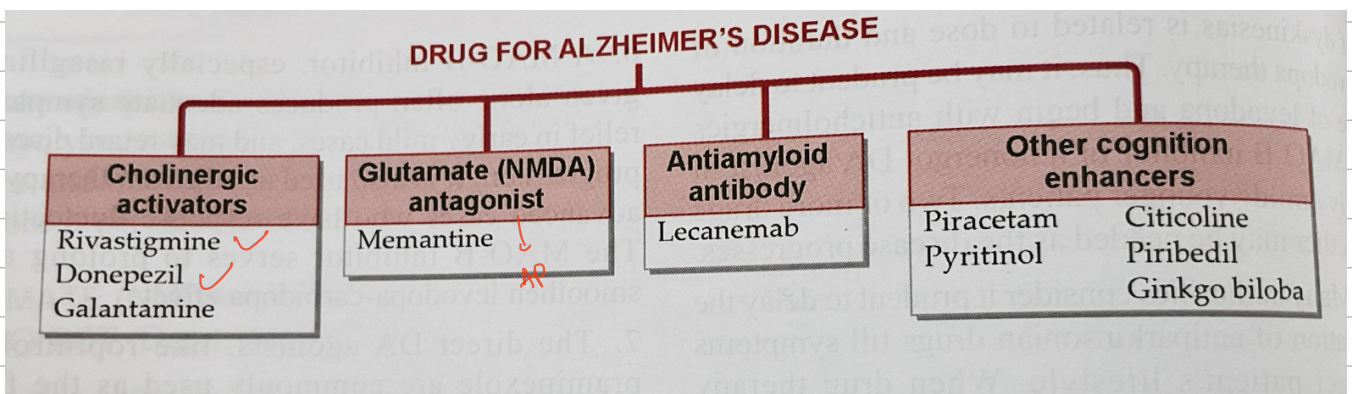
- Abnormal moods
- Behavioral effects
- Fluctuation in motor performance

↳ Administered along with levodopa, they increase its $t_{1/2}$ in the periphery & make a larger fraction of its available to cross blood-brain barrier & reach its site of action.

Benefits of combination :

- * Plasma $t_{1/2}$ of levodopa prolonged & its dose is reduced
- * Systemic conc. of DA reduced, nausea & vomiting minimized
- * Cardiac complications reduced
- * Pyridoxine reversal of levodopa effect does not occur
- * 'on-off' effect is minimized since cerebral DA levels are more sustained
- * Degree of improvement may be higher

ALZHEIMER'S DISEASE



Rivastigmine

- The carbamate derivative of physostigmine - inhibits both AChE & BuChE
- highly lipid soluble - enters brain easily
- The carbonyl residue converts to AChE, & dissociates slowly resulting in inhibiting of cerebral AChE for upto 10 hours despite the 2hr plasma $t_{1/2}$ of drug
- Disease progression not affected
- Not produced own damage
- 3-8 point improvement noticed in trials
- Apathy, delusions, hallucinations, agitation improved

Donepezil

- Carbamate derivative of reversible anti-AChE
- elevates ACh level in the cortex, esp in the surviving neurons
- PK - long $t_{1/2}$, administered once daily at bed time.
- can be used relatively in severe case of AD

MORPHINE

PHARMACOLOGICAL ACTIONS

- CNS: site specific depressant & stimulant actions by interacting with μ opioid.

The depressant actions are:

- * Analgesia
- * Sedation
- * Subjective effects & euphoria
- * Resp depression
- * Cough suppression
- * Temp regulation

- Neuro-endocrine actions

- Hypothalamic influence on pituitary is reduced



FSH, LH, ACTH levels are lowered

Prolactin & GH ↑

Sex hormone, cortisone levels ↓

- Heavy opioid abusers often suffer loss of libido, impotence

- Peripheral actions

a) CVS: causes VD due to →

- histamine release
- depression of vasomotor centre

b) GIT

- Atony & segmentation but ↓ propulsive motils
- Spasm of pyloric, ileocaecal & anal sphincters
- ↓ all GI secretions

c) Other smooth muscles

- Causes spasm of sphincter of Oddi → biliary colic
- Urinary urgency & difficulty in micturition
- Occasionally prolong labour
- Bronchoconstriction

ADR

- Side effects: Sedation, mental clouding, lethargy, vomiting, constipation
- Idiosyncrasy & allergy
- Apnea of the newborn
- Acute morphine poisoning

↳ human lethal dose: 250mg

manifestations: coma, shallow & occasional breathing, cyanosis, pinpoint pupils

Treatment:

- resp support
- maintenance of BP
- Gastric lavage should be done with pot. permanganate to remove unabsorbed drug
- Specific antidote: Naloxone 0.4-0.8 mg w repeated every 2-3 min till resp picks up.

→ Tolerance & dependence

- High degree of dependence
- morphine produces pronounced addiction & physical dependence
- withdrawal of morphine: lacrimation, sweating, yawning, anxiety, fear, aggression, hot & cold flashes, body ache, tremor.

Treatment:

↳ consists of withdrawal of morphine & substitution with oral methadone, followed by gradual withdrawal of methadone

- clonidine, α_2 adrenergic agonist found to partially suppress manifestations of opioid withdrawal. (0.1mg, 2-3 times daily for 1-2 weeks)

ALCOHOLS, DRUG DEPENDENCE & DRUG ADDICTION

Alcohol withdrawal syndrome

Treatment → Psychological & medical supportive measures

- CNS depressants have been used as substitution therapy in the past
- Benzodiazepines / lorazepam preferred

Disulfiram (Aldehyde dehydrogenase inhibitor)

- inhibits aldehyde dehydrogenase