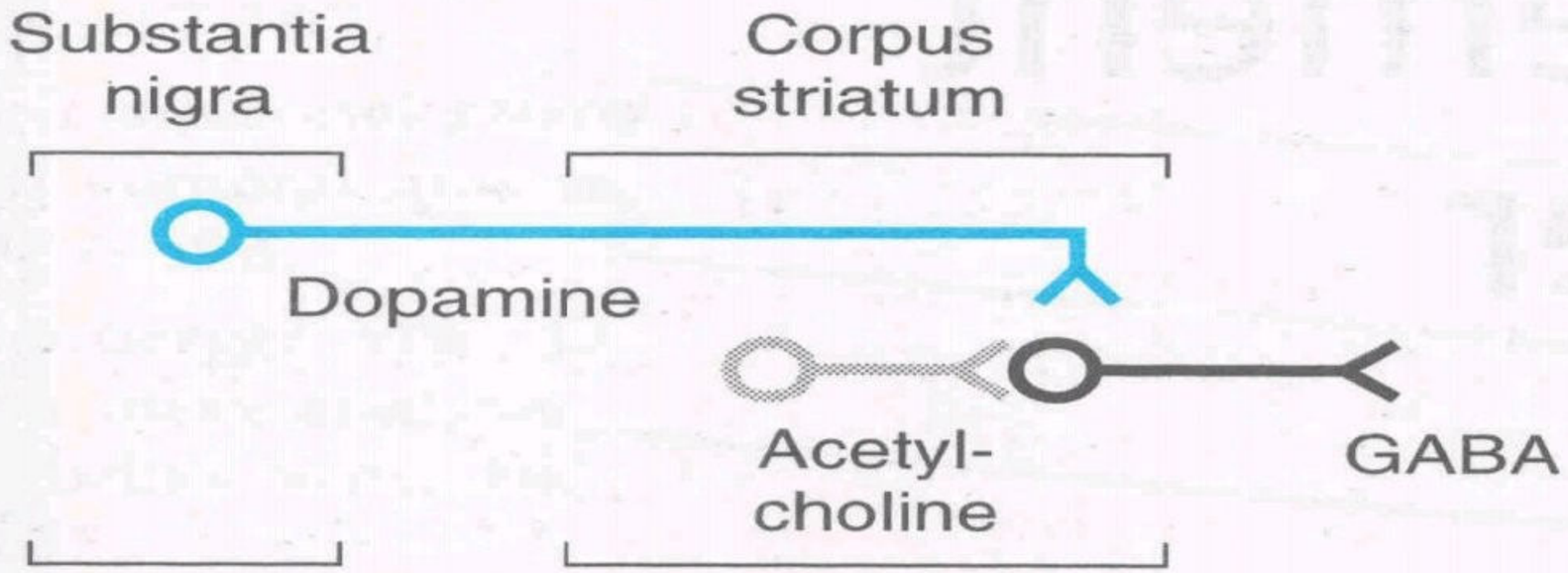
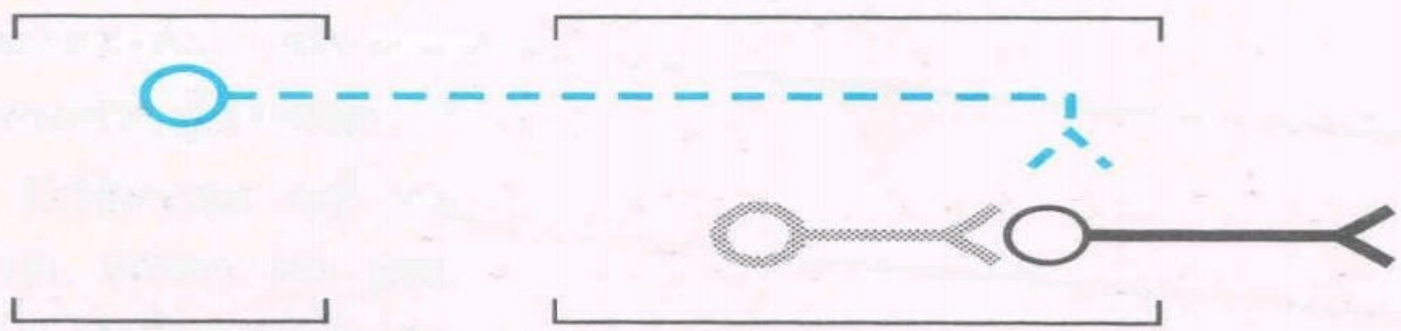
Drugs Used in Parkinson's Disease

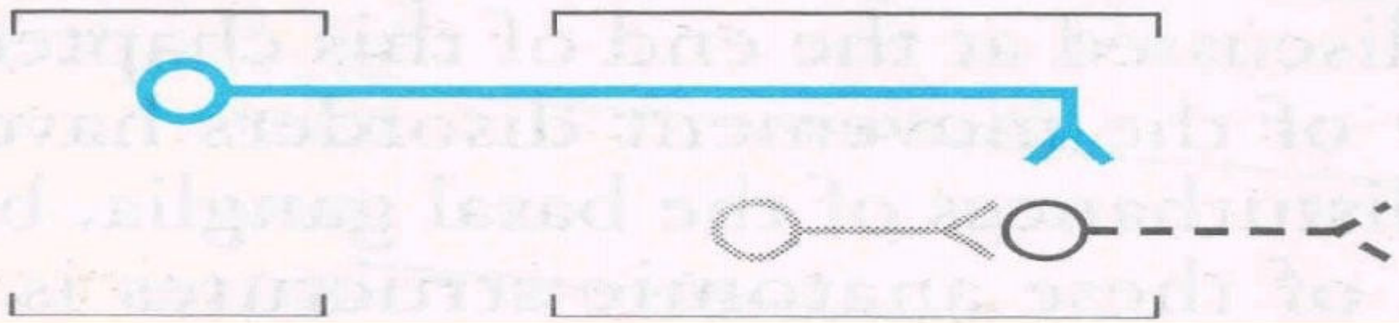
Normal



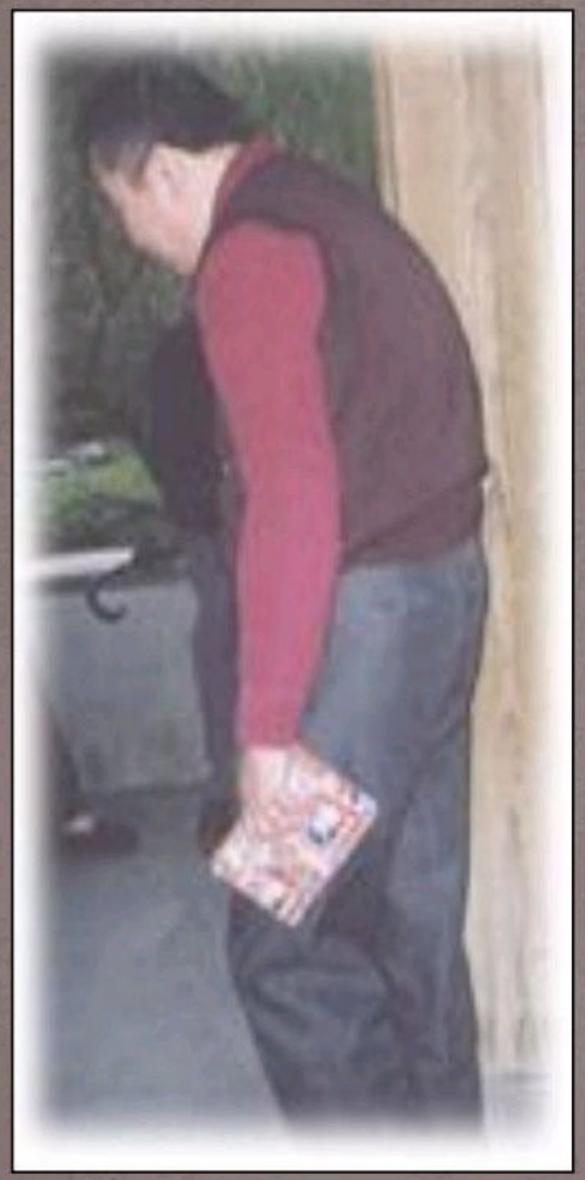
Parkinsonism

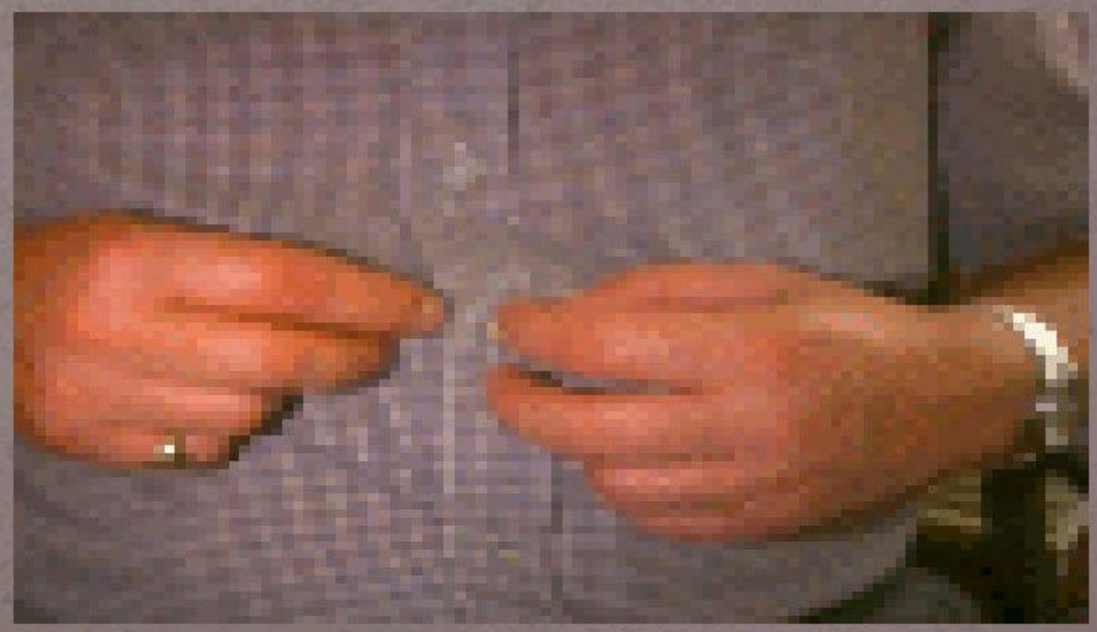


Huntington's disease



Symptoms of Parkinsonism

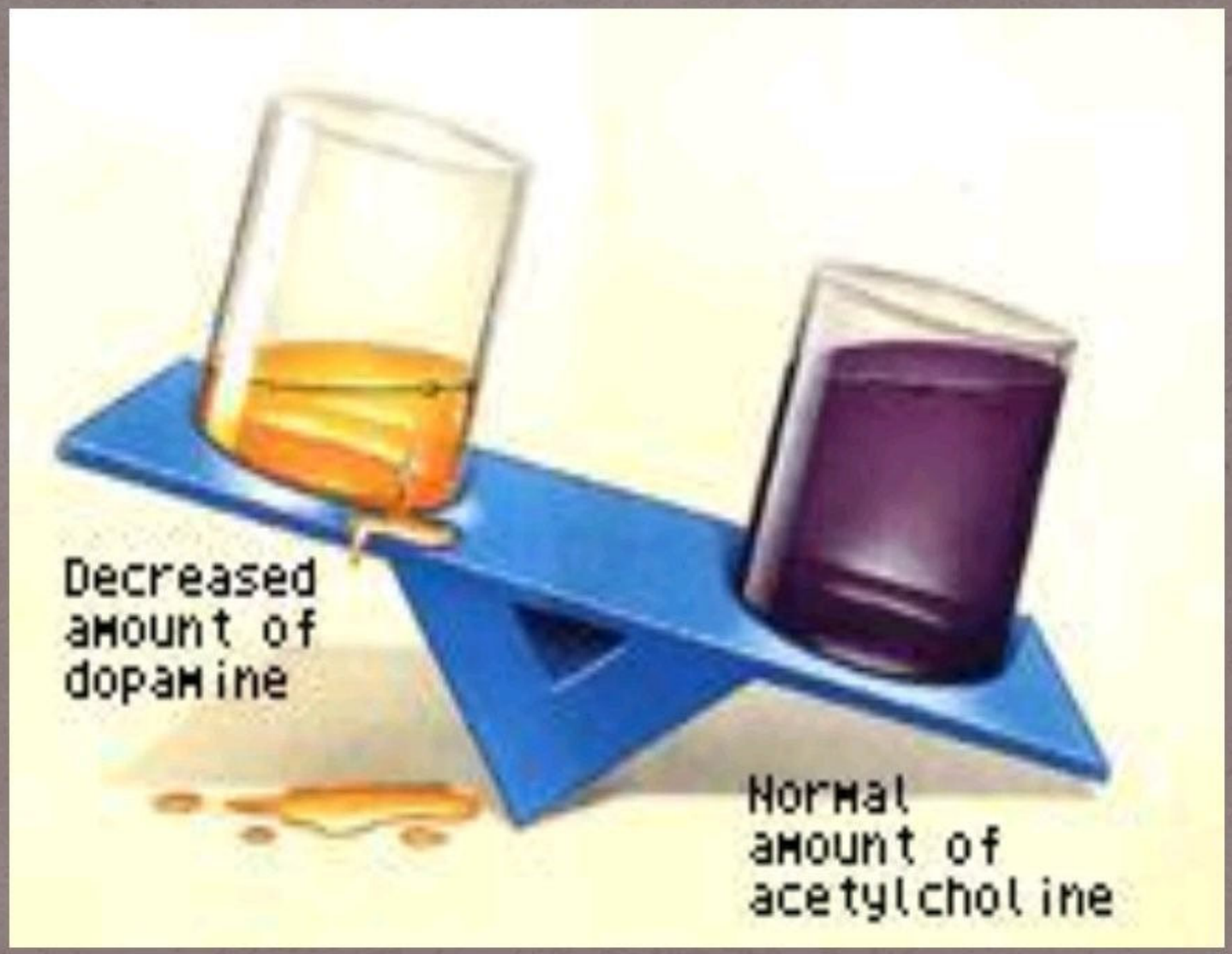




Introduction

- Characterized by **rigidity, tremor & hypokinesia**
- Secondary manifestation – defective posture & gait, mask like facies, sialorrhea, dementia
- Death due to chest infection/ embolism
- Deficiency of Dopamine in substantia nigra
- Mostly Idiopathic, then due to arteriosclerosis, Wilson's disease, toxin (N-methyl-4-phenyl tetrahydropyridine (MPTP)), Drugs

Strategy of Treatment



Classification

- Drugs affecting Brain Dopaminergic System

1. Dopamine Precursor's – Levodopa
2. Peripheral Decarboxylase inhibitors – Carbidopa, Benserazide
3. Dopaminergic Agonist – Bromocriptine, Pergolide, Piribedil, Ropinirole, Pramipexole
4. MAO-B inhibitors – Selegiline
5. COMT inhibitor – Entacapone, Tolcapone
6. Dopamine Facilitator – Amantidine

- Drugs affecting Brain Cholinergic System

1. Central Anticholinergics – Trihexyphenidyl, Biperiden
2. Antihistaminics – Orphenadrine, Promethazine

Dopamine Receptors

Type	Subtype	Receptor subtype	Location
D1 type	D1	Excitatory , ↑cAMP & PIP2	Striatum
	D5	Excitatory , ↑cAMP & PIP2	Neocortex, Midbrain, Medulla, Hippocampus
D2 type	D2	Inhibitory, ↓AC, ↑K^+	Striatum, Pituitary
	D3	Inhibitory, ↓AC, ↑K^+	Nucleus Accumbans, Hypothalamus
	D4	Inhibitory, ↓AC, ↑K^+	Neocortex, Midbrain, Medulla, Hippocampus

Levodopa

- Immediate precursor of Dopamine, > 95% decarboxylated in the peripheral tissues, 1-2% enters the crosses the BBB – taken up, stored & released as transmitter
- Action – CNS – marked symptomatic improvement – hypokinesia > rigidity > secondary symptoms (posture, gait, handwriting, speech, facial expression, mood, self care, interest in life) – general alerting response - progress to frank psychosis
- CVS – Tachycardia, postural hypotension,
- CTZ – excitatory – elicits nausea & vomiting
- Endocrine – inhibits prolactin release, increases GH release,

Levodopa (cont'd)

- P/K – rapidly absorbed in small intestine, gastric emptying slows absorption, amino acid decrease absorption, high first pass metabolism, plasma half life 1-2 hrs
- AE – frequent, troublesome, dose related, reversible

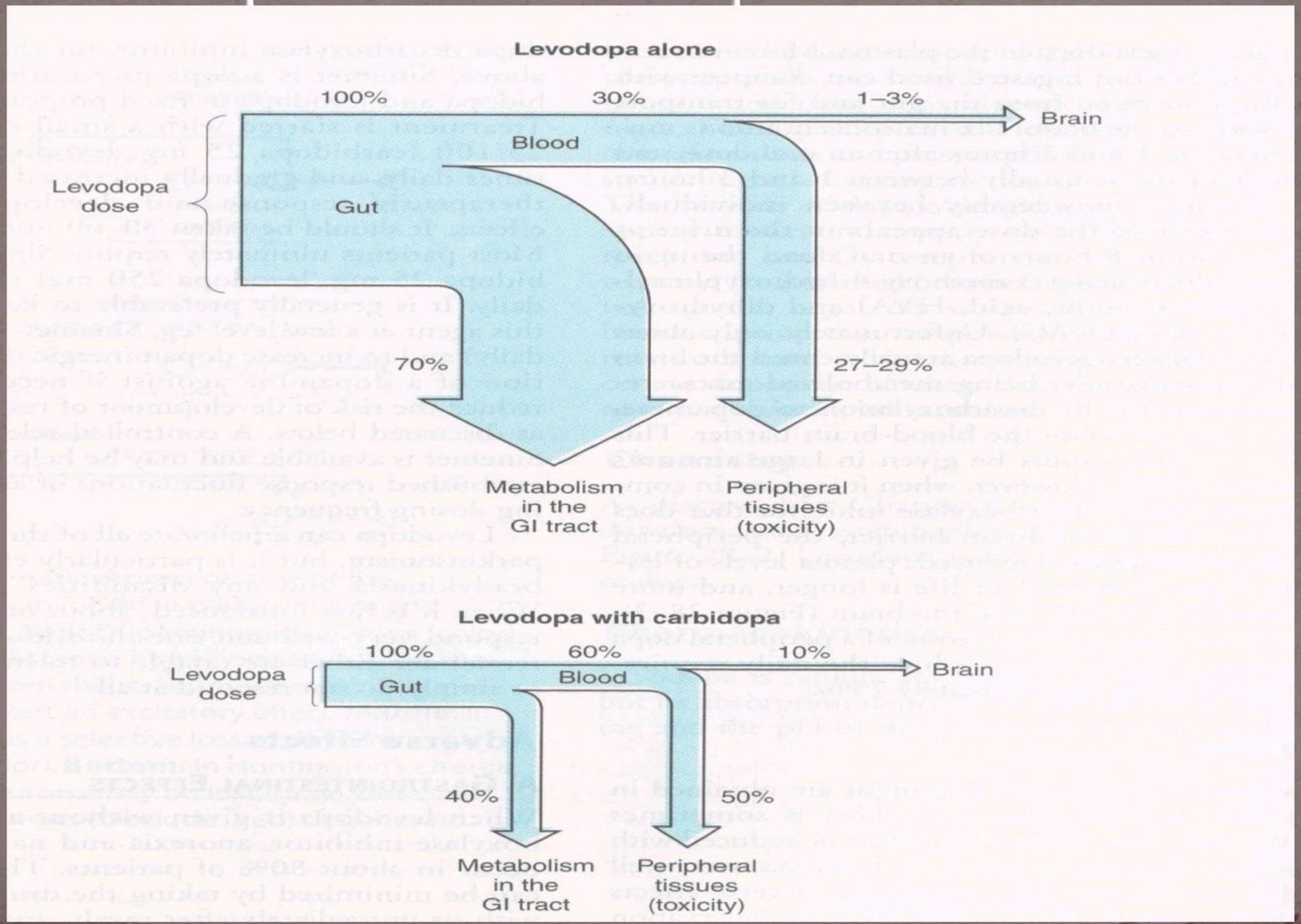
1. At the initiation of therapy – Nausea & vomiting, postural hypotension, cardiac arrhythmia, exacerbation of angina, alteration in taste
2. After Prolonged therapy – Abnormal movement (facial tics, grimacing, choreoathetoid movement – reduction in dose), behavioral effects (mild anxiety, nightmares, depression, frank psychosis), Fluctuation in motor performance – end of dose detioration (on-off effect, all or none response)

Levodopa (cont'd)

- Caution – elderly, IHD, cerebrovascular , psychiatric, hepatic & renal disease, peptic ulcer glaucoma, gout
- Interactions

1. Pyridoxine – abolish therapeutic effect
2. Phenothiazines, Butyrophenols, & Metoclopromide – diminish therapeutic effect
3. Non selective MAO – Inhibitors – hypertensive crisis
4. Antihypertensive – postural hypotension accentuated
5. Anticholinergic drugs – additive antiparkinsonian effect

Levodopa + Carbidopa



Peripheral Decarboxylase Inhibitors

- Extra cerebral dopa decarboxylase inhibitors – does not cross BBB – inhibits peripheral conversion of levodopa to dopamine
- Benefits – plasma t1/2 of Levodopa prolonged & dose reduced, systemic conc. of DA reduced, pyridoxine reversal effect of Levodopa does not occur, on-off effect minimized, higher improvement
- Problems not resolved/ accentuated - involuntary movements, behavioral abnormalities, postural hypotension
- Combination as co-careldopa – Levodopa + Carbidopa (10/25 mg + 100/250 mg)

Dopaminergic Agonist

- On Striatal DA receptor even in advanced disease, longer acting, more selective
- Bromocriptine – ergot derivative, potent D2 agonist & D1 partial agonist, improvement 1-1.5hrs & up to 6-10 hrs, high dose expensive & lots of AE (vomiting, hallucination, hypotension, nasal stuffiness, conjunctivitis, fall in BP) in late disease as Levodopa supplement (1.25 -10 mg thrice daily), smoothens end of dose & on-off fluctuation
- Pergolide – 10 times more potent than Bromocriptine, clinical efficacy & role similar
- Piribedil – apomorphine like DA agonist

Dopaminergic Agonist (cont'd)

- Ropinirole & Pramipexole – D2/D3 agonist, supplementary drug to levodopa, AE like Bromocriptine, dose titration, also used as monotherapy, afford symptomatic relief like Levodopa, less dyskinesia & motor fluctuation, rapidly absorbed, PPB, metabolized in liver
- AE – nausea, dizziness, hallucination, postural hypotension

MAO – Inhibitors

- Selegiline – selective MAO-B inhibitor, in low doses no interference with metabolism of peripheral catecholamine metabolism, intracerebral degradation of DA retarded, high dose cause hypertensive interaction
- Mild antiparkinsonism action in early cases, prolong Levodopa action, attenuates motor fluctuation & decrease wearing off, early therapy might delay the progression of disorder
- AE – Postural hypotension, nausea, confusion, accentuation of Levodopa induced involuntary movement
- C/I – Convulsion
- Interaction – pethidine (excitement, rigidity, hyperthermia, respiratory depression)

COMT Inhibitor

- Selective , potent & reversible as adjuvant to Levodopa – Carbidopa, prolongs the half life of Levodopa, large fraction crosses the brain, Entacapone & Tolcapone have peripheral effect
- Smoothen wearing off, increase on time & decrease off time, improves activity of daily living, & allows Levodopa dose to be reduced
- Worsening of Levodopa AE, diarrhea, yellow orange discoloration of urine
- Tolcapone causes acute fatal hepatitis & Rhabdomyolysis

Dopamine Facilitator

- Amantidine – acts rapidly, low efficacy acts by promoting Presynaptic synthesis & release of DA in brain
- For milder cases/ short courses to supplement submaximal dose of Levodopa
- AE – insomnia, dizziness, confusion, nightmares, hallucinations, livedo reticularis (vasoconstriction)

Central Anticholinergics

- 10-25% improvement in clinical features, lasting 4-8 hrs after single dose, tremor benefitted more then rigidity, hypokinesia, controls sialorrhea
- Cheap & produce less side effects, used alone or in combination with Levodopa, for drug induced parkinsonism
- Trihexyphenidyl most commonly used

General points

- None of the drugs alter disease pathology
- For mild cases – central anticholinergics, Dopaminergic agonist monotherapy
- Standard therapy – Levodopa + Carbidopa – full benefit lasts for 2-3 years
- Subsequently levodopa benefit wean off
- Combination of Decarboxylase inhibitor – increase efficacy & reduces early AE
- Advanced case two-three drug combination used