ANTIPARKINSONIAN DRUGS

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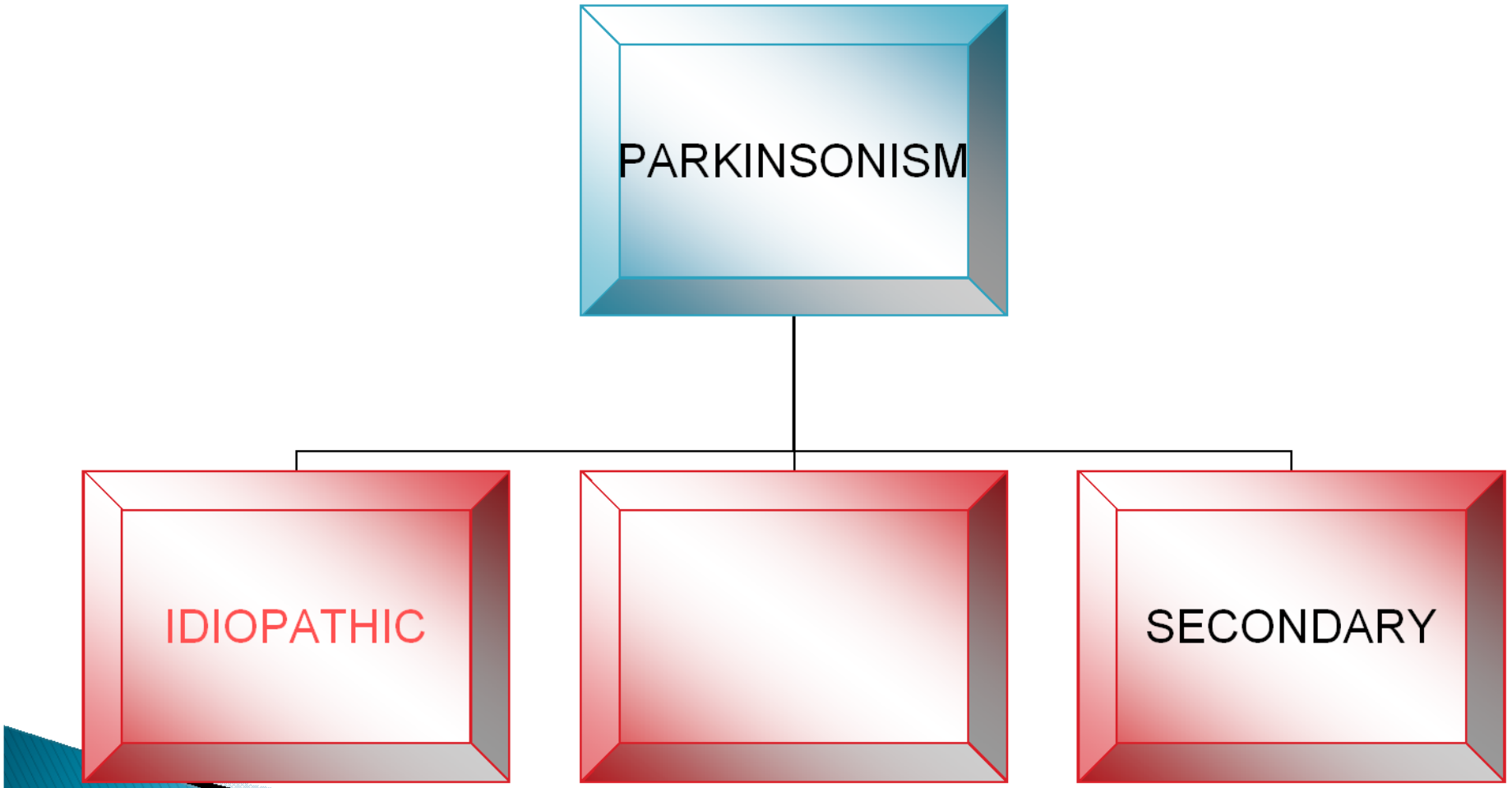
PARKINSONISM DISEASE (PD)

- Sir James Parkinsonism (1817)

- **Marked deficiency of dopamine (20-40%) and an ↑ed activity of Ach in Corpus striatum and Substantia nigra → Hypokinesia, Rigidity and Tremor.**

- **Neurotoxin - MPTP produces destruction of Nigrostriatal dopaminergic neurones**


PARKINSONISM
IDIOPATHIC
SECONDARY

Primary Manifestations

- Tremors
- Rigidity
- Hypokinesia

Secondary Manifestations

- Mask like face
- Sialorrhoea
- Dementia
- Shuffling Gait with short paces
- Defective posture
- Speech, hand writing, mood disturbance

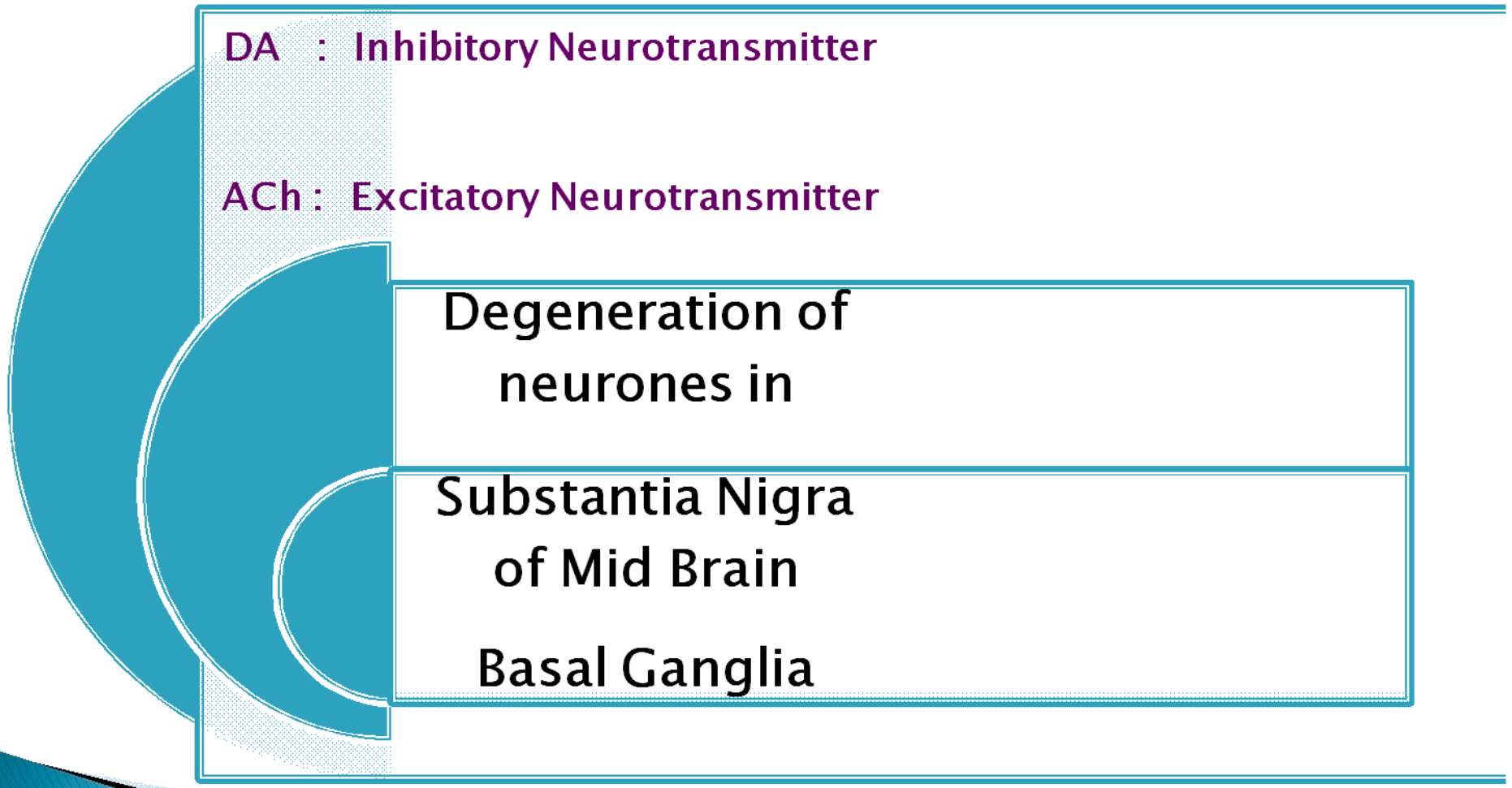
Drug – Induced Parkinsonism

- Anti-psychotics :- Chlorpromazine, Haloperidol
- Prokinetics : – Metoclopramide
- Reserpine – Depletes Dopamine store
- Alpha – Methyldopa – Decreases dopamine synthesis

Treatment of Drug – Induced Parkinsonism

- Centrally acting Anti-cholinergic Agents : – Benztropine, Benzhexol (Trihexyphenidyl)
- Antihistaminic drugs with Cholinergic Activity :– Diphenhydramine and Promethazine
- LEVODOPA NOT USEFUL IN DRUG – INDUCED PARKINSONISM

Extra – pyramidal disorder



CLASSIFICATION

(I) Drugs influencing brain Dopaminergic system:-

a) Dopamine precursor : Levodopa (L – dopa)

b) Dopamine agonists (D1 and D2) :

- **Ropinirole , Pramipexole**
- **Bromocriptine, Lisuride, Pergolide**
- **Apomorphine, Piribedil**

c) Peripheral Decarboxylase Inhibitor :

* **Carbidopa, Benserazide**

d) Dopamine releasing drug : Amantadine

e) Selective MAO-B inhibitor : Selegiline

f) COMT inhibitor :- Entacapone, Tolcapone

II) Drugs affecting brain cholinergic system :

1. Centrally acting Anti – cholinergics:
   Benztropine, Benzhexol (Trihexyphenidyl)

2. Antihistaminics with anti-cholinergic activity :Promethazine, Diphenhydramine, Orphenadrine

III. Implantation of dopamine rich fragments of brain or adrenal cortex into corpus striatum.

Levodopa (L-DOPA)

1. **CNS : In idiopathic parkinsonism**

2. **Is a Pro-drug ; (5%) of L-dopa crosses BBB and is converted to DA in brain ; while (95%) of L-dopa is converted peripherally to DA by decarboxylase enzyme.**

3. **Hence, used in combination with peripheral decarboxylase inhibitors – Carbidopa / Benserazide**

4. **L-dopa improves all symptoms of PD, but does not stop the progression of the disease.**

- **On behaviour : It produces general alerting response**
- **In some pts : frank psychosis**
- **Disproportionate ↑ in sexual activity**
- **Dementia does not improve**
- **In hepatic coma :Non– specific awakening**

PHARMACOKINETICS

- L-Dopa rapidly absorbed from small intestine by active transport

- AA in food affect absorption
- Hence, 30-60 mins before food
- Pyridoxine : ↓Bioavailability of L-dopa
- Gastric emptying-if slow : ↓ absorption

ADRs of L-dopa

Acute effects (At the Beginning of Therapy)

1. **GIT : N, V, Anorexia. (L-Dopa – induced vomiting treated with Domperidone & not with Metoclopramide). Taste altered.**

2. **CVS : Postural hypotension, Tachycardia, Palpitation & cardiac arrhythmias.**

3. **CNS : Psychosis like syndrome (Hallucinations, delirium, disorientation , insomnia , nightmares) due to excess DA. Give drug - free holidays.**

On Chronic Use of L-Dopa :-

4. **Abnormal involuntary movements (Dyskinesias) after (2) yrs of therapy**
5. **Fluctuations in motor performance after (2-5 yrs) of therapy.**

‘ On – Off ’ effect :-

Being ‘On’ (means relief of most of the symptoms but with disturbing dyskinesias).

Being ‘Off’ (means loss of beneficial effects)

SR –L–Dopa produces more stable pl. conc and helps reduces ‘On–Off’ Phenomenon.

ADRs of L-Dopa

6. ‘ **Wearing off’** → End of dose akinesia effect due to decrease in Plasma concentration of L-Dopa towards the end of dose interval.

   [Administer smaller & more frequent doses of L-Dopa to prevent **‘Wearing-off’** effect].

7. **Miscellaneous :-** Mydriasis, acute attack of glaucoma, brownish discoloration of saliva & urine, precipitation of gout.

Drug-interactions of L-Dopa

1. **Pyridoxine x L-dopa → Pyridoxine (Vit B6) enhances peripheral decarboxylation of L-dopa → Less L-dopa crosses BBB → Hence, abolishes L-dopa therapeutic effect.**

2. **MAOIs x L-dopa → Severe Hypertension. Stop 2 weeks before L-dopa therapy.**

3. **Reserpine x L-dopa → Reserpine antagonizes its action by preventing entry of dopamine into synaptic vesicles.**

4. **Metoclopramide/Phenothiazines x L-dopa → Antagonizes the action of L-dopa, because they crosses BBB and antagonizes DA2 receptors in brain.**

Rationale of L-dopa(100mg) + Carbidopa (25mg) Combination

Carbidopa is a inhibitor of decarboxylase enzyme peripherally.

Hence, prevents peripheral conversion of L-dopa and drives more L-dopa in brain.

Benefits produced are :-

1) **Prolongs plasma – half (t1/2) of L-dopa → reduces its dose**
2) **Helps attain therapeutic dose of L-dopa by reducing systemic concentration & nausea & vomiting**
3) **Minimizes cardiac side effects**
4) **'On-Off' effect minimized due to sustained cerebral DA conc.**
5) **Pyridoxine can be given , since levodopa effect is not reversed by Pyridoxine in presence of carbidopa.**
6) **Achieves higher degree of improvement**

DOPAMINERGIC AGONISTS (ROPINIROLE AND PRAMIPEXOLE)

- Non-ergoline selective D2(Ropinirole)/D3 (Pramipexole) receptors agonists
- Also acts on post synaptic DA receptors & on pre synaptic autoreceptors (D2).
- Has minimal affinity for D1 or non-dopaminergic receptors
- Used as monotherapy for early PD
- Used in combination with L-dopa in advanced cases of PD → smoothens out the response of L-dopa → reduces dose of L-dopa.

DOPAMINERGIC AGONISTS (ROPINIROLE AND PRAMIPEXOLE)

- By acting on pre-synaptic receptors → reduces DA production & its release → diminish oxidative stress
- Has neuro-protective effect → scavenges H_2O_2 → enhance neuro-trophic activity.
- Well tolerated, can be initiated more quickly
- Preferred as initial treatment of PD over L-dopa because of longer t1/2, less on/off effect & less dyskinesias
- **Adverse Effects are :-**
- Postural hypotension, somnolence, fatigue, peripheral edema, constipation, hallucinations and confusion.
- Ropirinole : Dose ; 0.25mg TDS; Pramipexole : Dose: 0.125 mg TDS

DOPAMINERGIC AGONISTS (Bromocriptine)

- Is an ergot alkalod
- Is a D2 receptor agonist
- Has partial agonist or antagonist effect on D1 receptors
- Inhibits prolactin release
- In PD, rapid improvement in symptoms within 1hr of oral administration → effects lasts up to 8-10 hrs
- In PD, not used alone because high doses needed & increase risk of severe S/Es.

DOPAMINERGIC AGONISTS (Bromocriptine)

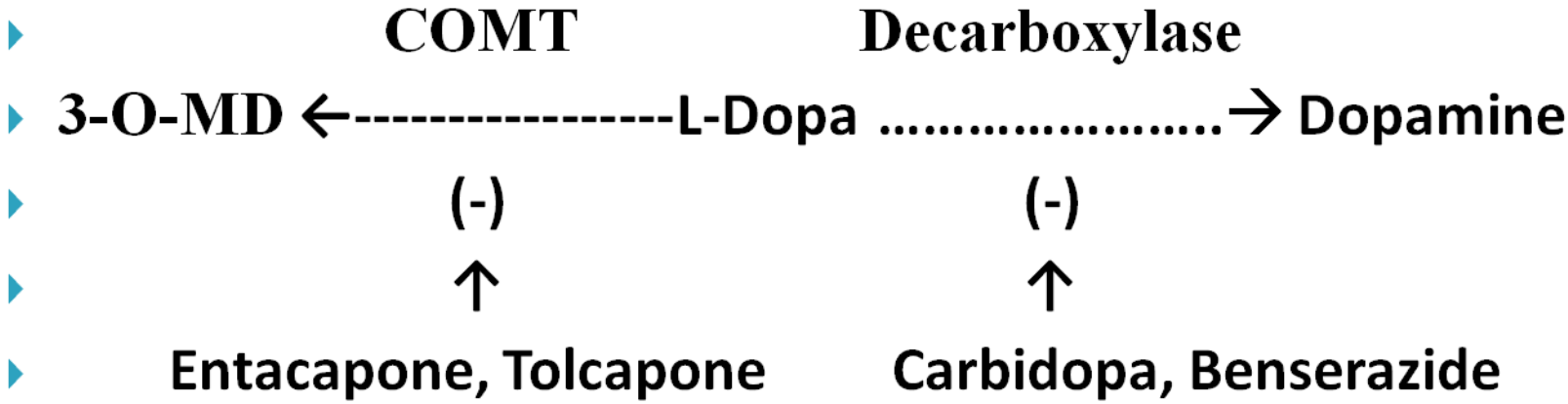
- **USES :-**
- 1) PD in advance case with L-dopa.
- 2) In PD who do not respond to L-dopa and have become resistant because of loss of dopaminergic neurones
- 3) Hyperprolactinaemia causing amenorrhoea –galactorrhoea →leading to infertility in females. Reduces size of adenoma .
- 4) Acromegaly
- 5) Neuroleptic malignant syndrome
- 6) To suppress puerperal lactation
- 7) Chronic post-systemic encephalopathy (cause arousal)
- 8) Acute cocaine withdrawal syndrome

(Bromocriptine – Adverse Effects)

- Postural Hypotension, GI upset
- Bleeding from peptic ulcer, drowsiness, nasal congestion
- Leg cramps, psychiatric & neurological disturbances
- Cardiac arrhythmias, digital vasospasm
- Retroperitoneal fibrosis
- Avoid :-
- In pregnancy
- In Patients with heart disease, PVD

COMT – Inhibitors

- **Eg. Entacapone and Tolcapone**
- **Both are potent and selective reversible inhibitors of COMT**
- **They inhibit methylation of L-dopa centrally & peripherally**
- **They reduce the clinical symptoms of 'Wearing – Off' in patients treated with L-dopa / Carbidopa**



Entacapone vs Tolcapone

Entacapone	Tolcapone
Peripheral effect → More L-dopa enters brain	Central and peripheral action
Less potent	More potent
Shorter duration of action. T1/2 = 2 hrs. Given with each dose of L-dopa	Longer duration of action
Dose ; 200 mg with each meal → 4-6 times in a day	Dose : 100 mg TDS
Not Hepatotoxic	Hepatotoxic . Increases liver enzymes → Acute fatal Hepatitis and rhabdomyolysis. Withdrawn in Europe & Canada

Advantages of COMT-inhibitors

- Selectivity of central & peripheral action
- Given as adjuvant with L-dopa+ Carbidopa in advance PD
- Blocks methylation pathway & prevent conversion of L-dopa to 3- O- MethylDopa
- Prolongs T1/2 of L-dopa → allows larger fraction of drug to cross BBB & enters brain
- COMT degrades DA in brain, COMT-inhibitors prevents degradation & preserves DA in brain
- Enhance & prolongs therapeutic effect of L-dopa/carbidopa in Advance & fluctuating PD
- Smoothen 'Wearing – off' ; increase 'on' time & decrease 'off' time → improves daily living activities.

Selective MAO-B Inhibitors (Selegiline)

- **Selegiline is a selective inhibitor of MAO-B**
- **Prevents breakdown of Dopamine**
- **Leads accumulation of DA in brain**
- **Used alone in early stages of PD → Retards progression of symptoms**
- **Used with L-dopa to prolong its action, attentuates motor fluctuations & decreases 'wearing-off' effect**
- **Beneficial in 50-70% pts with early symptoms.**
- **Clinical effects are short lasting (6-24 months)**
- **It inhibits oxidation of Neurotoxin MPTP to active metabolite MPP → prevents Neurotoxin formation**

SELEGILINE

MOA : Dopamine

MAO –B (–)← selegiline

(DOPAC) Dihydroxy phenylacetic acid)

COMT

HVA

- Selegiline →
- **Prolongs L–dopa action**
- **↓ motor fluctuations**
- **↓ wearing off effect**
- **20-30 % reduction in L- dopa dose**
- **May modify the natural course of the disease**

Selegiline -- ADRs

- **Post–hypotension**
- **Nausea**
- **Confusion**
- **Psychosis**
- **Aggravation of L-dopa induced involuntary movements**

Selegiline :

C / I : Epilepsy

Preparation : tab : 5 mg

Dose : 5mg b.i.d.

Amantadine

- **Discovered as an antiviral drug for prophylaxis of Influenza A2, but Found useful in PD**
- **Antagonises NMDA type of Glutamate receptors → promotes pre-synaptic synthesis & release of DA in the brain (Acts As DA –Facilitator). Also ↓ neuronal uptake.**
- **OOA is Rapid and lasts for 8-12 hrs. Dose : 100mg BD**
- **Effective in milder cases or short course along with L-dopa in advanced disease → Suppress motor fluctuations and abnormal movements.**
- **ADRs – *Livedo Reticularis* (due to local release of CAs causing vasoconstriction) and *ankle edema*.**

Principles of Anti-Parkinsonism Therapy

- **1) Anti-parkinsonian drugs only provides symptomatic relief and extends happier and productive life for 3-6 yrs.**

- **2) None of the drugs alter the basic patho-physiology of the PD. The disease continues to progress even with treatment.**

- **3) In mild, initial stage of disease, treat the patient with Selegiline or anticholinergic drugs.**

Principles of Anti-Parkinsonism Therapy

- **4) In early cases, mono therapy with DA- agonists Ropinirole or Pramipexole can be used.**
- **5) Selegiline + L-dopa combination started during deterioration phase to overcome 'wearing-off' effect.**
- **6) L-dopa + Carbidopa combination therapy should be started slowly over 2-3 months, and dose titrated towards increase dose, once the tolerance to early side effects has developed.**

Principles of Anti-Parkinsonism Therapy

- **7) Full benefits with L-dopa+Carbidopa lasts upto 2-3 yrs, then response starts declining.**

- **8) Levodopa alone can be used only once the patient develops intolerable dyskinesias with L-dopa+ Carbidopa combination.**

- **9) Amantadine + Levodopa used for brief period during exacerbation phase.**

Principles of Anti-Parkinsonism Therapy

- **10) In Late cases, directly acting DA agonists Ropinirole / Pramipexole / Bromocriptine can be supplemented with L-dopa to smoothen 'On-off' phenomenon ; to reduce l-dopa dose and to minimize dyskinesias.**

- **11) In advanced cases, COMT – inhibitors Entacapone can be added to L-dopa+ Carbidopa combination or Selegiline or DA agonists to prolong the action.**

FAQs on AntiParkinsonian drugs

- 1) Classify antiparkinsonian drugs. Describe the drug therapy of Parkinsonism disease.

- 2) Justify the rationale behind use of :-
- i) Levodopa + carbidopa combination in PD
- ii) Ropirinole in PD
- iii) Selegiline in PD
- iv) Entacapone in PD

FAQs on AntiParkinsonian drugs

- Name the drugs which induces parkinsonism like symptoms. What is the treatment of drug-induced parkinsonism?

- Why domperidone and not metoclopramide is used as an anti-emetic to prevent vomiting -induced by anti-parkinsonian drugs?

THANK YOU ALL