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PSYCHIATRIC DRUG HANDBOOK



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Om Prakash Singh

2nd Edition

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CHAPTER 4

Dopamine and Drugs Used for Parkinson's Disease

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DOPAMINE

- First synthesized in 1910.
- Consists of a catechol moiety linked to ethylamine.
- Closely related to melatonin.
- Transitional compound in the synthesis of noradrenaline (NA) and adrenaline.
- Polar compound does not cross blood-brain barrier (BBB) easily.
- Amino acids phenylalanine and tyrosine are precursors.
- Dopamine (DA) is neither excitatory nor inhibitory, it is rather modulator; influenced by both excitatory glutamate and inhibitory GABA input **(*see* Flowchart 2, Chapter 1)**.
- Drugs of abuse cause increase in DA in nucleus accumbens.
- D_2 receptor plays important role in schizophrenia. Hence, antipsychotic drugs are high affinity antagonists for the D_2 receptor.
- DA receptor agonists are now used in treatment of Parkinson's disease, restless leg syndrome, and hyperprolactinemia; major limitation being lack of receptor selectivity.

Physiologic Actions

Heart

- At low concentrations, stimulates vascular D_1 receptors, causing vasodilation and reducing cardiac afterload,

hence decrease in blood pressure (BP) and increase in cardiac contractility. In high concentrations, DA stimulates β receptors to increase cardiac contractility.

- In even higher concentrations, circulating DA activates α receptors, hence vasoconstriction and increase in BP.

Kidney

- Binds to both D_1 and D_2 receptors.
- Renal DA causes natriuresis, increase in both renal blood flow and glomerular filtration rate (GFR).
- Activation of D_1 receptors influences renal sodium transport and vascular hemodynamics.

Pituitary Gland

Secretion of prolactin from the pituitary gland.

Catecholamine Release

- D_2 receptor provides tonic inhibition of epinephrine release from the adrenal medulla and norepinephrine (NE) release from sympathetic nerve terminals.
- D_1 receptor stimulates release of epinephrine from adrenal medulla and NE from nerve terminals.

Central Nervous System

- DA in brain is projected via four main pathways: (1) Mesolimbic, (2) mesocortical, (3) nigrostriatal, and (4) tuberoinfundibular pathways.
- Parkinson's disease is a neurodegenerative disorder of unknown etiology, characterized by extensive degeneration of dopaminergic neurons in substantia nigra, resulting in tremor, rigidity, and bradykinesia.

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- Neurodegenerative disorders are characterized by progressive and irreversible loss of neurons from specific regions of the brain, e.g., Parkinson's disease, Huntington's disease, Alzheimer's disease, loss of neurons of hippocampus and cortex leading to impairment of memory and cognition. Parkinson's disease and Huntington's disease cause loss of neurons of basal ganglia leading to abnormalities in control of movement. Amyotrophic lateral sclerosis causes degree of spinal, bulbar, and cortical motor neurons.
- Abnormal proteins associated with neurogenic disorders, alpha synuclein seen in Parkinson's disease, huntingtin seen in Huntington's disease, amyloid beta in Alzheimer's disease, and TDP-43 seen in amyotrophic lateral sclerosis.
- Parkinson's disease was first described by James Parkinson in 1817 as paralysis agitans or "shaking palsy", presents with bradykinesia, muscular rigidity, resting tremor, impairment of postural balance leading to gait disturbance and fall.
- Pathological hallmark of disease is loss of pigmented dopaminergic neurons of the substantia nigra with the appearance of intracellular inclusions known as Lewy bodies.
- Idiopathic cause is the most common cause though stroke; dopamine receptor antagonists toxicity can also occur.
- Drug-induced parkinsonism can occur due to chronic drug therapy with DA receptor antagonists such as antipsychotics (e.g., haloperidol and chlorpromazine) and antiemetics (e.g., prochlorperazine and metoclopramide) which is generally treated with centrally acting anticholinergics.
- Disease progresses over 5–10 years to rigid, akinetic state.
- Death occurs from aspiration pneumonia or pulmonary embolism.

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DRUGS USED IN PARKINSONISM

Dopaminergic therapy is the mainstay treatment of parkinsonism. However, current approaches are directed toward identification of the cause and attempt to modify the neurodegenerative process. An excess of glutamate in brain leading to excitotoxicity and cell death, hence glutamate antagonists are used as neuroprotective therapy.

- DA precursor levodopa in combinations with peripheral decarboxylase inhibitors, carbidopa, or benztropine.
- *COMT inhibitors:* Entacapone and tolcapone
- *DA receptor agonists:* Apomorphine, bromocriptine, pramipexole, and ropinirole
- *MAO-B inhibitors:* Selegiline and rasagiline
- *Other medications:* Amantadine, centrally acting anticholinergics, e.g., trihexyphenidyl and benztropine
- *Others:* Glutamate antagonists—riluzole and memantine
- *Monoclonal antibody:* Aducanumab

Drugs/Combinations in Use

- *Carbidopa + levodopa:* 25 mg + 100 mg or 50 mg + 200 mg → two to three times daily.
- *Entacapone:* 200 mg with levodopa and carbidopa.
- *Tolcapone:* 100 mg with levodopa and carbidopa. May be hepatotoxic.
- *Apomorphine:* 2 mg subcutaneous (SC) → 6–18 mg/day causes vomiting.
- *Bromocriptine:* 1.25 mg → 2.5–15 mg/day. Long-term use associated with cardiac valve fibrosis.
- *Pramipexole:* 0.125 mg TDS.
- *Ropinirole SR:* 2 mg/day → 2–24 mg maximum dose per day.
- *Rasagiline:* 1 mg daily → 0.5–1 mg maximum dose per day.

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- *Selegiline:* 5 mg BD daily → 2.5–10 mg maximum dose per day.
- *Trihexyphenidyl:* 1 mg BD daily → 2–15 mg maximum dose per day.
- *Amantadine:* 100 mg BD daily → 100–200 mg maximum dose per day.

Levodopa

- L-3, 4-dihydroxyphenylalanine, the metabolic precursor of DA.
- Rapidly absorbs orally from small intestine by transport system of amino acids.
- Concentration of drug in plasma peak in 0.5–2 hours after an oral dose.
- Half-life is 1–3 hours.
- Rate and extent of absorption of levodopa depends on the rate of gastric emptying, pH of gastric juice, time of exposure to degenerative enzyme of gastric and intestinal mucosa, and presence of amino acids in diet.
- Entry of the drug into central nervous system (CNS) across the BBB is mediated by membrane transporter for aromatic amino acids.
- Levodopa is converted to DA by decarboxylation in the presynaptic terminals of dopaminergic neurons in the striatum.
- This DA is available for therapeutic action.
- After release it is either transported back to dopaminergic terminals by uptake mechanism or metabolized by MAO or COMT.

▪ DA COMT	→ 3 methoxytyramine
▪ ↓MAO	↓ MAO
▪ 3, 4-dihydroxyphenylacetic acid (DOPAC)	3-methoxy-4OH-phenylacetic acid (HVA)

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- In clinical practice, levodopa is always administered in combination with peripherally acting inhibitor of aromatic L-amino acid decarboxylase, e.g., carbidopa or benserazide.
- If levodopa is administered alone, the drug is largely decarboxylated by enzymes in the intestinal mucosa and peripheral sites, such that <1% of levodopa can ultimately cross the BBB.
- 25 mg of carbidopa and 100 mg of levodopa combination given three times or more daily.
- Levodopa produces dramatic improvement in early phase of disease but with time its buffering capacity is lost with onset of motor complications, "wearing-off" phenomenon disabling dyskinesias and the on-off phenomenon.

Adverse Effects of Levodopa

- Nausea, motor complications, hallucinations, and confusion, especially occur in elderly (clozapine and quetiapine appear to be effective).
- Activation of vascular DA receptors may produce orthostatic hypotension.
- *"Wearing-off" phenomenon:* Each dose of levodopa being effective only for a period of 1–2 hours; with reappearance of symptoms increase the dose and frequency can benefit to some extent but will result in:
  - *Dyskinesia:* Excessive and abnormal involuntary movements, especially when plasma concentration of levodopa is high.
  - "On-off" phenomenon.
  - Abrupt withdrawal of levodopa or other dopaminergic medications may precipitate leading to "neuroleptic malignant syndrome" of confusion, rigidity and hyperthermia, and may be potentially lethal.

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Treatment of levodopa-induced adverse effects:

- Levodopa-induced psychosis—atypical antipsychotics such as clozapine and quetiapine can be used in advanced Parkinson's disease.
- Pimavanserin an inverse agonist at 5-HT2 receptor is the Food and Drug Administration (FDA) approved for psychosis developed during levodopa therapy but itself can induce QT prolongation.
- Abrupt withdrawal of L-DOPA can recipitate neuroleptic malignant syndrome, so needs to be tapered off.
- Impulse control disorders, especially suicidal ideation can be treated with addition of MAO inhibitors but can induce hypertensive crisis, hence should be omitted at least before 14 days.

Formulations of levodopa used recently:

- Carbidopa + levodopa ER capsule
- Carbidopa + levodopa intestinal gel
- Levodopa inhalational powder (also effective during "off" periods)
- SC levodopa underdevelopment.

Dopamine Receptor Agonists

- Direct agonists of striatal DA receptors.
- Enzymatic conversion is not required for necessary activity; hence does not depend on functional capacities of nigrostriatal neurons.
- Longer duration of action and less propensity to cause dyskinesias compared to levodopa are an advantage.
- Often used in the management of dose-related fluctuations in motor state.
- May modify the course of Parkinson's disease by reducing endogenous release of DA, need of exogenous L-DOPA and

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decrease in formation of free radical; many practitioners prefer DA receptor agonists for younger patients.

- Ropinirole and pramipexole are better tolerated than older agents, bromocriptine, and pergolide.
- Selective activity at D_2 and D_3 receptor, no action on D_1 family.
- Absorbed orally, relieve symptoms of Parkinson's disease (like DOPA).
- *Side effects:* Sleep disturbances and impulse control disorders are of concern. Other adverse effects such as hallucinosis, confusion, nausea, orthostatic hypotension, fatigue, and somnolence can occur.
- Initiated at low dose and titrated slowly.
- It is better to switch over to some other agents if somnolence is troublesome.

Apomorphine

- Dopaminergic agonist administered SC.
- It has been used as "rescue therapy" in management of "on-off phenomenon" of L-DOPA therapy.
- Highly emetogenic, side effects similar to other DA agonists; used when other alternative therapies fail; available as sublingual and SC formulations.
- Concomitant use of apomorphine and 5-HT3 antagonist like ondansetron is contraindicated due to profound hypotension and loss of consciousness.
- It has high affinity to D_4 with moderate affinity to D_2, D_3, and D_5 receptors, low affinity to D_1 receptors. It also has moderate affinity to α_{1D}, α_{2B}, and α_{2C} receptors **(Table 1)**.
- Apomorphine therapy should be initiated with a 2 mg test dose in a setting where the patient can be monitored carefully.

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TABLE 1: Classification, distribution, and functions of dopamine (DA) receptors.

	D_1	D_2	D_3	D_4	D_5
Sites	Highest in CNS kidney, retina, and CVS	Predominantly expressed in brain	Limbic areas of brain	Retina (most abundant), partly in brain	Brain
Actions	Activates c-AMP PKA pathway and interacts with A_1 receptors, NMDA receptors, Na^+K^+ATPase calnexin, and caveolin	Occurs postsynaptically, regulates K^+ channels, L type and N type Ca^{+2} channels, arachidonic acid DA transporter			

(CNS: central nervous system; CVS: cardiovascular system)

- Apomorphine has been FDA approved for "rescue therapy" in acute intermittent "off" episodes of levodopa therapy.

COMT Inhibitors

- Principal therapeutic action of COMT inhibitor is to block the peripheral conversion of levodopa to 3-O-methyl DOPA, increasing both plasma t½ of levodopa as well as fraction of levodopa (each dose) which reaches CNS.
- The COMT inhibitors tolcapone and entacapone differ only in pharmacokinetic activities and adverse effects.
- Tolcapone has longer duration of action and appears to inhibit both peripheral and central COMT.

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- Entacapone has a shorter duration of action and principally inhibits peripheral COMT.
- Common adverse effects are nausea, orthostatic hypotension, confusion, and hallucination.
- Important adverse effect of tolcapone is hepatotoxicity; fatal fulminant hepatic failure has been reported.
- Opicapone is the new COMT inhibitor approved for use by the FDA.

Selective MAO Inhibitors

- The isoenzyme MAO-B is the predominant form in the striatum and responsible for most of the oxidative metabolism of DA in brain.
- Two selective MAO-B inhibitors commonly used are selegiline and rasagiline.
- Produce modest beneficial effects on symptoms of Parkinson's disease.
- Selegiline has been used for years and tolerated well in younger patients with early or mild disease.
- In advanced stage, selegiline may accentuate the adverse motor and cognitive effects of levodopa therapy.
- Recently orally disintegrating tablet or transdermal patch of selegiline is being used to prevent first pass metabolism and formation of amphetamine metabolites.
- Rasagiline does not produce amphetamine metabolites; effective as monotherapy in early Parkinson's disease, significantly reducing levodopa-related "wearing-off" symptoms.
- Rasagiline may have a neuroprotective role.
- MAO-B inhibitors are well tolerated but drug interactions are troublesome.

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- Newer addition, safinamide is the FDA approved for use. It also decreases glutamate release but should be avoided in hepatic disease.

Muscarinic Receptor Antagonists

- Trihexyphenidyl (2–4 mg TDS) and benztropine (1–4 mg BD) are currently used.
- Diphenhydramine also with antihistaminic action can also be used.
- All are adjunct drugs to dopaminergic therapy.
- *Side effects:* Sedation, mental confusion, constipation, urinary retention, and blurred vision are other adverse effects.

Amantadine

- Antiviral drug against influenza A appears to alter DA release in striatum.
- It also has anticholinergic activity and blocks NMDA glutamate receptors.
- Its action is modest, hence if used in initial treatment of mild Parkinson's disease, provides symptomatic relief.
- *Dose:* 100 mg BD.
- *Side effects:* Dizziness, lethargy, sleep disturbance, anticholinergic effects, nausea, and vomiting. Adverse effects are dose or duration related.

Istradefylline

- Adenosine A2A receptor antagonist, FDA approved for use as "adjunct therapy" during "off" periods of L-DOPA therapy.

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- A2A receptors are colocalized in the striatum with the D_2 receptors. A2A signaling can promote DA signaling and cause motor boosting.
- Well tolerated; side effects are nausea, daytime sleepiness, and dizziness.

Clinical Pearls

- Levodopa in combination with carbidopa is DOC as therapy.
- DA receptor agonists may be used as sole therapy initially or when L-DOPA fails to produce effect.
- Anticholinergics are preferred in young patients, where tremor is the main symptom, relieves tremor and rigidity more than bradykinesia.
- Drugs in general may be grouped as symptomatic therapy and neuroprotective therapy.
- DA agonists and rasagiline have neuroprotective role and are effective in both in early as well as late stages of the disease.
    - DA agonists are associated with a lower incidence of response fluctuations and dyskinesias.
    - Nowadays these drugs are either administered before initiation of L-DOPA therapy or along with low dose L-DOPA carbidopa combination.
    - Bromocriptine, pergolide, and cabergoline had severe adverse effects such as cardiac valvular damage and pulmonary fibrosis hence are not used. They have been replaced by the second-generation nonergot derivatives.
    - Selective MAOIs and COMT inhibitors can be added to L-DOPA carbidopa combination to minimize its

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