Pharmacology II, 4th Stage

Lippincott's Illustrated Reviews, 6th ed.

Unit III: Drugs Affecting the Central Nervous System

Neurodegenerative Diseases

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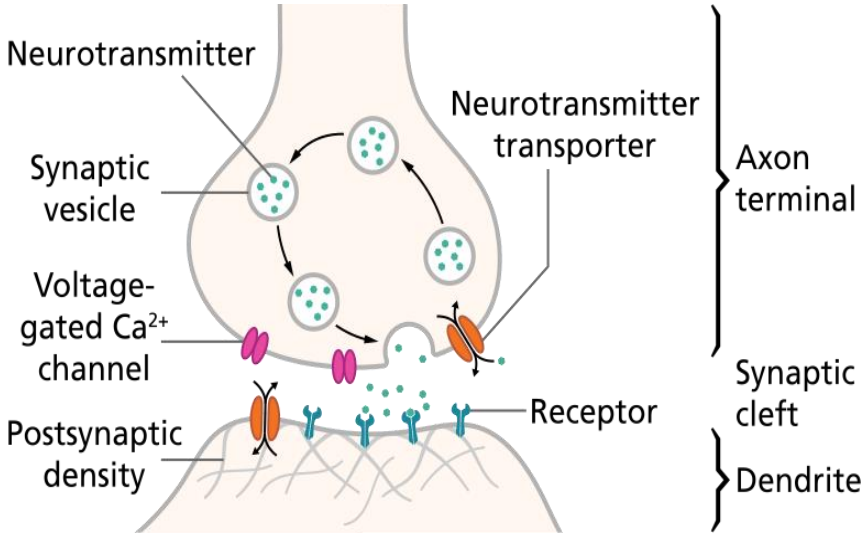
Introduction to CNS Pharmacology

- **Overview:**
- **Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process.**
- **Drugs affecting the CNS may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters.**
- **Other agents may activate or block postsynaptic receptors.**



Neurotransmission in the CNS

1- The CNS, unlike the peripheral ANS, contains powerful networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission.

2- In addition, the CNS communicates through the use of multiple neurotransmitters, whereas the ANS uses only two primary neurotransmitters, acetylcholine and norepinephrine.

3- In the CNS, receptors at most synapses are coupled to ion channels. Binding of the neurotransmitter to the postsynaptic membrane receptors results in a rapid but transient opening of ion channels. Open channels allow specific ions inside and outside the cell membrane to flow down their concentration gradients. The resulting change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either depolarization or hyperpolarization of the postsynaptic membrane (ion types and their direction of movement)

Synaptic potentials

Neurotransmitters can be classified as either excitatory or inhibitory, depending on the nature of the action they elicit.

A. Excitatory pathways

Stimulation of excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane. These excitatory postsynaptic potentials (EPSP) are generated by the following:

1) **Stimulation of an excitatory neuron causes the release of neurotransmitter molecules, such as glutamate or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium (Na+) ions.**
2) **The influx of Na+ causes a weak depolarization, or EPSP, that moves the postsynaptic potential toward its firing threshold.**
3) **If the number of stimulated excitatory neurons increases, more excitatory neurotransmitter is released. This ultimately causes the EPSP depolarization of the postsynaptic cell to pass a threshold, there by generating an all-or-none action potential. (Fig 8.2)**

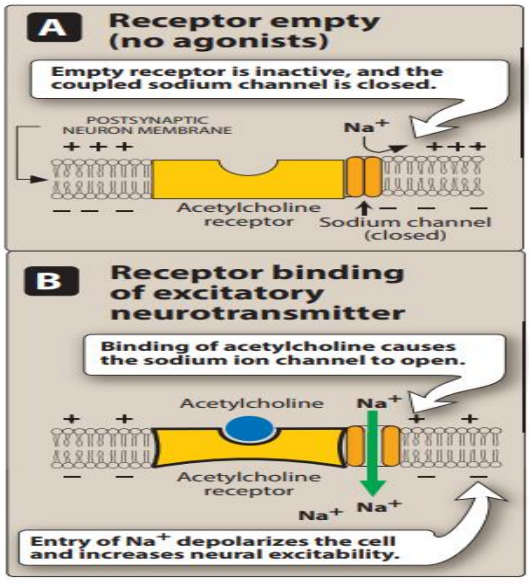


Figure 8.2
Binding of the excitatory neurotransmitter, acetylcholine, causes depolarization of the neuron.

B. Inhibitory pathways **Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane.**

These inhibitory postsynaptic potentials (IPSP) are generated by the following:

1) Stimulation of inhibitory neurons releases neurotransmitter molecules, such as γ-aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of specific ions, such as potassium (K+) and chloride (Cl−).

2) The influx of Cl− and efflux of K+ cause a weak hyperpolarization, or IPSP, that moves the postsynaptic potential away from its firing threshold. This diminishes the generation of action potentials.(Fig. 8.3)

C. Combined effects of the EPSP and IPSP **Most neurons in the CNS receive both EPSP and IPSP input. Thus, several different types of neurotransmitters may act on the same ways.**

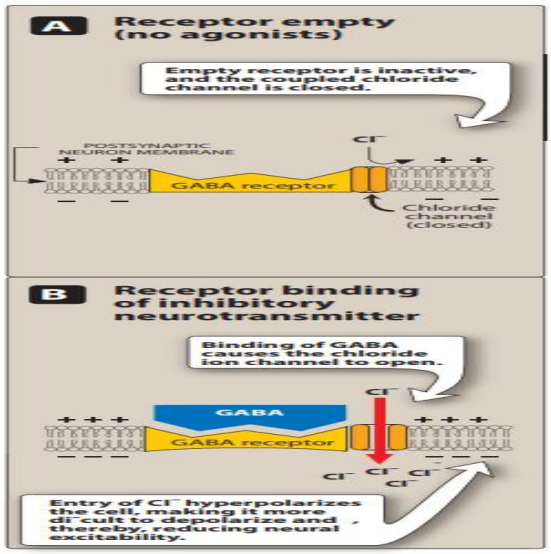
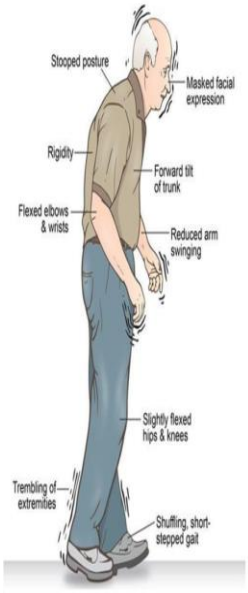


Figure 8.3
Binding of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), causes hyperpolarization of the neuron.

NEURODEGENERATIVE DISEASES

- **Neurodegenerative diseases of the CNS include Alzheimer's disease (AD), Parkinson's disease (PD),Multiple sclerosis (MS), and Amyotrophic lateral sclerosis (ALS).**
- **These devastating illnesses are characterized by the progressive loss of selected neurons in discrete brain areas (neurodegeneration), resulting in characteristic disorders of movement, cognition, or both.**
- **1- Parkinson disease (PD): is a progressive neurological disorder of muscle movement, characterized by rest tremors, muscular rigidity, bradykinesia (slowness in initiating and carrying out voluntary movements), and postural and gait abnormalities (cardinal signs).**

Most cases involve people over the age of 65, among whom the incidence is about 1 in 100 individuals.



T Tremor: shaking, usually starting on one side

R Rigidity: stiffness of the limbs, neck, or trunk

A Akinesia: loss or impairment in power of voluntary movement

P Posture and balance

- **Etiology**

A- The cause of PD is idiopathic for most patients, and is correlated with destruction of dopaminergic neurons in the substantia nigra with a consequent reduction of dopamine actions in the corpus striatum, parts of the basal ganglia system that are involved in motor control.

1. **Substantia nigra: The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons (Fig 8.4) that terminate in the neostriatum.**

Each dopaminergic neuron makes thousands of synaptic contacts within the neostriatum and, therefore, modulates the activity of a large number of cells.

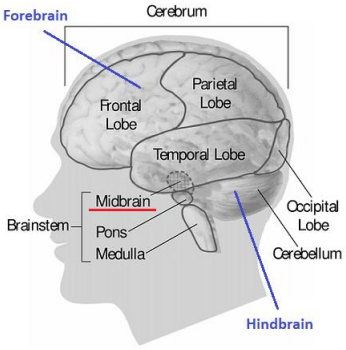
These dopaminergic projections from the substantia nigra fire tonically rather than in response to specific muscular movements or sensory input. Thus, the dopaminergic system appears to serve as a tonic, sustaining influence on motor activity, rather than participating in specific movements.

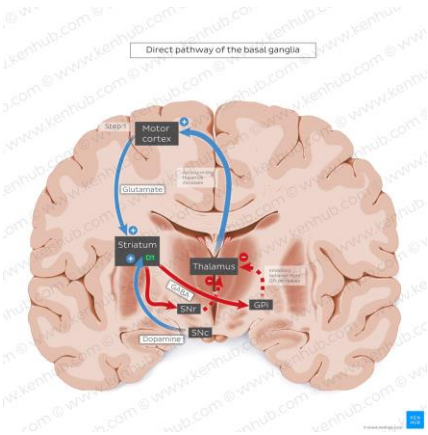
2. Neostriatum: Normally, the neostriatum is connected to the substantia nigra by neurons (Fig. 8.4) that secrete the inhibitory transmitter GABA at their termini.

In turn, cells of the substantia nigra send neurons back to the neostriatum, secreting the inhibitory transmitter dopamine at their termini.

This mutual inhibitory pathway normally maintains a degree of inhibition of both areas. In PD, destruction of cells in the substantia nigra results in the degeneration of the nerve terminals that secrete dopamine in the neostriatum.

Thus, the normal inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction or a relative overactivity of acetylcholine by the stimulatory neurons. This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements.





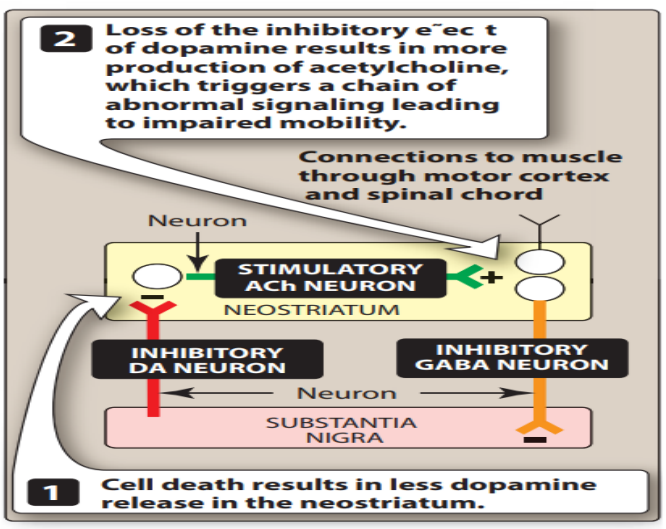


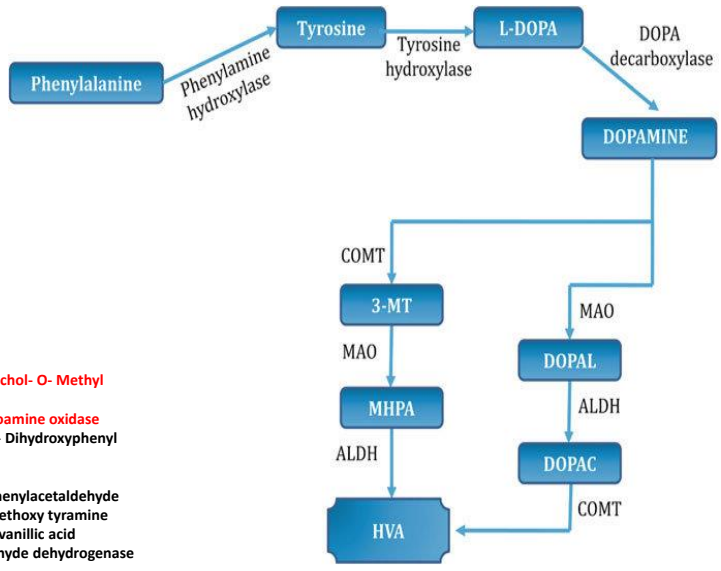
Figure 8.4
Role of substantia nigra in Parkinson's disease. DA = dopamine; GABA = γ-aminobutyric acid; ACh = acetylcholine.

B- Secondary parkinsonism:

- **Drugs such as the phenothiazines and haloperidol, whose major pharmacologic action is blockade of dopamine receptors in the brain, may produce parkinsonian symptoms (also called pseudoparkinsonism). These drugs should be used with caution in patients with PD.**
- **Strategy of treatment**

Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons.

Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.



- COMT= Catechol- O- Methyl transferase
- MAO= Monoamine oxidase
- DOPAC= 3,4- Dihydroxyphenyl acetic acid
- DOPAL= 3,4- Dihydroxyphenylacetaldehyde
- 3- MT= 3- Methoxy tyramine
- HVA= Homovanillic acid
- ALDH= Aldehyde dehydrogenase

Enzymes that affect dopamine molcule

DRUGS USED IN PARKINSON'S DISEASE

- **Many currently available drugs aim to maintain CNS dopamine levels as constant as possible. They offer temporary relief from the symptoms of the disorder, but they DO NOT arrest or reverse the neuronal degeneration caused by the disease.**
- **A. Levodopa and carbidopa Levodopa is a metabolic precursor of dopamine . It restores dopaminergic neurotransmission in the neostriatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra. In early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about 20% of normal) is adequate for conversion of levodopa to dopamine. Thus, in new patients, the therapeutic response to levodopa is consistent, and the patient rarely complains that the drug effects "wear off."**

- **Unfortunately, with time, the number of neurons decreases, and fewer cells are capable of converting exogenously administered levodopa to dopamine. Consequently, motor control fluctuation develops.**
- **Relief provided by levodopa is only symptomatic, and it lasts only while the drug is present in the body. The effects of levodopa on the CNS can be greatly enhanced by coadministering carbidopa, a dopamine decarboxylase inhibitor that does not cross the blood–brain barrier.**
- **1. Mechanism of action: Dopamine does not cross the blood–brain barrier, but its immediate precursor, levodopa, is actively transported into the CNS and converted to dopamine (Figure 8.5).**
- **Levodopa must be administered with carbidopa. Without carbidopa, much of the drug is decarboxylated to dopamine in the periphery, resulting in nausea, vomiting, cardiac arrhythmias, and hypotension.**

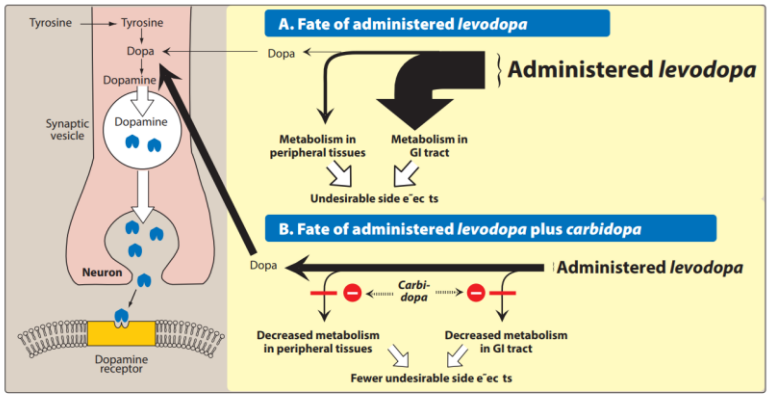


Figure 8.5
Synthesis of dopamine from *levodopa* in the absence and presence of *carbidopa*, an inhibitor of dopamine decarboxylase in the peripheral tissues. GI = gastrointestinal.

- **Carbidopa: a dopamine decarboxylase inhibitor, diminishes the metabolism of levodopa in the periphery, thereby increasing the availability of levodopa to the CNS. The addition of carbidopa lowers the dose of levodopa needed by four- to fivefold and, consequently, decreases the severity of the side effects arising from peripherally formed dopamine.**
- **2. Therapeutic uses: Levodopa in combination with carbidopa is an efficacious drug regimen for the treatment of PD.**
- **It decreases rigidity, tremors, and other symptoms of parkinsonism. Patients typically experience a decline in response during the 3rd to 5th year of therapy. Withdrawal from the drug must be gradual.**

- **3. Absorption and metabolism: The drug is absorbed rapidly from the small intestine , an extremely short half-life (1 to 2 hours), which causes fluctuations in plasma concentration. (fluctuations in motor response= "on–off" phenomenon, in which the motor fluctuations are not related to plasma levels in a simple way. Motor fluctuations that may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and immobility. Ingestion of meals, particularly if high in protein, interferes with the transport of levodopa into the CNS.**
- **4. Adverse effects: a. Peripheral effects: Anorexia, nausea, and vomiting, Tachycardia and ventricular extrasystoles, Hypotension may also develop, mydriasis. In some individuals, blood dyscrasias and a positive reaction to the Coombs test are seen. Saliva and urine are a brownish color because of the melanin pigment produced from catecholamine oxidation.**

- **b. CNS effects: Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur.**
- **These effects are the opposite of parkinsonian symptoms and reflect overactivity of dopamine in the basal ganglia. Levodopa can also cause mood changes, depression, psychosis, and anxiety.**

- **5. Interactions:**
- **Concomitant administration of levodopa and non-selective monoamine oxidase inhibitors (MAOIs), such as phenelzine, can produce a hypertensive crisis caused by enhanced catecholamine production.**
- **Antipsychotic drugs are generally contraindicated in PD, because they potently block dopamine receptors and may augment parkinsonian symptoms. However, low doses of atypical antipsychotics are sometimes used to treat levodopa-induced psychotic symptoms.**

- **B. MAO-Inhibitors (Selegiline and rasagiline) Selegiline, selectively inhibits monoamine oxidase (MAO) type B (metabolizes dopamine) at low to moderate doses. It does not inhibit MAO type A (metabolizes norepinephrine and serotonin) unless given above recommended doses, where it loses its selectivity, when selegiline is administered with levodopa, it enhances the actions of levodopa and substantially reduces the required dose.**
- **Unlike nonselective MAOIs, selegiline at recommended doses has little potential for causing hypertensive crises. However, the drug loses selectivity at high doses, and there is a risk for severe hypertension.**
- **Selegiline is metabolized to methamphetamine and amphetamine, whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon.**
- **Rasagiline , an irreversible and selective inhibitor of brain MAO type B, has five times the potency of selegiline. Unlike selegiline, rasagiline is not metabolized to an amphetamine-like substance.**

Comparison of Selgeline to Rasagiline

Selgeline	Rasagiline
Selectively and irreversibly inhibits monoamine oxidase (MAO) type B (metabolizes dopamine) at low to moderate doses.	Selectively and irreversibly inhibits brain MAO type B.
At high doses it loses the selectivity for MAO- B	selective inhibitor of brain MAO type B, has five times the potency of selegiline
Selegiline is metabolized to methamphetamine and amphetamine, whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon.	Unlike selegiline, rasagiline is not metabolized to an amphetamine-like substance.

C. COMT- inhibitors (Tolcapone and Entacapone) Normally, the methylation of levodopa by catechol-O-methyltransferase (COMT) to 3-O-methyldopa is a minor pathway for levodopa metabolism. However, when peripheral dopamine decarboxylase activity is inhibited by carbidopa, a significant concentration of 3-O-methyldopa is formed that competes with levodopa for active transport into the CNS. Entacapone and tolcapone selectively and reversibly inhibit COMT. Inhibition of COMT by these agents leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine.

Both of these agents reduce the symptoms of "wearing-off" phenomena seen in patients on levodopa–carbidopa. The two drugs differ primarily in their pharmacokinetic and adverse effect profile .

1. Pharmacokinetics: Oral absorption of both drugs occurs readily and is not influenced by food. Tolcapone has a relatively long duration of action (probably due to its affinity for the enzyme) compared to entacapone, which requires more frequent dosing.

2. Adverse effects: diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, and sleep disorders. Most seriously, fulminating hepatic necrosis is associated with tolcapone use. Therefore, it should be used, along with appropriate hepatic function monitoring, only in patients in whom other modalities have failed. Entacapone does not exhibit this toxicity and has largely replaced tolcapone.

Comparison of Entacapone and Tolcapone

Entacapone	Tolcapone
selectively and reversibly inhibit COMT Leading to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine.	selectively and reversibly inhibit COMT Leading to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine.
has a relatively short duration of action and require more frequent dosing	has a relatively long duration of action (probably due to its affinity for the enzyme) and require less frequent dosing
Entacapone does not exhibit hepatic toxicity and has largely replaced tolcapone.	Most seriously, fulminating hepatic necrosis is associated with tolcapone use. Therefore, it should be used, along with appropriate hepatic function monitoring, only in patients in whom other modalities have failed

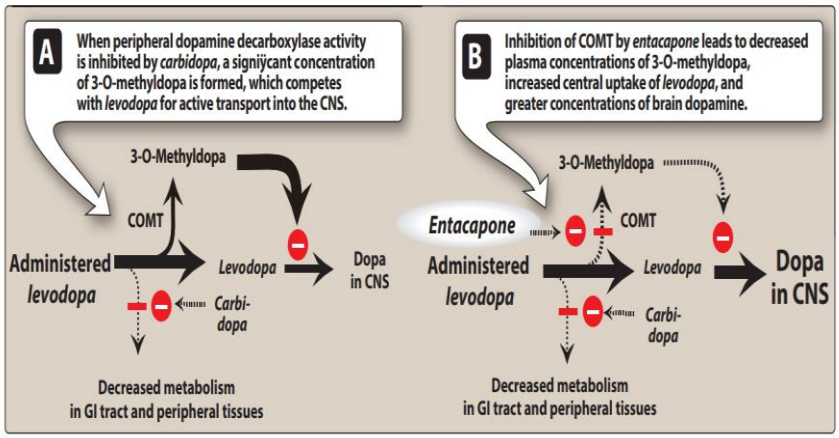


Figure 8.9

Effect of *entacapone* on dopa concentration in the central nervous system (CNS). COMT = catechol-O-methyltransferase.

- **D. Dopamine receptor agonists**
- **Either ergot derivative (bromocriptine), or nonergot drugs (ropinirole, pramipexole , rotigotine, and the newer agent, apomorphine.**
- **These agents have a longer duration of action than that of levodopa and are effective in patients exhibiting fluctuations in response to levodopa. Initial therapy with these drugs is associated with less risk of developing dyskinesias and motor fluctuations as compared to patients started on levodopa.**
- **Apomorphine is an injectable dopamine agonist that is used in severe and advanced stages of the disease to supplement oral medications .**
- **1. Bromocriptine: The actions of the ergot derivative bromocriptine are similar to those of levodopa, except that hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common, whereas dyskinesia is less prominent. It should be used with caution in patients with a history of myocardial infarction or peripheral vascular disease. Because bromocriptine is an ergot derivative, it has the potential to cause pulmonary and retroperitoneal fibrosis .**
- **2. Apomorphine, pramipexole, ropinirole, and rotigotine: These are non ergot dopamine agonists that are approved for the treatment of PD. Pramipexole and ropinirole are orally active agents. Apomorphine and rotigotine are available in injectable and transdermal delivery systems, respectively. Apomorphine is used for acute management of the hypomobility "off" phenomenon in advanced Parkinson's disease.**

- **Rotigotine is administered as a once-daily transdermal patch that provides even drug levels over 24 hours.**
- **These agents alleviate the motor deficits in patients who have never taken levodopa and also in patients with advanced Parkinson's disease who are treated with levodopa.**
- **Dopamine agonists may delay the need to use levodopa in early Parkinson's disease and may decrease the dose of levodopa in advanced Parkinson's disease.**
- **Unlike the ergotamine derivatives, these agents do not exacerbate peripheral vascular disorders or cause fibrosis. Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are among the more distressing side effects of these drugs, but dyskinesias are less frequent than with levodopa.**
- **Pramipexole is mainly excreted unchanged in the urine, and dosage adjustments are needed in renal dysfunction.**
- **Cimetidine inhibits renal tubular secretion of organic bases and may significantly increase the half-life of pramipexole.**
- **The fluoroquinolone antibiotics and other inhibitors of the cytochrome P450 (CYP450) 1A2 isoenzyme (for example, fluxetine) may inhibit the metabolism of ropinirole, requiring an adjustment in ropinirole dosage.**

- **E. Amantadine: It was accidentally discovered that the antiviral drug amantadine, used to treat influenza, has an antiparkinsonian action.**
- **Mechanism of action: increasing the release of dopamine, blocking cholinergic receptors, and inhibiting the N-methyld-aspartate (NMDA) type of glutamate receptors.**
- **The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur. Amantadine is less efficacious than levodopa, and tolerance develops more readily. However, amantadine has fewer side effects.**
- **F. Antimuscarinic agents: The antimuscarinic agents are much less efficacious than levodopa and play only an adjuvant role in antiparkinsonism therapy.**
- **The actions of benztropine, trihexyphenidyl, procyclidine, and biperiden are similar, although individual patients may respond more favorably to one drug.**
- **Blockage of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission, since it helps to correct the imbalance in the dopamine/acetylcholine ratio .**
- **These agents can induce mood changes and produce xerostomia (dryness of the mouth), constipation, and visual problems typical of muscarinic blockers . They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis.**

2- DRUGS USED IN ALZHEIMER'S DISEASE:

Dementia of the Alzheimer type has three distinguishing features:

1) accumulation of senile plaques (β-amyloid accumulations).

2) formation of numerous neurofibillary tangles, and 3) loss of cortical neurons, particularly cholinergic neurons.

Current therapies aim to either improve cholinergic transmission within the CNS or prevent excitotoxic actions resulting from overstimulation of NMDA-glutamate receptors in selected areas of the brain.

- **Pharmacologic intervention for Alzheimer's disease is only palliative and provides modest short-term benefit None of the available therapeutic agents alter the underlying neurodegenerative process.**
- **A. Acetylcholinesterase inhibitors Numerous studies have linked the progressive loss of cholinergic neurons and, presumably, cholinergic transmission within the cortex to the memory loss that is a hallmark symptom of Alzheimer's disease.**
- **It is postulated that inhibition of acetylcholinesterase (AChE) within the CNS will improve cholinergic transmission, at least at those neurons that are still functioning.**
- **The reversible AChE inhibitors approved for the treatment of mild to moderate Alzheimer's disease include donepezil, galantamine, and rivastigmine.**
- **All of them have some selectivity for AChE in the CNS, as compared to the periphery. Galantamine may also augment the action of acetylcholine at nicotinic receptors in the CNS. At best, these compounds provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer patients.**
- **Rivastigmine is the only agent approved for the management of dementia associated with Parkinson's disease and also the only AChE inhibitor available as a transdermal formulation.**

- **Rivastigmine is hydrolyzed by AChE to a carbamylate metabolite and has no interactions with drugs that alter the activity of CYP450 enzymes. The other agents are substrates for CYP450 and have a potential for such interactions.**
- **Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps .**
- **B. NMDA receptor antagonist Stimulation of glutamate receptors in the CNS appears to be critical for the formation of certain memories. However, overstimulation of glutamate receptors, particularly of the NMDA type, may result in excitotoxic effects on neurons and is suggested as a mechanism for neurodegenerative or apoptotic (programmed cell death) processes.**
- **Binding of glutamate to the NMDA receptor assists in the opening of an ion channel that allows Ca^{2+} to enter the neuron. Excess intracellular Ca^{2+} can activate a number of processes that ultimately damage neurons and lead to apoptosis.**
- **Memantine is an NMDA receptor antagonist indicated for moderate to severe Alzheimer's disease. Memantine is well tolerated, with few dose-dependent adverse events. Expected side effects, such as confusion, agitation, and restlessness, are indistinguishable from the symptoms of Alzheimer's disease. is often given in combination with an AChE inhibitor.**


THANK YOU