

# **Neurodegenerative Diseases**

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# 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**: influencing the production, storage, release, or termination of action of neurotransmitters.

# Overview

- Drugs affecting the CNS may act **postsynaptically**: may activate or block postsynaptic receptors.
- Common neurodegenerative disorders: Parkinson's and Alzheimer's disease occur as a result of neurodegenerative processes.

# Neurodegenerative Diseases

- Neurodegenerative diseases of the CNS include Alzheimer's disease and Parkinson's disease.
- These devastating illnesses are characterized by the **progressive loss of selected neurons** in discrete brain areas, resulting in characteristic disorders of movement, cognition, or both.

# Neurodegenerative Diseases

- **Alzheimer's disease** is characterized by the loss of **cholinergic neurons** in the nucleus basalis of Maynert, whereas **Parkinson's disease** is associated with a loss of **dopaminergic neurons** in the substantia nigra.
- The most prevalent of these disorders is Alzheimer's disease.

# Parkinson's Disease

- Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia, and postural and gait abnormalities.

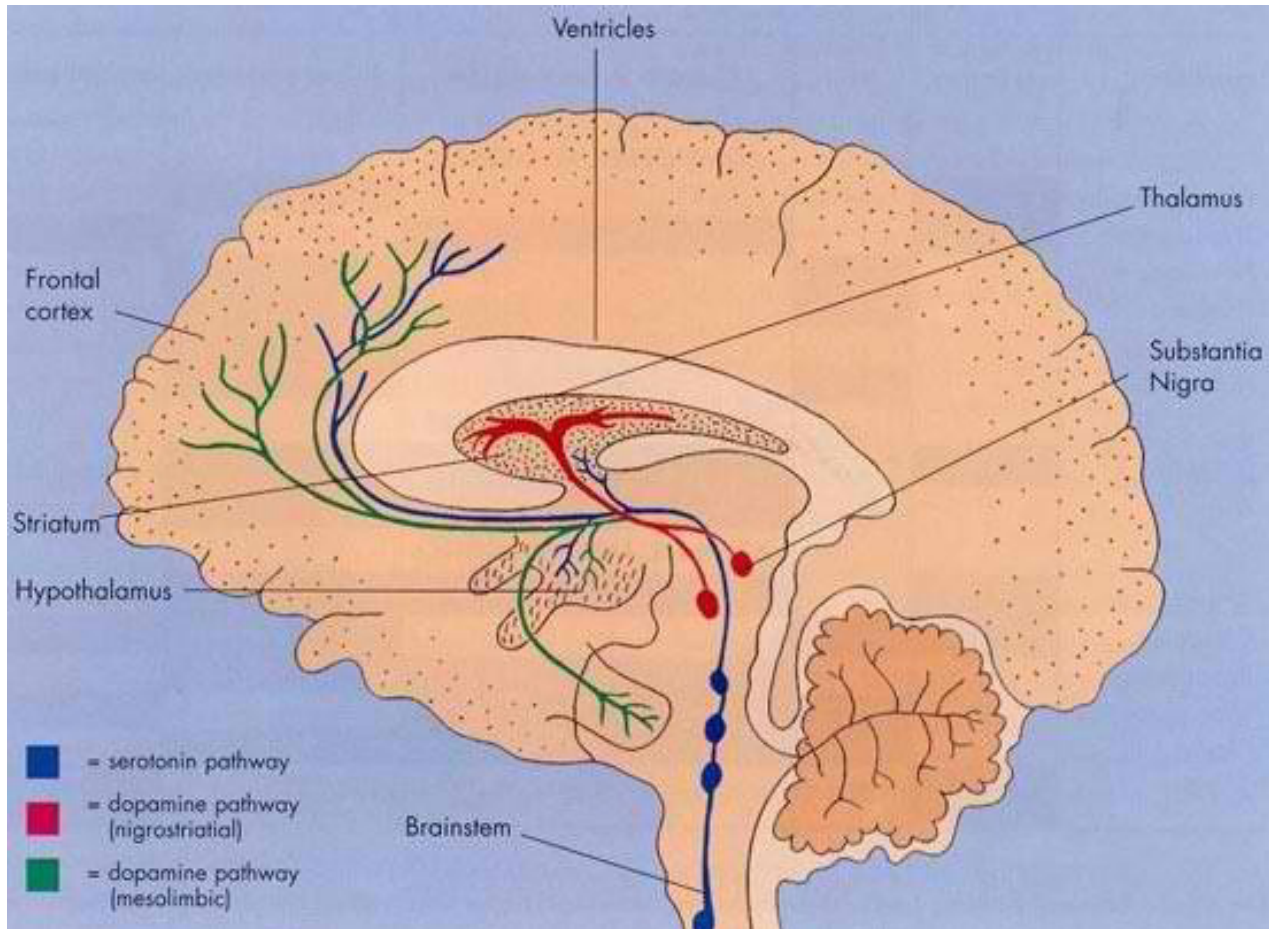
# Parkinson's disease

- Progressive neurological disorder caused by progressive loss of *dopamine* in the CNS causing
- tremor
- muscle rigidity
- bradykinesia (slowness in initiating and carrying out voluntary movements )
- postural gait abnormalities

# Etiology

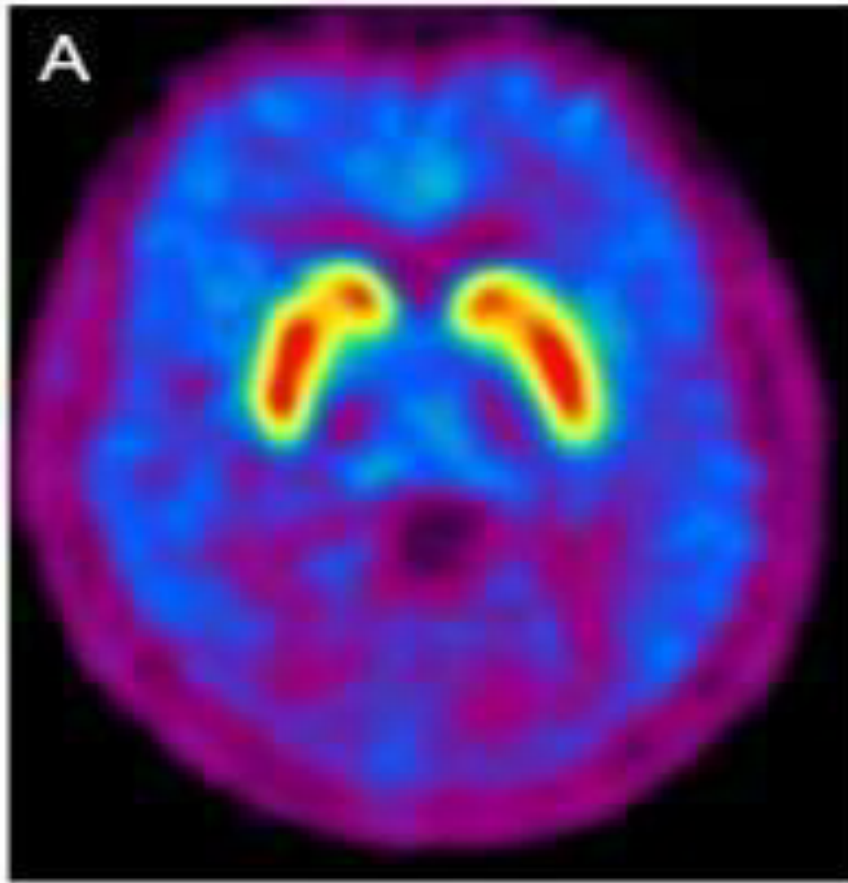
- The disease is correlated with destruction of dopaminergic neurons in the substantia nigra with a consequent reduction of dopamine actions in the corpus striatum— parts of the brain's basal ganglia system that are involved in motor control.





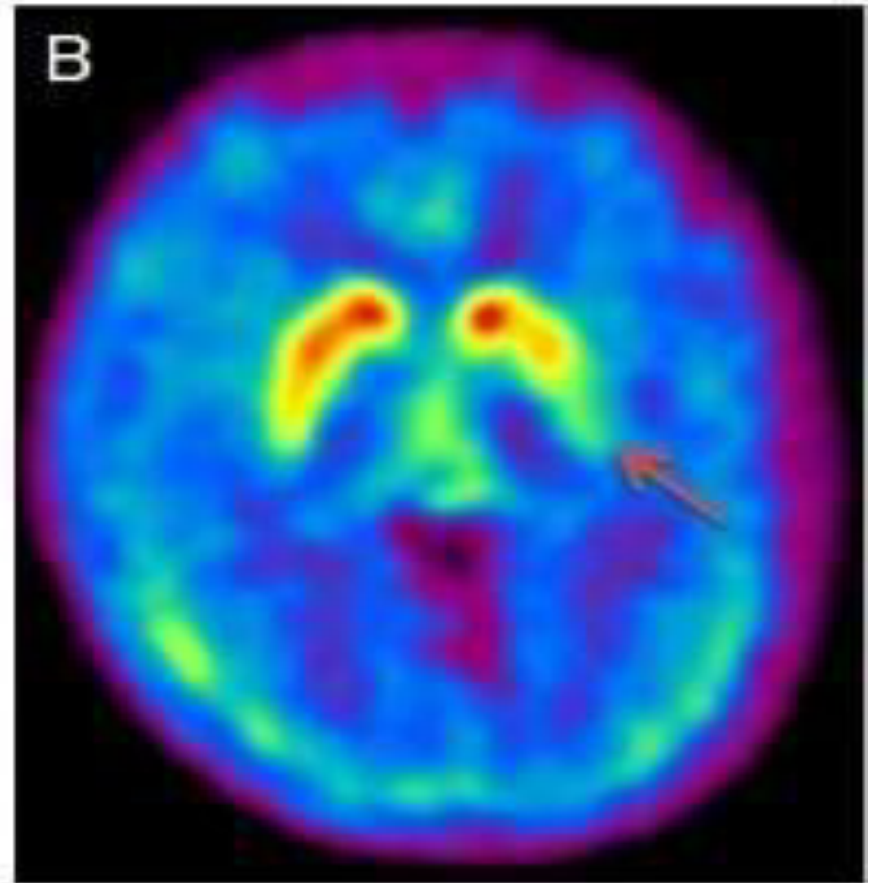
- The loss of dopamine neurons in the substantia nigra is evidenced by diminished overall uptake of dopamine precursors in this region

Control



- Positron-emission tomography

PD Patient



- Dopamine analog *fluorodopa*

# Strategy of treatment

- In addition to an abundance of **inhibitory dopaminergic neurons**, the neostriatum is also rich in **excitatory cholinergic neurons** that oppose the action of dopamine.

# 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.

# Strategy of treatment

- 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.

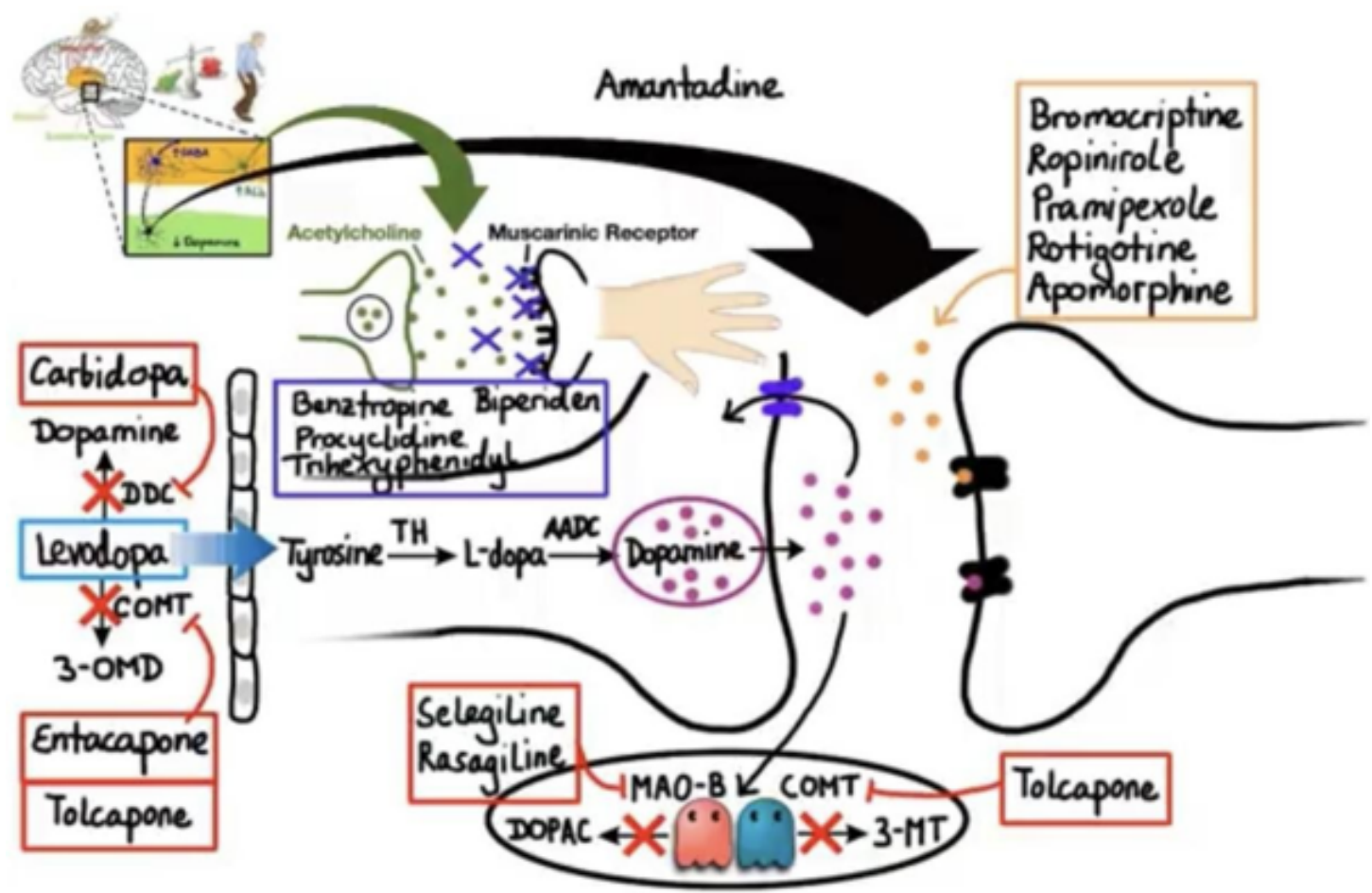
# Drugs Used in Parkinson's Disease

- Currently available drugs offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration caused by the disease.

# **Parkinsonism Drugs/ Antiparkinsonism agents**

- Given to restore balance of dopamine and acetylcholine in specific regions of the brain





# Dopaminergics

- Either
- restore dopamine function
- stimulate dopamine receptors located within the brain

- **Goal of pharmacotherapy for parkinson's disease** is to increase the ability of the client to perform normal activities of living (ADLs).

# **Treating Parkinsonism with Dopaminergic drugs**

Drug	Functions	Adverse Effects
amantadine (Symmetrel)	<ul style="list-style-type: none"> <li>An antiviral agent, causes the release of dopamine from its nerve terminals</li> </ul>	<p><i>Dizziness, light-headedness, difficulty concentrating, confusion, anxiety, headache, sleep dysfunction, fatigue, nausea, vomiting, constipation, orthostatic hypotension, choreiform and involuntary movements, dystonia, dyskinesia</i></p>
carbidopa-levodopa (Sinemet) levodopa (L-Dopa, Larodopa)	<ul style="list-style-type: none"> <li>A precursor of dopamine synthesis</li> <li>Supplying this directly leads to increased biosynthesis of dopamine within nerve terminals</li> <li>Whereas levodopa can cross the blood-brain barrier, dopamine cannot; thus, dopamine itself is not used for therapy</li> <li>The effectiveness of levodopa can be “boosted” by combining it with <b>carbidopa</b>. This combination, marketed as <b>Sinemet</b>, makes more levodopa available to enter the CNS</li> </ul>	<p><u>Acute MI, shock, neuroleptic malignant syndrome, agranulocytosis, depression with suicidal tendencies, EPS (extrapyramidal side effects), fulminant liver failure, severe hepatocellular injury</u></p> <p><b>Note:</b> <i>italics</i> indicate common adverse effects; <u>underlining</u> indicates serious adverse effects</p>
bromocriptine (Parlodel) pergolide (Permax) pramipexole dihydrochloride (Mirapex) ropinirole hydrochloride (Requip)	<ul style="list-style-type: none"> <li>Directly activate the dopamine receptor and are called <i>dopamine agonists</i></li> </ul>	
entacapone (Comtan) selegiline hydrochloride (L-Deprenyl, Eldepryl, Carbex) tolcapone (Tasmar)	<ul style="list-style-type: none"> <li>Inhibit enzymes that normally destroy levodopa and dopamine</li> </ul>	

# Treating Parkinsonism with Dopaminergic drugs

- Dopaminergic drugs are used to increase dopamine levels in corpus striatum of the brain.
- Drug of choice for Parkinsonism is ***levodopa*** (***Larodopa***)

# Levodopa and carbidopa

- *Levodopa* is a metabolic precursor of dopamine.
- It restores dopaminergic neurotransmission in the corpus striatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra.

# Levodopa and carbidopa

- Unfortunately, with time, the number of neurons decreases and fewer cells are capable of taking up exogenously administered *levodopa* and converting it to dopamine for subsequent storage and release. Consequently, motor control fluctuation develops.
- Relief provided by *levodopa* is only symptomatic, and it lasts only while the drug is present in the body.



# Mechanism of Action

## Levodopa

- Dopamine itself does not cross the BBB, but its immediate precursor, *levodopa* is actively transported into the CNS and is converted to dopamine in the brain
- Large doses of *levodopa* are required, because much of the drug is decarboxylated to dopamine in the periphery, resulting in side effects that include **nausea, vomiting, cardiac arrhythmias, and hypotension.**

# Mechanism of Action

## Carbidopa

- The effects of *levodopa* on the CNS can be greatly enhanced by coadministering *carbidopa*, a dopa decarboxylase inhibitor that does not cross the blood-brain barrier.
- *Carbidopa* diminishes the metabolism of *levodopa* in the gastrointestinal tract and peripheral tissues; thus it increases the availability of *levodopa* to the CNS.
- The addition of *carbidopa* lowers the dose of *levodopa* needed by four-to five-fold and, consequently, decreases the severity of the side effects arising from peripherally formed dopamine.

# Actions:

- *Levodopa* decreases the rigidity, tremors, and other symptoms of Parkinsonism.

# Therapeutic uses:

- Two-thirds of patients with Parkinson's disease, *levodopa-carbidopa* treatment substantially reduces the severity of the disease for the first years of treatment.
- Patients then typically experience a decline in response during the third or fifth year of therapy.

# Absorption and Metabolism

- The drug is absorbed rapidly from the small intestine (when empty of food). *Levodopa* has an extremely short half-life (1-2 hours), which causes fluctuations in plasma concentration. Motor fluctuations may cause the patient to *suddenly lose normal mobility and experience tremors, cramps, and immobility.*

# Absorption and Metabolism

- Ingestion of meals particularly if high in protein, interferes with the transport of *levodopa* into the CNS.
- Thus, *levodopa* should be taken on an empty stomach, typically 45 minutes before a meal.
- Withdrawal from the drug must be gradual.

# Adverse Effects:

## Peripheral effects:

- Anorexia
- Nausea
- Vomiting
- Tachycardia
- Ventricular extra systoles
- Hypotension
- Adrenergic action on the iris causes mydriasis (an excessive dilation of the pupil due to disease, trauma or the use of drugs), and in some individuals, blood dyscrasias (a condition where any of the blood components are abnormal in any way) and a positive reaction to the Coombs' test are seen.
- Saliva and urine are a brownish color because of the melanin pigment produced from the catecholamine oxidation.

# Adverse Effects:

## CNS effects:

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



# Interactions:

- The vitamin pyridoxine (B6) increases the peripheral breakdown of *levodopa* and diminishes its effectiveness.
- Concomitant administration of *levodopa* and monoamine oxidase (MAO) inhibitors, such as *phenelzine*, can produce a hypertensive crisis caused by enhanced catecholamine production; therefore, caution is required when they are used simultaneously.

# Interactions:

- In many psychotic patients, *levodopa* exacerbates symptoms, possibly through the buildup of central catecholamines.
- In patients with glaucoma, the drug can cause an increase in intraocular pressure.
- Cardiac patients should be carefully monitored because of the possible development of cardiac arrhythmias.

# Interactions:

- Antipsychotic drugs are generally contraindicated in parkinsonian patients, because these potently block dopamine receptors and produce a parkinsonian syndrome themselves.
- However low doses of certain “atypical” antipsychotic agents are sometimes employed to treat levodopa-induced psychiatric symptoms.

# Selegiline and rasagiline

- *Selegiline*, also called *deprenyl*, selectively inhibits MAO Type B (which metabolizes dopamine) at low to moderate doses but does not inhibit MAO Type A (which metabolizes norepinephrine and serotonin) unless given at above recommended doses, where it loses its selectivity.
- By thus decreasing the metabolism of dopamine, *selegiline* has been found to increase dopamine levels in the brain.

# Selegiline and rasagiline

- Therefore, it enhances the actions of *levodopa* when these drugs are administered together.
- *Selegiline* substantially reduces the required dose of *levodopa*.
- Unlike nonselective MAO inhibitors, *selegiline* at recommended doses has little potential for causing hypertensive crises.
- However, if *selegiline* is administered at high doses, the selectivity of the drug is lost, and the patient is at risk for severe hypertension.

# Selegiline and rasagiline

- *Selegiline* is metabolized to methamphetamine and *amphetamine*, whose stimulating properties may produce insomnia if the drug is administered later than midafternoon.
- *Rasagiline*, an irreversible and selective inhibitor of brain (MAO) Type B, has five times the potency of *selegiline*. Unlike *selegiline*, it is not metabolized to an amphetamine-like substance.

# Catechol-O-methyltransferase inhibitors

- Inhibition of COMT by *entacapone* or *tolcapone* leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of *levodopa*, and greater concentrations of brain dopamine.
- Both of these agents have been demonstrated to reduce the symptoms of “wearing-off” phenomena seen in patients on *levodopa-carbidopa*.
- *Entacapone* and *tolcapone* are nitrocatechol derivatives that selectively and reversibly inhibit COMT.

# Pharmacokinetics:

- Oral absorption of both drugs occurs readily and is not influenced by food.
- *Tolcapone* differs from *entacapone* in that the former penetrates the blood-brain barrier and inhibits the COMT in the CNS. However, the inhibition of COMT in the periphery appears to be the primary therapeutic action.
- *Tolcapone* has a relatively long duration of action (probably due to its affinity for the enzyme) compared to *entacapone*, which requires more frequent dosing.
- Both drugs are extensively metabolized and eliminated in the feces and urine.
- Dosage may need to be adjusted in patients with moderate or severe cirrhosis.



# Adverse effects:

- Both drugs exhibit adverse effects that are observed in patients taking *levodopa-carbidopa*, including ***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*.

# Dopamine-receptor agonists

- This group of anti-Parkinson compounds includes *bromocriptine*; an ergot derivative, and two newer, nonergot drugs, *ropinirole*, *pramipexole* and *rotigotine*.
- These agents have durations of action longer than that of *levodopa*, and, thus, have been effective in patients exhibiting fluctuations in their response to *levodopa*.

# Dopamine-receptor agonists

- Initial therapy with the newer drugs is associated particularly with less risk of developing dyskinesias and motor fluctuations when compared to patients started with levodopa therapy.
- *Bromocriptine, pramipexole* and *ropinirole* are all effective in patients with advanced Parkinson's disease complicated by motor fluctuations and dyskinesias.

# Dopamine-receptor agonists

- However, these drugs are ineffective in patients who have shown no therapeutic response to *levodopa*.
- *Apomorphine* is also used in severe and advanced stages of the disease as an injectable dopamine agonist to supplement the oral medications commonly prescribed.
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# Bromocriptine:

- *Bromocriptine*, a derivative of the vasoconstrictive alkaloid, ergotamine, is a dopamine-receptor agonist. The dose is increased gradually during a period of 2 to 3 months. Side effects severely limit the utility of the dopamine agonists.
- The actions of *bromocriptine* are similar to those of *levodopa*, except that hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common, whereas dyskinesia is less prominent.

# Bromocriptine:

- In psychiatric illness, *bromocriptine* and *levodopa* may cause the mental condition to worsen.
- Serious cardiac problems may develop, particularly in patients with a history of myocardial infarction.
- In patients with peripheral vascular disease, a worsening of the vasospasm occurs, and in patients with peptic ulcer, there is a worsening of the ulcer.
- Because *bromocriptine* is an ergot derivative, it has the potential to cause pulmonary and retroperitoneal fibrosis.

# Apomorphine, pramipexole, ropinirole, and rotigotine:

- These are nonergot dopamine agonists that have been approved for the treatment of parkinson's disease.
- *Pramipexole* and *ropinirole* are agonists at dopamine receptors.
- *Apomorphine* and *rotigotine* are newer dopamine agonists available in injectable and transdermal delivery systems, respectively.

# Apomorphine, pramipexole, ropinirole, and rotigotine:

- *Apomorphine* is meant to be used for the acute management of the hypomobility “off” phenomenon. These agents alleviate the motor deficits in both *levodopa*-naïve patients (patients who have never been treated with *levodopa*) and patients with advanced parkinson’s disease who are taking *levodopa*.
- Dopamine agonists may delay the need to employ *levodopa* therapy in early parkinson’s disease and may decrease the dose of *levodopa* in advanced parkinson’s disease.



# Apomorphine, pramipexole, ropinirole, and rotigotine:

- Unlike the ergotamine derivatives, *pramipexole* and *ropinirole* do not exacerbate peripheral vasospasm, nor do they cause fibrosis.
- Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are among the more distressing side effects of these drugs; dyskinesias are less frequent than with *levodopa*.

# Apomorphine, pramipexole, ropinirole, and rotigotine:

- The dependence of *pramipexole* on renal function for its elimination cannot be overly stressed. For example, *cimetidine*, which inhibits renal tubular secretion of organic bases, increases the half-life of *pramipexole* by 40 percent.
- The fluoroquinolone antibiotics and other inhibitors of the CYP450-1A2 hepatic enzyme have been shown to inhibit the metabolism of *ropinirole* and to enhance the AUC (area under the concentration vs. the time curve) by some 80 percent.

# Apomorphine, pramipexole, ropinirole, and rotigotine:

- *Rotigotine* is a dopamine agonist used in the treatment of the signs and symptoms of early stage parkinson's disease. It is administered as a once-daily transdermal patch that provides even pharmacokinetics over 24 hours.

# Amantadine

- It was currently discovered that the antiviral drug *amantadine*, which is effective in the treatment of influenza, has an antiparkinsonism action.
- *Amantadine* has several effects on a number of neurotransmitters implicated in causing Parkinsonism, including increasing the release of dopamine, blockading cholinergic receptors, and inhibiting the N-methyl-D-aspartate (NMDA) type of glutamate receptors.

# Amantadine

- Current evidence supports an action at NMDA receptors as the primary action at therapeutic concentrations
- Note: if dopamine release is already at a maximum, *amantadine* has no effect.
- The drug may cause ***restlessness , agitation, confusion, and hallucinations, and at high doses, it may induce acute toxic psychosis***

# Amantadine

- ***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. The drug has little effect on tremor, but is more effective than the anticholinergics against rigidity and bradykinesia.

# **Additional Information on Dopaminergic Agents**

# ***ropinirole hydrochloride (Requip)***

- More twice as effective in controlling dyskinesia symptoms
- Clients taking this alone may also experience less progressive dyskinesia symptoms



***pramipexole dihydrochloride (Mirapex)***  
***ropinirole hydrochloride (Requip)***

- Have proven to be safe and effective for the initial sole therapy and when combined with L-dopa
- Side effects are intense and may include *nausea and constipation, headache, orthostatic hypotension, nasal congestion, sudden sleep attacks and hallucinations.*

# Drugs Reducing the Requirements for L-Dopa

- Includes ***Catechol-O-methyl transferase(COMT) inhibitors***
- Like L-Dopa, these agents increase concentrations of existing dopamine in the brain and improve motor fluctuations relating to the wearing-off effect.
- Examples of this drug class is entacapone (Comtan)
- Side effects of COMT inhibitors include *mental confusion and hallucination, nausea and vomiting, cramps, headache, diarrhea and possible liver damage*

# Anti-cholinergics

- Inhibit the action of acetylcholine in the brain
- Used early in the course of therapy for Parkinsonism disease

# Treating Parkinsonism with Anti-Cholinergics

- By blocking the effect of acetylcholine, anticholinergics inhibit the overactivity of this neurotransmitter in the corpus striatum of the brain
- Anticholinergics such as atropine were the first agents used to treat parkinsonism
- Although anticholine act on the CNS, autonomic effects such as ***dry mouth, blurred vision, tachycardia, urine retention, and constipation*** are still troublesome

# Treating Parkinsonism with Anti-Cholinergics

- The centrally acting anticholinergics are not as effective as levodopa at relieving severe symptoms of Parkinsonism.
- They are used early in the course of the disease when symptoms are less severe, in clients who cannot tolerate levodopa and in combination therapy with other parkinsonism drugs

# Treating Parkinsonism with Anti-Cholinergics

Drug	Adverse Effects
benztropine mesylate (Cogentin)	<i>Sedation, nausea, constipation, dry mouth, blurred vision,</i>
biperiden hydrochloride (Akineton)	<i>drowsiness, dizziness, tachycardia, hypotension,</i>
diphenhydramine hydrochloride (Benadryl)	<i>nervousness</i>
procyclidine hydrochloride (Kemadrin)	<u>Paralytic ileus, cardiovascular collapse</u>
trihexyphenidyl hydrochloride (Artane)	

**Note:** *italics* indicate common adverse effects; underlining indicates serious adverse effects

# 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.

# Antimuscarinic agents

- All of these drugs can induce mood changes and produce xerostomia (dryness of the mouth) and visual problems, as do all muscarinic blockers.
- They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis.



# Antimuscarinic agents

- Blockage of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission.
- Adverse effects are similar to those caused by high doses of *atropine*—for example, papillary dilation, confusion, hallucination, sinus tachycardia, urinary retention, constipation, and dry mouth.

# Alzheimer's Disease

Causes, Effects, and Treatments

# Alzheimer's Disease

- Degenerative brain disorder
- 4 million Americans
- 10% of all people over 65
- 50% of all people over 85
- 19 million people are family members of an Alzheimer's patient
- 22 million people worldwide will be diagnosed by 2025

# The History of Alzheimer's

- Alois Alzheimer in 1906 performed an autopsy
- “Peculiar formations”
- “Dense bundles”

# Functioning Brain

- Cerebrum- 2 hemispheres
  - Higher order functioning- reasoning, planning, analyzing, creating
  - Lobes
    - Frontal
    - Parietal
    - Temporal
    - Occipital

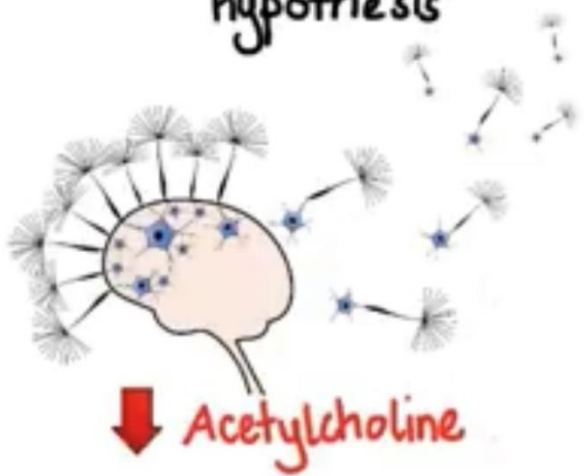
# Functional Brain

- Hippocampus
  - Part of limbic system
  - Role in memory formation
    - Sorts and sends new info to correct part of brain to be stored and recalled when necessary

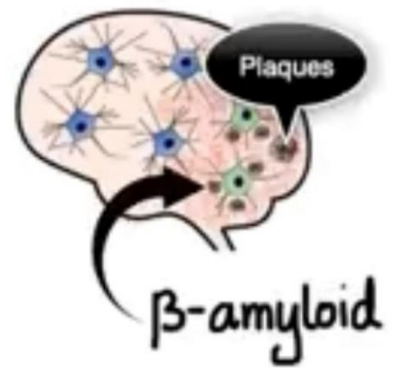
# Neurons

- Basic unit of nervous system- nerve cells
- Stimulus causes neuron to send an electric impulse through the cell body to the tip of the axon where neurotransmitters carry the signal across the synapse to the next neuron

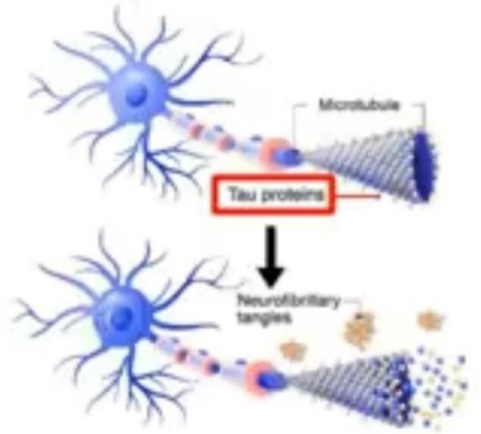
### Cholinergic hypothesis



### Amyloid hypothesis



### Tau hypothesis





# What Alzheimer's does

- Neuron degeneration
  - First in hippocampus
  - Spreads to frontal, parietal, temporal lobes
  - Loss in basal nucleus of Meynert
  - Goes on to rest of brain
  - Brain mass shrinks

# What Alzheimer's Does

- Amyloid plaques
  - Abnormal build-up of a protein called beta-amyloid
- Neurofibrillary tangles
  - Threads of protein tau begin to twist and structure of cell collapses
- Do plaques and tangles cause Alzheimer's or are they a result of the disease?

# BETA-AMYLOID PLAQUES

# AMYLOID PLAQUES

- Plaques form when specific protein in the neuron cell membrane is processed differently

# NORMAL PROTEIN PROCESS

- Normally an enzyme called alpha-secretase snips amyloid precursor protein or APP releasing a fragment

- A second enzyme called gamma secretase also snips amyloid pre-cursor protein in another place
- This release APP fragments function in synapse repair and formation.

# in ALZHEIMER'S DISEASE

- The first cut in APP is done with another enzyme called beta-secretase

- The first cut made by beta-secretase combined with the cut made by gamma secretase results for the release of short fragments of APP called **Beta-Amyloid**



- When these fragments clamp together they become toxic and clamp to neuron
- As more fragments are added these oligomers increase in size and become insoluble eventually forming **BETA-AMYLOID PLAQUES**

# TAU PROTEIN AND NEUROFIBRILLARY TANGLES

# NORMAL TAU PROTEIN

- Neurofibrillary tangles are made when a protein called tau is modified.
- In normal brain cells, tau stabilizes structures critical to the cell's internal transport system.
- Nutrients and other cellular cargo are carried up and down the structures called microtubules to all parts of the neuron.

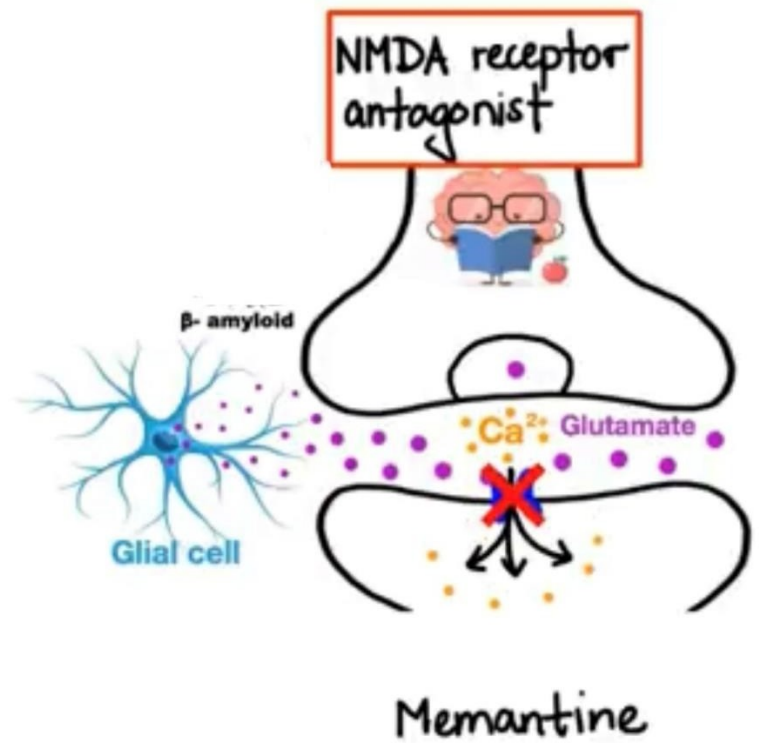
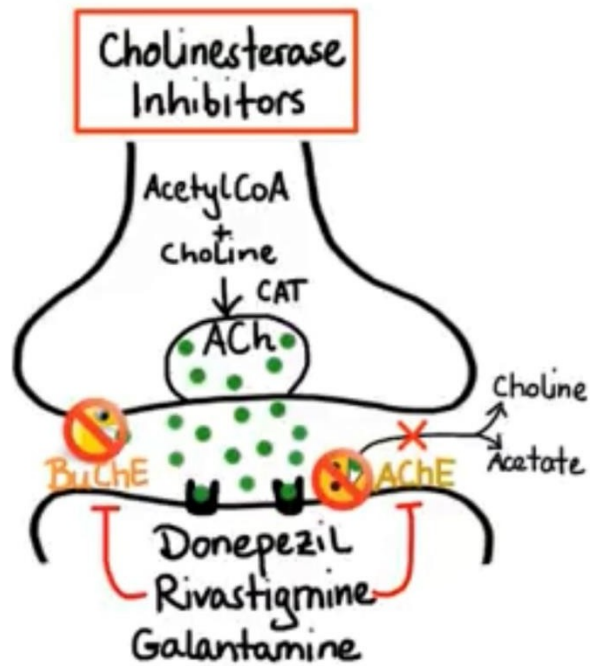
# In ALZHEIMER'S DISEASE

- abnormal tau separates from the microtubules, causing them to fall apart.
- Strands of this tau combine to form tangles inside the neuron, disabling the transport system and destroying the cell.

- Neurons in certain brain regions disconnect from each other and eventually die, causing memory loss. As these processes continue, the brain shrinks and loses function.

# Signs and Symptoms

- Severe memory loss
- Confusion
- Inability to formulate abstract thoughts
- Difficulty concentrating
- Difficulty carrying out routine or complex tasks
- Personality changes
- Paranoid or bizarre behavior



# The future of Alzheimer's

Currently, Alzheimer's disease is treatable, but incurable. Researchers are, however, feeling ever closer to pin-pointing the specific causes and biological basis of the disease, which will lead to a possible cure.



# THANK YOU

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