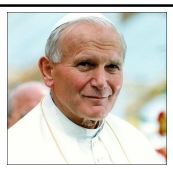
Antiparkinson' agents: dopamine agonists, dopamine releasing agents and synthetic anticholinergics.

The second most common age-related neurodegenerative disorder (after Alzheimer disease), Parkinson disease (PD) affects more than 1 million Americans.

Treatments for PD have been primarily based on correcting the characteristic nigrostriatal dopamine deficiency.

Parkinson's symptoms are recognized by most people as tremors, limb stiffness, impaired balance, and slow movement.

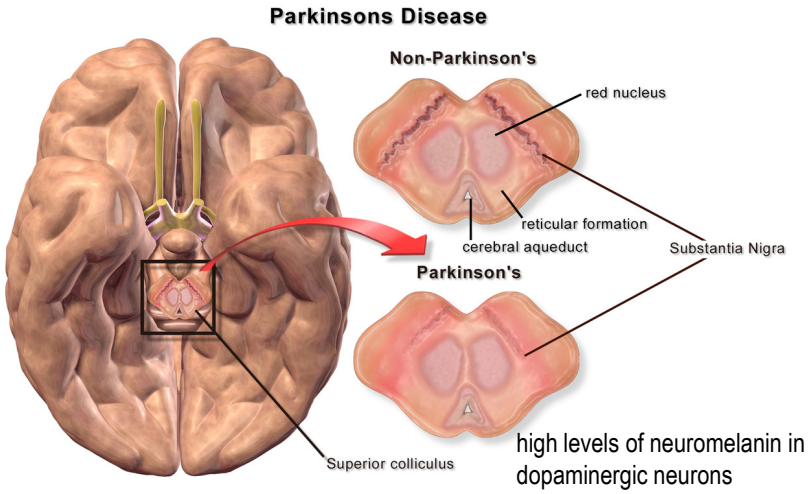
However, over the course of this disease, more than half of all patients are affected by what's called Parkinson's psychosis, which causes them to see, hear, or experience things that are not real (hallucinations), or believe things that are not true (delusions).


Parkinson's disease (PD) is a progressive neurodegenerative disorder. It is caused by ***degeneration of substantia nigra in the midbrain***, and consequent loss of DA-containing neurons in the nigrostrial pathway.

Two balanced systems are important in the extrapyramidal control of motor activity at the level of the corpus striatum and substantia nigra; first is ACh, in the second – DA.

The symptoms of PD are connected with **loss of nigrostrial neurons and DA depletion**.



high levels of neuromelanin in dopaminergic neurons

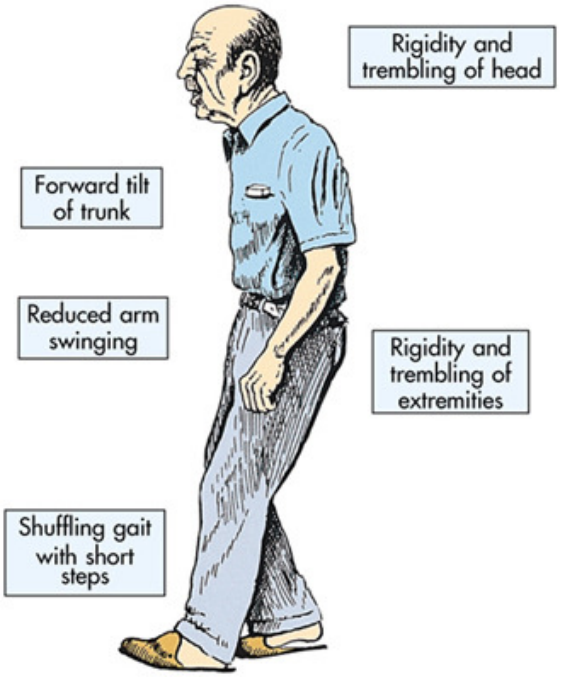
The substantia nigra is a brain structure located in the midbrain that plays an important role in reward, addiction, and movement.

Substantia nigra is Latin for “black substance”, reflecting the fact that parts of the substantia nigra appear darker than neighboring areas due to high levels of neuromelanin in dopaminergic neurons.

Neuromelanin (NM) is a dark pigment found in the brain which is structurally related to melanin. It is a polymer of 5,6-dihydroxyindole monomers.

Neuromelanin is found in large quantities in catecholaminergic cells of the substantia nigra pars compacta and locus coeruleus, giving a dark color to the structures

The symptomatic triad includes **bradykinesia, rigidity and tremor** with secondary manifestations like defective posture and gait, mask-like face and sialorrhoea; dementia may accompany.



Bradykinesia: Slow movement.

Bradykinesia is often associated with an impaired ability to adjust the body's position.

Bradykinesia can be a symptom of nervous system disorders, particularly Parkinson's disease, or a side effect of medications.

Parkinson's Disease:

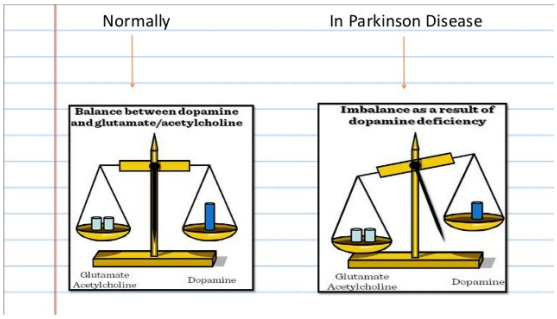
- progressive neurodegenerative disorder.
  - Disease of the basal ganglia & related neuronal groups + neurotransmitter deficiencies
- The normally high concentration of DA in the basal ganglia of the brain is reduced in PD
  - "shaking palsy"
    - **Bradykinesia** – slowing down in the initiation & execution of movement
    - **Rigidity** – increased muscle tone
    - **Tremor at rest**
    - **Impaired postural reflexes**

Imbalance of dopamine and acetylcholine

- Degeneration of dopamine-producing neurons in the substantia nigra of the midbrain
  - **Disrupts the balance of:**
    - **dopamine (DA)** – neurotransmitter for normal functioning of the extrapyramidal motor system (control of posture, support, and voluntary motion)
    - **Acetylcholine (Ach)**
- Symptoms do not occur until 80% of the neurons in the substantia nigra are lost

In fact, Parkinson's disease is characterized by an **imbalance** between **acetylcholine and dopamine (which becomes deficient)** which probably results from the degeneration of a **dopaminergic** nigrostriatal pathway.

This overgrowth could result in the cholinergic innervation of neuronal membranes vacated by degenerated **dopaminergic** terminals.



Role of Free Radicals in the Aging Brain and Parkinson's Disease

Free radical production and their targeted action on biomolecules have roles in aging and age-related disorders such as Parkinson's disease (PD).

Aging is considered as one of strongest risk factors for PD

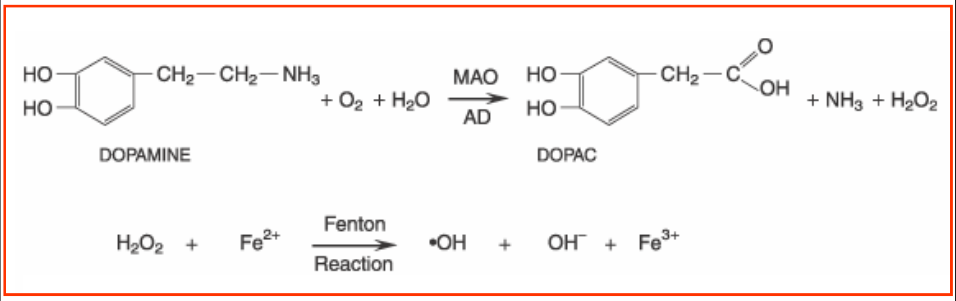
There is an age-associated increase in oxidative damage to the brain, and aging is considered a risk factor for PD.

Dopaminergic neurons show linear fallout of 5–10% per decade with aging; however, the rate and intensity of neuronal loss in patients with PD is more marked than that of aging.

During aging or under pathological states, the oxidation frequency of biological targets increases as repair processes slow down and detection of oxidized proteins, lipids, and DNA becomes more apparent

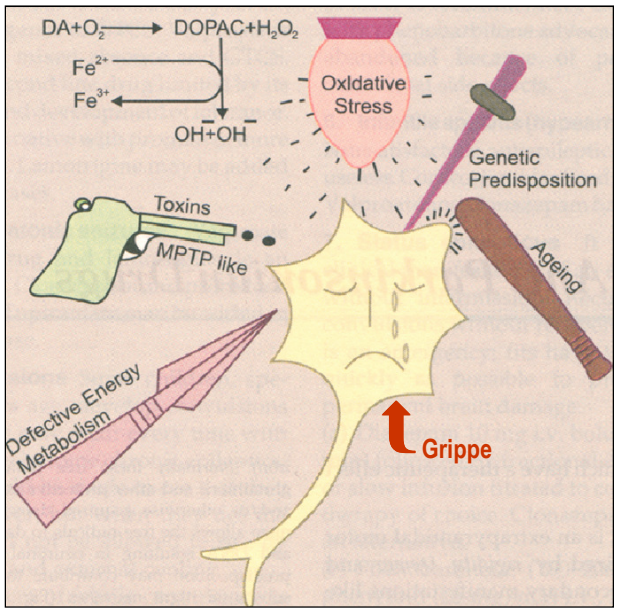
Notably, up to 50% of proteins may be oxidized in an 80-year-old human.

Mitochondria are both the source and target of free radicals.



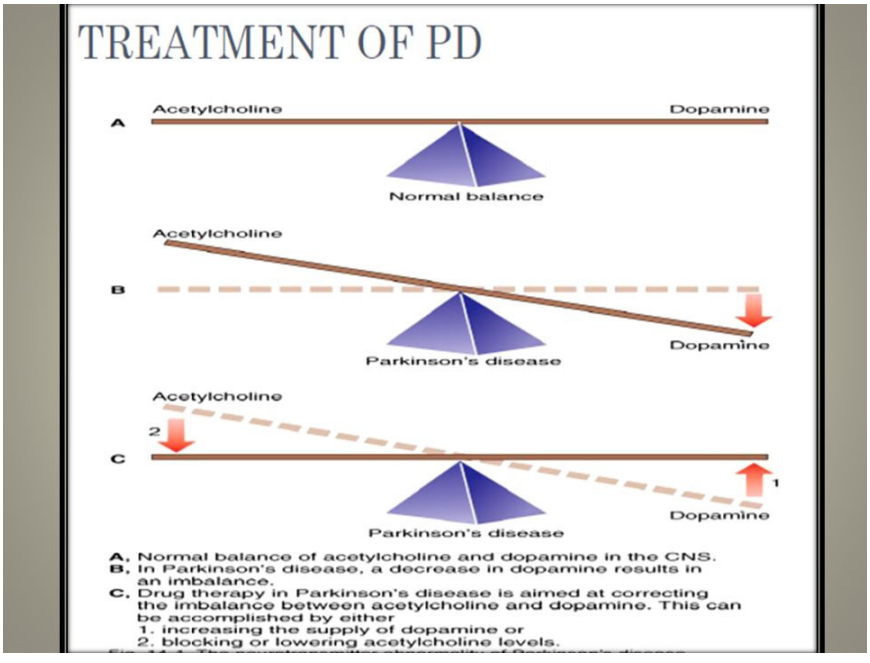
Production of free radical by the metabolism of dopamine (DA). DA is converted by MAO and aldehyde dehydrogenase (AD) in 3,4-dihydroxyphenylacetic acid (DOPAC), producing hydrogen peroxide (H_2O_2). In the presence of ferrous ion hydrogen peroxide undergoes spontaneous conversion, forming a hydroxyl free radical (***The Fenton reaction***).

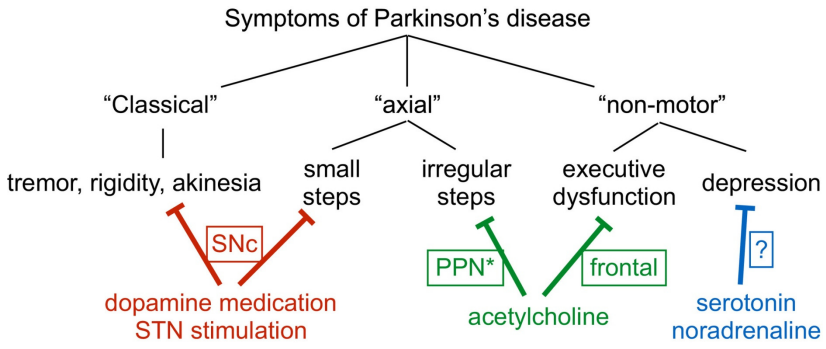
Goodman & Gilman's The Pharmacologic Basis of Therapeutics - 11th Ed. (2006)



Essential of Medical Pharmacology – 5st Ed. (2003)

Factors contributing to degeneration of nigrostrial DA-ergic neurones causing PD





*) Janickova *et al.*, this issue

Pharmacotherapy of PD

The main features that require alleviation are ***tremor, rigidity and bradykinesia.***

Drug therapy has the most important role in symptom relief, but it *does not alter the progressive course of PD.*

Treatment should begin only when it is judged necessary in each individual case.

There is a debate as to whether the treatment should commence with levodopa or a synthetic DA agonist.

Objectives of antiparkinsonian pharmacotherapy

The dopaminergic/cholinergic balance may be restored by two mechanisms.

1. Enhancement of DA-ergic activity by drugs which may:
(a) replenish neuronal DA by supplying levodopa, which is its natural precursor; administration of DA itself is ineffective as it does not cross the BBB;
(b) act as DA agonists (bromocriptine, pergolide, cabergoline, etc.);
(c) prolong the action of DA through selective inhibition of its metabolism (selegiline);
(d) release DA from stores and inhibit reuptake (amantadine).

2. Reduction of cholinergic activity by antimuscarinic (anticholinergic) drugs; this approach is *most effective against tremor and rigidity, and less effective in the treatment of bradykinesia*.

A **dopamine releasing agent** (**DRA**) is a type of drug which induces the release of dopamine in the body and/or brain.

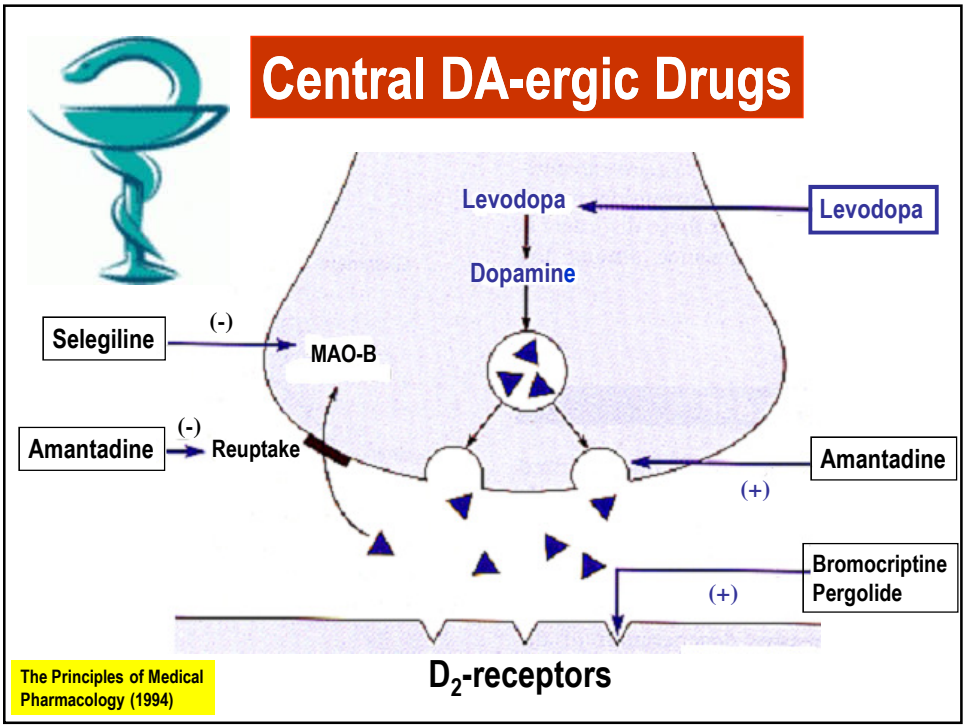
No selective DRAs are currently known.

Many releasing agents of both dopamine and norepinephrine (norepinephrine-dopamine releasing agents, or NDRAs) and of serotonin, norepinephrine, and dopamine are known (serotonin-norepinephrine-dopamine releasing agents, or SNDRAs), however. Serotonin-dopamine releasing agents are much rarer and are not selective for monoamine release.

Examples of NDRAs include amphetamine and methamphetamine, and an example of an SNDRA is MDMA.

The most selective dopamine releaser is 4-methylaminorex, but it also has considerable activity as a norepinephrine releaser.

These drugs are frequently used for recreational purposes and encountered as drugs of abuse.



Dopamine agonists fall into 2 major classes:

First-generation ergot derivatives (eg, bromocriptine, pergolide [no longer marketed in the United States])

Second-generation non-ergolines (eg, pramipexole, ropinirole).

The first- and second-generation agonists also show different pharmacological properties because they tend to act on different subsets of receptors.

For example, the older, ergoline agents bind with high affinity to D-2 family receptors but also show affinity of varying degrees for D-1, adrenergic, and 5HT receptors.

On the other hand, the non-ergolines bind only to D-2 and D-3 receptors with high affinity; pramipexole is more potent at D-3 binding.

Side effects dopamine agonists

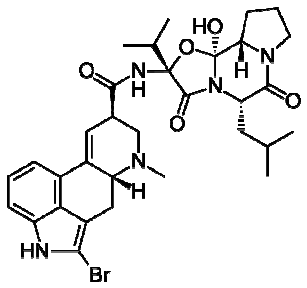
All dopamine agonists are associated with CNS side effects in varying degrees, which may include insomnia, somnolence, and visual hallucinations (neuropsychiatric adverse effects).

Dopamine agonists can also cause GI side effects, including nausea and vomiting.

Bromocriptine (originally marketed as **Parlodel**, subsequently under many names) is an ergoline derivative, is a dopamine agonist that is used in the treatment of pituitary tumors, Parkinson's disease (PD), hyperprolactinaemia, neuroleptic malignant syndrome, and type 2 diabetes.

Bromocriptine is a potent agonist at dopamine D2 receptors.

This dopamine agonist directly stimulates both pre- and postsynaptic receptors



Combination therapy: levodopa plus bromocriptine

In a study of levodopa monotherapy versus levodopa plus bromocriptine (as partial substitution for more than 30% of levodopa) in de novo patients with early PD, the severity and extent of motor dysfunction was significantly less in those receiving combination therapy.

Pergolide

A strong D-2 and a weak D1 receptor agonist, pergolide is effective in reducing motor complications as both monotherapy and adjunctive therapy to levodopa.

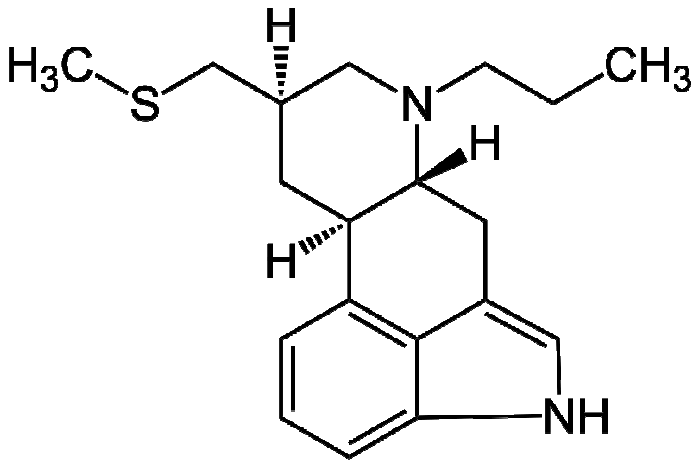
Pergolide is an Ergot-derived Dopamine Receptor Agonist. The **chemical** classification of **pergolide** is Ergot Alkaloids.

P**ergolide** is an oral dopamine receptor agonist used predominantly in the therapy of Parkinson disease.

At least 4 more studies have described the association of pergolide with valvular heart disease.

In 2007 the US FDA announced that the manufacturers of pergolide were voluntarily withdrawing it from the market.

Pergolide



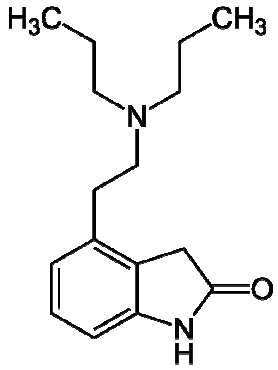
NON-ERGOT DOPAMINE AGONISTS

The introduction of non-ergoline agents with more rapid titration schedules and greater tolerability has also superseded bromocriptine in the treatment of levodopa-induced dyskinesia and on-off phenomena.

Ropinirole.
A highly selective non-ergoline D-2 agonist, ropinirole is effective as early monotherapy and as an adjunct to levodopa.

A study of ropinirole as monotherapy in patients with early-stage PD demonstrated a 24% improvement in motor function at 6 months in the monotherapy group compared with a 3% worsening in the placebo group.

Early PD can be managed successfully for up to 5 years with a reduced risk of dyskinesia by initiating treatment with ropinirole alone and supplementing it with levodopa if necessary.



Pramipexole

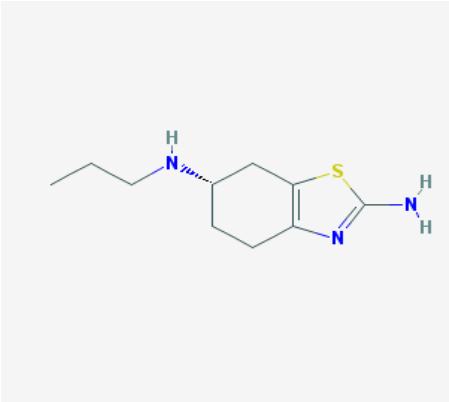
This non-ergot synthetic amino-benzathiazol derivative binds to D3 receptors with 7-fold greater affinity than it does to either D 2 or D4 receptors.

Its terminal half-life is about 8 hours in young healthy volunteers and about 12 hours in elderly volunteers.

The drug was safe and significantly improved motor function and activities of daily living. Pramipexole is used to treat symptoms of Parkinson's disease, such as stiffness, tremors, muscle spasms, and poor muscle control.

In the assessment of adverse events, nausea, insomnia, constipation, somnolence, and visual hallucinations occurred more frequently in the pramipexole.

Pramipexole



Dopamine replacement therapy-L-DOPA

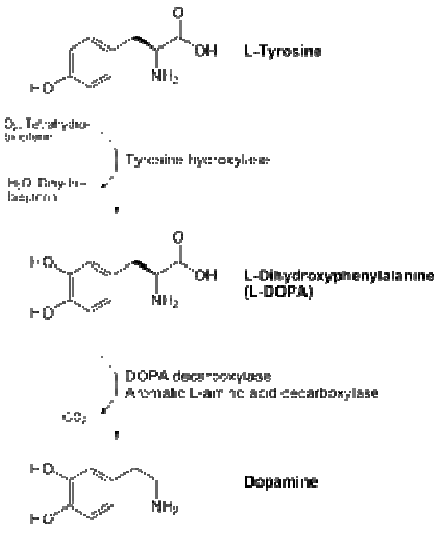
The cornerstone of symptomatic treatment for Parkinson disease (PD) is dopamine replacement therapy.

The criterion standard of symptomatic therapy is levodopa (L-dopa), the metabolic precursor of dopamine, in combination with carbidopa, a peripheral decarboxylase inhibitor (PDI).

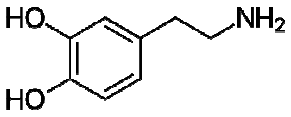
This combination provides the greatest symptomatic benefit with the fewest short-term adverse effects.

Side effect: Levodopa provides the biggest improvement in motor activity but its use is associated with the development of dyskinesia (involuntary movement of the face and limbs) after 5–10 years, and sometimes sooner.

L-DOPA is converted into **dopamine** by the enzyme aromatic **L**-amino acid decarboxylase (also known as **DOPA** decarboxylase), with pyridoxal phosphate as the cofactor. **Dopamine** itself is used as precursor in the synthesis of the neurotransmitters norepinephrine and epinephrine.



Dopamine is synthesized in plants and most animals. In the brain, dopamine functions as a neurotransmitter—a chemical released by neurons (nerve cells) to send signals to other nerve cells.



It is an amine synthesized by removing a carboxyl group from a molecule of its precursor chemical L-DOPA, which is synthesized in the brain and kidneys.

Dopamine (**DA)** is an organic chemical of the catecholamine and phenethylamine families that plays several important roles in the brain and body.

▼LEVODOPA

(DOPA – **D**ihydro**O**xy-**P**henyl**A**lanine; ($t_{1/2}$ 1,5 h) is a natural amino acid precursor of DA.

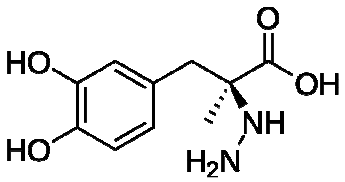
The major disadvantage is the extensive decarboxylation of levodopa to DA in peripheral tissues. So that only 1–3% of an oral dose reaches the brain.

Levodopa corrects the primary motor dysfunction, but with continuing use **and disease** progression is associated with levodopa-induced dyskinesia (LID).

L-DOPA can produce several adverse side effects, including:

Arrhythmia.
Gastrointestinal discomfort (taking L-DOPA with low protein snacks may help avoid stomach upset)
Breathing disturbances.
Hair loss.
Confusion.
Extreme emotional variability with prevalent anxiety.
Vivid dreams.
Hallucinations.

Carbidopa
(An inhibitor of DDC)



Carbidopa (**Lodosyn**) is a drug given to people with Parkinson's disease in order to inhibit peripheral metabolism of levodopa. This property is significant in that it allows a greater proportion of peripheral levodopa to cross the blood–brain barrier for central nervous system effect.

Carbidopa inhibits aromatic-L-amino-acid decarboxylase (DOPA decarboxylase or DDC), an enzyme important in the biosynthesis of L-tryptophan to serotonin and in the biosynthesis of L-DOPA to dopamine (DA).

This medication is used with a combination levodopa/*carbidopa* product to treat symptoms of Parkinson's disease or Parkinson-like symptoms (such as shakiness, stiffness, difficulty moving).

Combination therapy: L-DOPA/Carbidopa/Entacapone

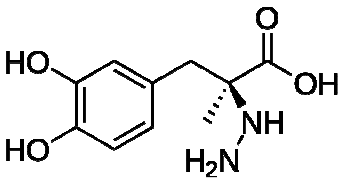
Entacapone (an inhibitor of COMT), sold under the brand name **Comtan** among others, is a medication commonly used in combination with other medications for the treatment of Parkinson's disease.

Entacapone together with levodopa and carbidopa allows levodopa to have a longer effect in the brain and reduces Parkinson's disease signs and symptoms for a greater length of time than levodopa and carbidopa therapy alone.

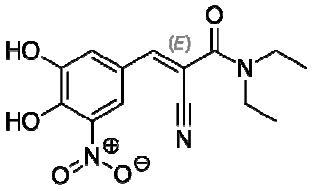
Entacapone is a selective and reversible inhibitor of the enzyme catechol-*O*-methyltransferase (COMT).

When taken together with levodopa (L-DOPA) and carbidopa, entacapone stops catechol-*O*-methyltransferase from breaking down and metabolizing levodopa, resulting in an overall increase of levodopa remaining in the brain and body.

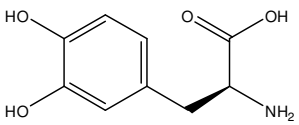
Carbidopa/levodopa/entacapone (Stalevo), a medication is a single tablet formulation that contains levodopa, carbidopa, and entacapone.



Carbidopa

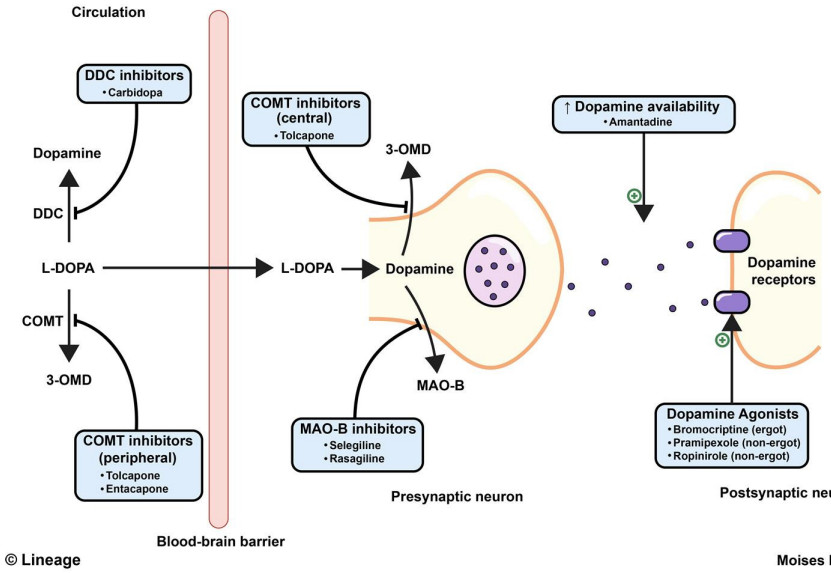


Entacapone

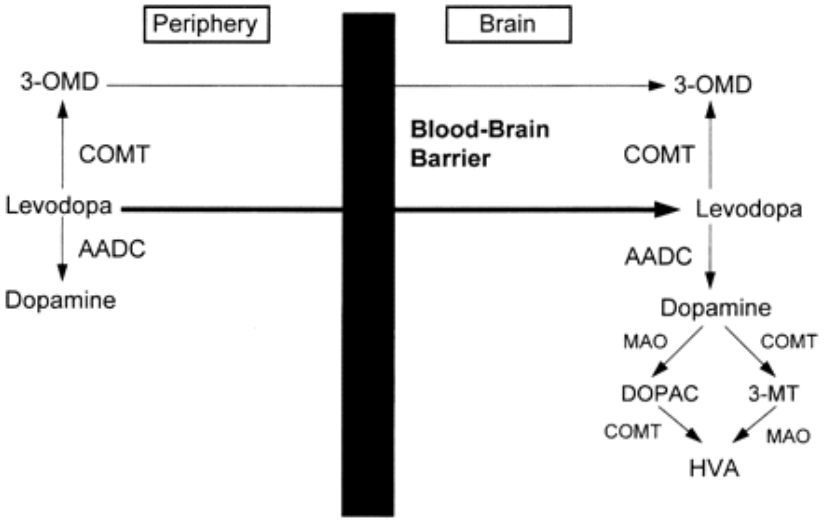


L-DOPA

Parkinson's Disease Drugs

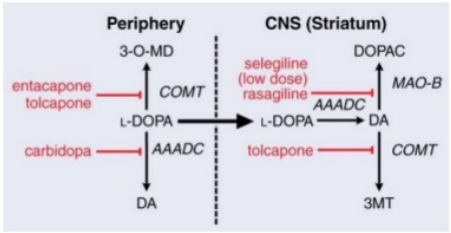


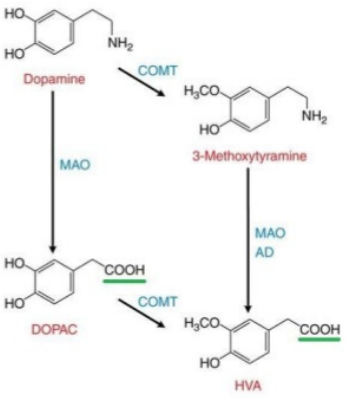
Moises Dominguez



HVA = Homovanillic acid

- catechol-O-methyl transferase is found centrally & peripherally





COMT: catechol-O-methyl transferase
3-O-MD: 3-O-methyl DOPA
3MT: 3-methoxyltyramine

Dopaminergic synapse.:

L-dopa passes through capillary and the blood brain barrier and enters the terminal to be converted into dopamine.

The dopamine is then collected in vesicles by VAT. An action potential triggers the natural production of dopamine by phosphorlating tyrosine hydroxylase (TH) and also releases vesicles across the synapse.

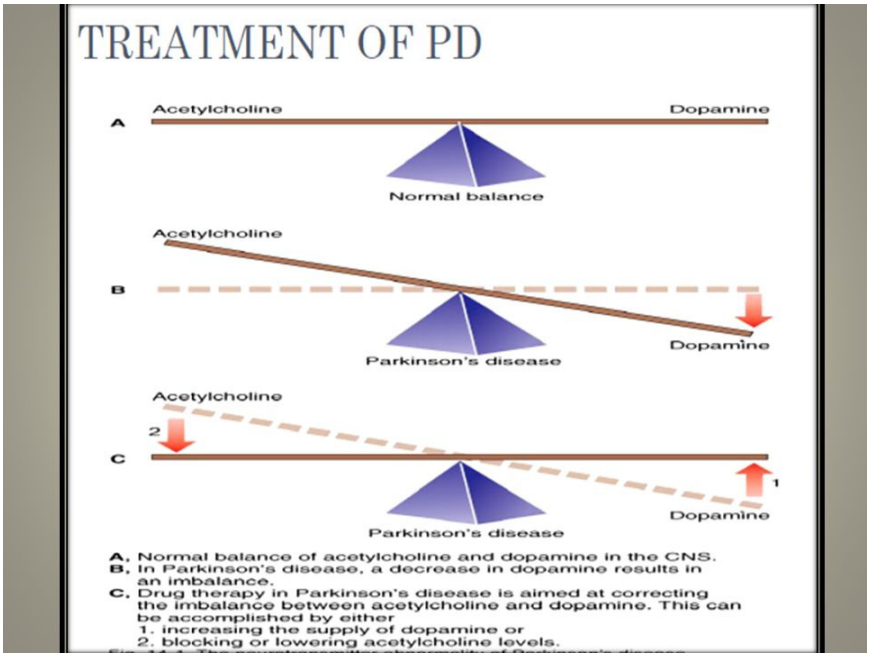
Dopamine binds to the post synaptic receptors which trigger one of the four pathways depending on their location.

When dopamine unbinds it is taken back up into the terminal by DAT or metabolized into DOPAC or HVA which return to circulation for excretion.

Why can't dopamine cross the blood-brain barrier, while L-dopa or other substituted phenethylamines can?

Dopamine is a member of the catecholamines, along with other molecules like epinephrine or adrenaline. They all share a dihydroxy benzene ring, along with an amine group. This leads to a similar structure between the three. All three are also **polar**, thus unable to diffuse across the membrane.

Levodopa or L-dopa on the other hand, is the second stage product (of 3) to synthesize dopamine, and the other catecholamines. It too is polar, though it is also an amino acid, and so happens to have a specialized 12 pass transmembrane transporter called L-type amino acid transporter or LAT-1. This is also called *SLC7A5* as per the name of the encoding gene. This transporter is what allows L-dopa to pass using facilitated diffusion as opposed to dopamine.



Synthetic anticholinergics for PD

Anticholinergics are a class of medications that are used to treat the symptoms of Parkinson's disease (PD), particularly the tremor that is characteristic of PD.

Therefore, anticholinergics are usually reserved for the treatment of tremor that is not adequately controlled with dopaminergic medications.

Anticholinergics are classified according to the receptors that are affected. Anticholinergic drugs or cholinergic antagonists are drugs that bind to cholinergic receptors (muscarinic and nicotinic) to prevent the effect of acetylcholine and other cholinergic agonists.
These drugs are also called parasympatholytics.

Anticholinergic drugs are classified into 3 groups: antimuscarinic drugs, antinicotinic drugs (neuromuscular blockers and ganglionic blockers), and cholinesterase regenerators.

The majority of **anticholinergic** drugs are **antimuscarinics**.

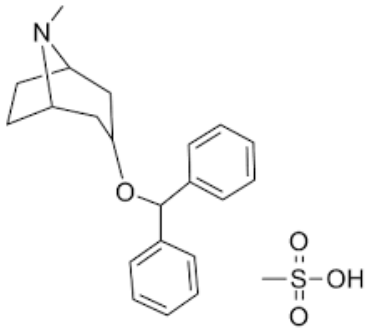
ANTICHOLINERGICS
An anticholinergic medication may be recommended to reduce symptoms of bothersome tremor in people with Parkinson disease under age 70 who do not have significant akinesia or difficulty walking.

Anticholinergics may be given alone, or with levodopa or dopamine agonists in people with more advanced disease who have a persistent tremor.

There are several anticholinergic drugs available for people with Parkinson disease, including trihexyphenidyl, benztropine, orphenadrine, procyclidine, and biperiden. These medications are believed to be equally effective.

Benzatropine

Benzatropine, also spelled benztropine, is a medication used to treat a type of movement disorder due to antipsychotics known as dystonia and parkinsonism.



Benztropine belongs to a class of medication called anticholinergics that work by blocking a certain natural substance (acetylcholine).

This helps decrease muscle stiffness, sweating, and the production of saliva, and helps improve walking ability in people with Parkinson's disease.

Benztropine is an agent with anti-muscarinic and antihistaminic effects.

Benztropine helps restore balance by blocking the action of acetylcholine in the central nervous system (brain and spinal cord).

Benztropine may also block the uptake and storage of dopamine in the central nervous system (CNS), resulting in the prolongation of the effects of dopamine.

Dosing — Trihexyphenidyl and benztropine are usually taken by mouth two or three times per day.

Side effects — The most common side effects of anticholinergics include dry mouth, blurred vision, constipation, nausea, difficulty emptying the bladder, impaired sweating, and rapid heart rate. Other side effects can be especially bothersome for older adults and anyone with difficulty thinking clearly. These can include difficulty with memory, confusion, and hallucinations.