**Drugs for Parkinson’s Disease**

* Parkinson’s disease (PD) is a neurodegenerative disorder first described by Dr. James Parkinson, a London physician, in 1817.
* The disease afflicts over 1 million Americans, making it second only to Alzheimer’s disease as the most common degenerative disease of nerves.
* Primary symptoms are tremor, rigidity, postural instability, and slower movement.
* The underlying cause is loss of dopaminergic neurons in the substantia nigra. Although there is no cure for PD, drug therapy can maintain good functional mobility for years, and can thereby substantially prolong life expectancy.
* The most effective drug for PD is levodopa, usually given in combination with carbidopa.
* Unfortunately, as PD advances, levodopa eventually becomes ineffective.

Pathophysiology of Parkinson’s Disease

* Parkinson’s disease is a disorder of the extrapyramidal system, a complex neuronal network that helps regulate movement.
* When extrapyramidal function is disrupted, dyskinesias (disorders of movement) results.
* The dyskinesias that characterize PD are tremor at rest, regidity, postural instability, and bradykinesia (slowed movement); in severe disease bradykinesia may progress to akinesia (complete absence of movement).
* In addition to movement disorders, patients frequently experience psychologic disturbances, including dementia, depression, and impaired memory.
* As a rule, symptoms of PD result from disruption of neurotransmission within the striatum, an important component of the extrapyramidal system.
* Proper functioning of the striatum requires a balance between two neurotransmitters: dopamine and acetylcholine (Ach).
* Dopamine is an inhibitory transmitter; ACh is excitatory. According to the model, the neurons that release dopamine inhibit neurons that release gamma-aminobutyric acid (GABA, another inhibitory transmitter)
* In contrast, the neurons that release Ach excite the neurons that release GABA.
* Movement is normal when the excitatory influence of ACh are in balance.
* Note that the neurons that supply dopamine originate in the substantia nigra.
* In PD, there is an imbalance between dopamine and ACh in the striatum.
* The cause is degeneration of the neurons that supply dopamine to the striatum.
* (Why these neurons degenerate is unknown, although environmental factors are suspected.)
* In the absence of dopamine, the excitatory influence of ACh becomes unopposed, causing excessive stimulation of the neurons that release GABA.
* Overactivity of these GABAergic neurons contributes to the movement disorders seen in PD.



**Overview of Drugs Employed**

* Table before presents an overview of the drugs used to treat PD. As indicated, these drugs fall into two major categories: (1) dopaminergic drugs (drugs that promote activation of dopamine receptors), and (2) anticholinergic drugs (drugs that prevent activation of cholinergic receptors).
* The dopaminergic agents act by a variety of mechanisms, including promotion of dopamine synthesis, prevention of dopamine degradation, promotion of dopamine release, and direct activation of dopamine receptors.
* In contrast, all of the anticholinergic agents act by the same mechanisms blockade of muscarinic cholinergic in the striatum.
* **Levodopa**

***Use in Parkinson’s Disease***

**Beneficial Effects.**  Levodopa [Dopar, Larodopa] is the drug of choice for PD. With initial treatment, about 75% of patients experience a 50% reduction in severity of symptoms.

Levodopa is so effective, in fact, that a diagnosis of PD should be questioned if the patient fails to respond.

* Full therapeutic responses may take several months to develop. Consequently, although the effects of levodopa can be significant, patients should not be informed that beneficial effects are likely to increase steadily over the firs few months of treatment.
* In contrast to the dramatic improvements seen during initial therapy, long-term therapy with levodopa has been disappointing.
* Although symptoms may be well controlled during the first 2 years of treatment, by the end of 5 years the patient’s ability to function may deteriorate to pretreatment levels.
* This probably reflects progression of the disease and not development of tolerance to levodopa.

**Mechanism of Action**

* Levodopa reduces symptoms of PD by promoting synthesis of dopamine in the striatum.
* Levodopa enters the brain via an active transport system that carries it across the blood-brain barrier.
* Once in the brain, the drug undergoes uptake into the few dopaminergic nerve terminals that remain in the striatum.
* Following uptake, levodopa, which has no direct effects of its own, is converted to dopamine, its active form.
* By promoting synthesis of dopamine, levodopa helps restore a proper balance between dopamine and ACh.
* The enzymatic conversion of levodopa to dopamine is depicted.
* As indicated, the enzyme that catalyzes this reaction is called a decarboxylase (because it removes a carboxyl group from levodopa)
* The activity of decarboxylases is enhanced by pyridoxine (vitamine B6).
* Why is PD treated with levodopa and not with dopamine itself?
* Dopamine cannot be enployed for two reasons.
* First, dopamine cannot cross the blood-brain barrier.
* As noted, levodopa crosses the barrier by means of an active transport system; this system will not transport dopamine.
* Second, dopamine has such a short half-life in the blood that it would be impractical to use even if it could cross the blood-brain barrier.

**Adverse Effects**

* Nausea and Vomiting
* Dyskinesias
* Cardiovascular Effects

**Drug interactions**

* Traditional Antipsychotic Drugs ;Monoamine Oxidase Inhibitors
* Anticholinergic Drugs; Pyridoxine

**Dopamine Agonists: Bromocriptine, Pergolide, Pramipexole, and Ropinirole**

* The dopamine agonists bind to dopamine receptors and thereby cause receptor activation.
* Beneficial effects in PD are believed to result from binding to the D2 subset of dopamine receptors in the striatum.
* Of the four dopamine agonists available, two are derivatives of ergot (an alkaloid found in plants) and two are not.
* The two nonergot derivatives-pramipexole and ropinirole- cause fewer side effects than the ergot derivatives-bromocriptine and pergolide. Why?
* Because the nonergot agents are highly selective for dopamine receptors, whereas the ergot derivatives activate other receptors in addition to those for dopamine.
* Also, the nonergot agents act as full agonists at dopamine receptors, whereas the ergot derivatives are only partial agonists.

**Bromocriptine**

* **Actions and Uses.** Bromocriptine [parlodel], a derivative of ergot, is a direct-acting dopamine agonist.
* Beneficial effects result from activation of depamine receptors in the striatum.
* Responses are superior to those of amantadine and the centrally acting anticholinergic drugs, but are inferior to those of levodopa.
* Although bromocriptine can be used as monotherapy, the drug is usually employed as an adjunct to levodopa.
* When combined with levodopa, bromocriptine can prolong therapeutic responses and reduce motor fluctuations.
* In addition, since bromocriptine allows the dosage of levodopa to be reduced, in the incidence of levodopa-induced dyskinesias may be reduced.
* Actions and Uses: Originally developed as an antiviral agent, amantadine [Summetrel, Symadine] is also effective in PD.
* The drug relieves symptoms by promoting release of dopamine from remaining dopaminergic terminals in the striatum.
* Responses develop rapidly (often within 2 to 3 days) but are less profound than those seen with levodopa.
* Furthermore, responses may begin to diminish with other drugs (levodopa/carbidopa, anticholinergic agents) later on.