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An Overview on “Some Novel Drug Treatment for Parkinson’s Disease”



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ABSTRACT

Parkinson's disease (PD) is a common neurodegenerative disorder. Parkinson's disease is a long-term degenerative disorder of the central nervous system. Parkinson's disease is commonly found in the older people after the age of 50. If this disease was found or occur or seen in young children then this disease known as young onset Parkinson's disease i.e. YOPD. This disease gives motor symptoms and they are commonly known as Parkinsonism or Parkinson syndrome. It can be classified into two types like Primary Parkinson diseases and secondary Parkinson diseases. Primary Parkinson's disease is also known as idiopathic disease. It also gives some nonmotor symptoms like autonomic dysfunction neuropsychiatric problem i.e. behavior, thought alteration, sensory and sleep problem are most common symptoms. This disease can be treated by using Dopamine agonists like Bromocriptine, Pergolide, Pramipexole, Ropinirole, Piribedil, Cabergoline, Apomorphine, and Lisuride.

INTRODUCTION:

Parkinson's disease is also known as PD, idiopathic Parkinsonism, and primary Parkinsonism, hypokinetic rigid syndrome i.e. HRS or Paralysis agitans. Parkinson's disease (PD) is a common neurodegenerative disorder¹. Parkinson's disease is a long-term degenerative disorder of the central nervous system. The symptoms generally come on slowly over time. There is no cure for Parkinson's disease, with treatment directed at improving symptoms². Common symptoms of this disease are related to movement of shaking, rigidity, slowness of movement and difficulty in walking and gait. This disease also gives behavioral problem, depression, sleep, emotional and sensory problem and thinking problem. Depression is common symptom of psychiatric problem. Parkinson's disease is mostly found in the older people after the age of 50. If this disease occurs or seen in young children then this disease is known as young onset Parkinson's disease i.e. YOPD³. The motor symptoms are commonly known as Parkinsonism or Parkinson syndrome. This disease can be classified into two types like Primary Parkinson diseases and secondary Parkinson diseases⁴. Primary Parkinson's disease is also known as idiopathic disease. Treatment of this disease contains L-DOPA and dopamine agonist. By surgery and deep brain stimulation has been decreases or reduces motor symptoms⁵.

Classification⁶⁻⁸:

Parkinson disease is used for a motor syndrome. It can be divided into four subtypes, according to their origin.

- Primary or idiopathic
- Secondary or acquired
- Hereditary Parkinson's
- Parkinson's plus syndrome

Sign and symptoms⁹⁻¹⁰:

Parkinson's disease can affect the movement, producing motor symptoms. It also gives some nonmotor symptoms like autonomic dysfunction neuropsychiatric problem i.e. behavior, thought alteration, sensory and sleep problem are most common symptoms.

Cause¹¹⁻¹⁴:

Parkinson's disease in most of the patient is idiopathic i.e. no specific known cause. Genetic factor is also main cause of Parkinson's disease. Various numbers of environmental factors are responsible for Parkinson's disease. Environmental factors like pesticide exposure, insecticide, herbicides, exposure of heavy metals, head injuries, farming and living in countries. Heavy metals are accumulating in the substantia nigra in brain. There is no cure for Parkinson's disease. There are some medications, surgery and multidisciplinary management can provide relief and decreases the symptoms of Parkinson's disease. The main drugs used in the treatment of motor Parkinson's disease are Levodopa, dopamine agonist and MAO-B inhibitor. Levodopa is an example of dopa decarboxylase inhibitors and COMT inhibitor.

Anti Parkinson's drug Classification¹⁵⁻¹⁸:

Anti Parkinson's drug can be divided into many types like

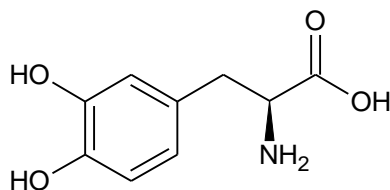
1. Levodopa
2. Dopamine agonists

For example;

- Bromocriptine
- Pergolide
- Pramipexole
- Ropinirole
- Piribedil
- Cabergoline
- Apomorphine
- Lisuride



L-DOPA or Levodopa:

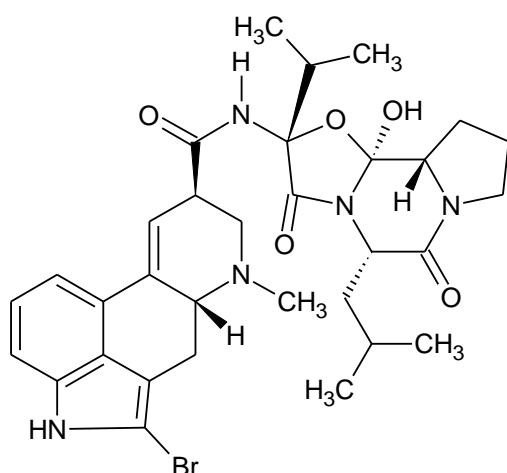


Systematic (IUPAC) name

(S)-2-Amino-3-(3,4-dihydroxyphenyl) propanoic acid

L-DOPA is also known as L-3, 4-dihydroxyphenylalanine. L-DOPA is a chemical and it is used as part of the normal biology of human. L-DOPA is precursor of neurotransmitter dopamine, norepinephrine and epinephrine i.e. adrenaline. They are also known as catecholamine. L-DOPA was synthesized and sold as psychoactive drug. It is used and sold in the market in the form of trade names like Sinemet, Parcopa, Atamet, Stalevo, Madopar and Prolopa. This drug is used in the treatment of Parkinson's diseases. This drug is also used in the treatment of dopamine responsive dystonia. Levodopa is used widely and effectively used for treatment of Parkinson's diseases for over 30 years. This drug was converted into dopamine in the dopaminergic neurons by dopa decarboxylase enzyme. A motor symptom was produced by a lack of dopamine in the substantia nigra of Central nervous system. After administration of L-DOPA, a motor symptom was diminished. About 5-10% drug of L-DOPA can cross the blood brain barrier i.e. BBB and then is converted into dopamine. About 90% drug was metabolized into dopamine. This drug can also give side effect like nausea, joint stiffness.

Bromocriptine:



Systematic (IUPAC) name

(5' α)-2-Bromo-12'-hydroxy-5'-(2-methylpropyl)-3',6',18-trioxo-2'-(propan-2-yl)ergotama

Bromocriptine is available in the form of trade names like Parlodel, Cycloset, and Brotin. This drug is an example of ergoline derivative. This drug acts as dopamine agonist. This drug is used in the treatment of pituitary tumors, Parkinson's diseases, hyperprolactinemia, neuroleptic malignant syndrome and diabetes type 2.

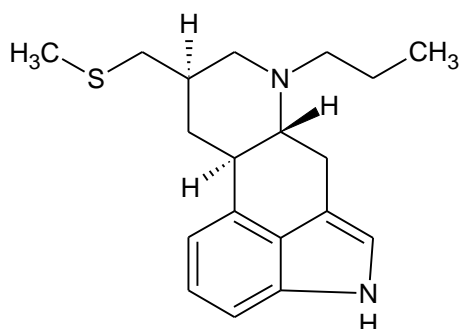
Uses:

- This drug is used in the treatment of pituitary tumors.
- This drug is used in the treatment of amenorrhea, female infertility, galactorrhea, hypogonadism caused by pituitary problem.
- This drug is used in the treatment of nonpuerperal mastitis.
- From 1980s, this drug is used in the treatment and to reduce the symptoms of cocaine withdrawal.
- This drug is used in the treatment of type II diabetes. This drug was approved by Food and Drug Administration for the treatment of type II diabetes. This drug is available in the form of brand names like Cycloset for the treatment of diabetes.

Mechanism of action:

This drug acts as potent agonist at dopamine D2 receptors and serotonin receptors. This drug also inhibits the release of glutamate by inhibiting glutamate GLT1 transporter. This drug gives agonist type activity on monoamine receptors like Dopamine D₁, Dopamine D₅, Dopamine D₂, Dopamine D₃, Dopamine D₄ and serotonin 5-HT_{1A}, serotonin 5-HT_{1B}, serotonin 5-HT_{1D}, serotonin 5-HT_{2A}, serotonin 5-HT_{2B}, serotonin 5-HT_{2C}, serotonin 5-HT₆, adrenergic α_{1A} , adrenergic α_{1B} , adrenergic α_{1D} , adrenergic α_{2A} , adrenergic α_{2C} , , adrenergic α_{2B} , and adrenergic β_1 , and adrenergic β_2 .

Pergolide:



Systematic (IUPAC) name

(8 β)-8-[(methylthio)methyl]-6-propylergoline

Pergolide is available in the form of trade name like Permax. This drug is an example of ergoline derivatives. This drug acts as an agonist for dopamine receptor. In some countries, this drug is used in the treatment of Parkinson's diseases. Parkinson's diseases can cause by low level of the neurotransmitter dopamine in the brain. This drug gives similar effect as dopamine in the body. In 2007, this drug was not used in United State for human use. This drug is used as veterinary drug also and sold under the trade name like Prascend. Prascend trade name is used in the treatment of Equine Cushing Syndrome i.e. ECS in horses. This drug is not used in United State for human. Prascend trade name was manufactured in United Kingdom.

Uses:

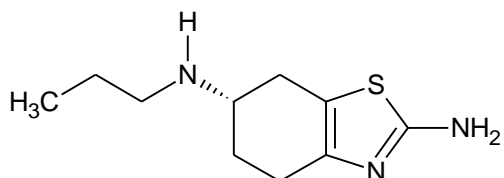
- This drug is used in the treatment of Parkinson disease, hyperprolactinemia and restless leg syndrome.
- This drug is also used as veterinary drug.
- This drug is used in the treatment of pituitary pars intermedia hyperplasia in horses and Equine Cushing Syndrome i.e. ECS in horses.

Mechanism of action:

This drug acts as potent agonist at dopamine D₂ receptors and serotonin receptors. This drug gives agonist type activity on monoamine receptors like Dopamine D₁, Dopamine D₅, Dopamine D₂, Dopamine D₃, Dopamine D₄ and serotonin 5-HT_{1A}, serotonin 5-HT_{1B}, serotonin 5-HT_{1D}, serotonin 5-HT_{2A}, serotonin 5-HT_{2B}, serotonin 5-HT_{2C}, and serotonin 5-

HT₆. This drug gives agonist activity at dopamine receptor subtype. This drug acts as weak agonist for Dopamine D₁ receptors. This drug increases the dopamine level in the brain.

Pramipexole:



Systematic (IUPAC) name

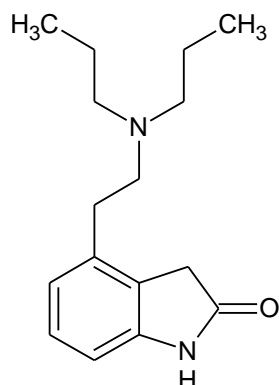
(S)-N⁶-propyl-4,5,6,7-tetrahydro-1,3-benzothiazole-2,6-diamine

Pramipexole is available in the form of trade names like Mirapex, Mirapexin and Sifrol. This drug acts as dopamine agonist. This drug is an example of non-ergoline class. This drug is used in the treatment of Parkinson's diseases and restless legs syndrome. Pramipexole was found to be highly effective in the treatment of bipolar depression and unipolar depression.

Mechanism of action:

This drug acts as partial or full agonist for some receptors like Dopamine D_{2S}, Dopamine D_{2L}, Dopamine D₃, and Dopamine D₄. This drug can possess or gives low affinity for the serotonin 5-HT_{1A}, serotonin 5-HT_{1B}, serotonin 5-HT_{1D}, serotonin 5-HT_{2A}, serotonin 5-HT_{2B}, serotonin 5-HT_{2C}, serotonin 5-HT₆, adrenergic α_{1A}, adrenergic α_{1B}, adrenergic α_{1D}, adrenergic α_{2A}, adrenergic α_{2C}, adrenergic α_{2B}. This drug gives negligible affinity for the D₁, D₅, 5HT₂ and α₁ adrenergic receptor and β-adrenergic receptors. Parkinson's disease is neurodegenerative diseases. it affects substantia nigra. Substantia nigra is component of basal ganglia. Substantia nigra contains higher quantity of dopaminergic receptors. These dopaminergic receptors are nerve cells that release the neurotransmitter like dopamine. When dopamine was released, it activates dopamine receptors in the striatum. Striatum is another component of the basal ganglia. When neurons of the substantia nigra affected in Parkinson's disease then the striatum does not receive dopamine signals. Basal ganglia can't regulate body movement effectively and motor function becomes impaired. When this drug was administered then it gives agonist type of activity for the D₂, D₃, and D₄ dopamine receptors. It may directly stimulate the under functioning dopamine receptors in the striatum.

Ropinirole:



Systematic (IUPAC) name

4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one

Ropinirole is available in the form of trade names like Requip, Repreve, Ronirol and Adartrel. This drug is an example of non-ergoline class. This drug was manufactured by GlaxoSmithKline, Cipla, Dr. Reddy Laboratory and Sun Pharmaceutical Company. This drug is used in the treatment of Parkinson's diseases and restless legs syndrome. This drug was approved by U.S. Food and Drug Administration for the treatment of restless legs syndrome. Patent for this drug was expired in May 2008 and this drug is now available in the form of generic form. This drug is available in the form of various dosage forms like 0.25 mg tablet and 5 mg tablet. For Parkinson's diseases, 24 mg of drug dose was recommended/ day. For restless legs syndrome, maximum dose of this drug is 4 mg/day, taken 1-3 hours before bedtime.

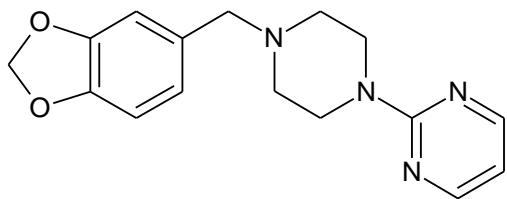
Uses:

- This drug is used in the treatment of Parkinson's disease.
- This drug is used in the treatment of restless legs syndrome and extrapyramidal symptoms.
- This drug can reduce the side effect caused by serotonin reuptake inhibitors.

Mechanism of action:

This drug gives agonist activity for Dopamine D₂, Dopamine D₃, and Dopamine D₄. This drug gives highest affinity for D₂. This drug gives weak activity against 5-HT₂ and α₂ receptors. This drug does not affect or no affinity for the 5-HT₁, GABA, α₁ and β-adrenoreceptors.

Piribedil:



Systematic (IUPAC) name

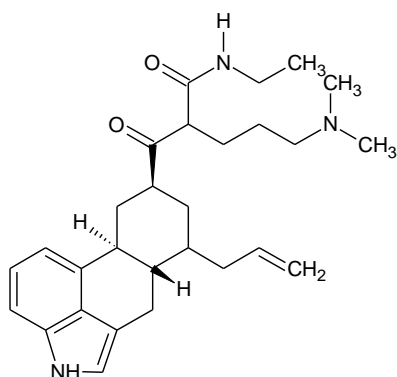
2-[4-(benzo[1,3]dioxol-5-ylmethyl)piperazin-1-yl]pyrimidine

Piribedil is available in the form of trade name like Pronoran, Trivastal, Retard, Trastal, Trivastan and Clarium. This drug is used in the treatment of Parkinson's diseases. This drug is an example of piperazine derivative. This drug acts as an agonist for D2 and D3 receptors. This drug acts as an antagonist for α_2 adrenergic receptors. This drug is available in the form of various dosage forms like sustained released tablet with 50 mg daily for first week.

Uses:

- This drug is used in the treatment of Parkinson diseases; this drug is used in combination with Levodopa.
- This drug is also used in the treatment of pathological cognitive deficits in elder patient.
- This drug is used in the treatment of impaired attention, motivation and memory problem.
- This drug is used in the treatment of dizziness.
- This drug is used in the treatment of retinal ischemic manifestation.
- This drug is used in the treatment of intermittent claudication and peripheral vascular diseases of lower limbs.
- This drug is used in the treatment of anhedonia and unipolar depression and bipolar depression.
- This drug is used in the treatment of gait disorder associated with Parkinson's diseases.
- This drug can increase the cognitive skill in healthy older adults.

Cabergoline:

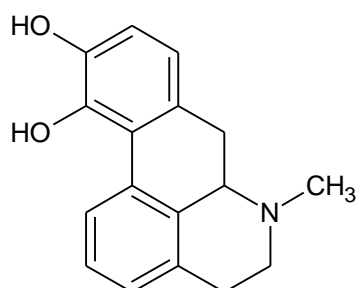


Systematic (IUPAC) name

(6a*R*,9*R*,10a*R*)-*N*-[3-(dimethylamino)propyl]-*N*-(ethylcarbamoyl)-7-prop-2-enyl-6,6a,8,9,10,10a-hexahydro-4*H*-indolo[4,3-*fg*]quinoline-9-carboxamide

Cabergoline is available in the form of brand names like Carberlin, Dostinex and Cabaser. This drug is an example of ergot derivative. This drug acts as an agonist for the dopamine receptors. This drug is potent in nature. This drug gives inhibitory effect on prolactin cells. This drug is used in the treatment of prolactinomas. It gives higher affinity on D₂ receptors.

Apomorphine:



Systematic (IUPAC) name

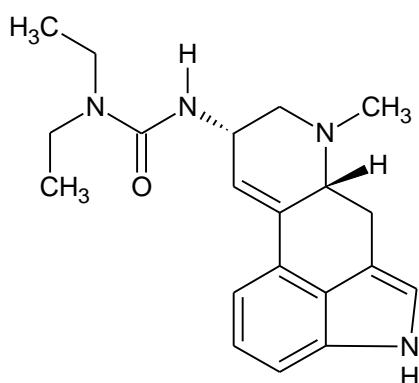
(6a*R*)-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[de,g]quinoline-10,11-diol

Apomorphine is available in the form of brand names like Apokyn, Ixense, Spontane and Uprima. This drug is an example of non selective dopamine agonist. This drug gives agonist activity for D1 and D2 like receptors. This drug is used in the treatment of homosexuality in the early 20th century. This drug is used in the treatment of erectile dysfunction. This drug is used in the treatment of Parkinson's diseases. This drug acts as potent emetic drug. Emetic means it induces vomiting. This drug should not be administered without an antiemetic drug like domperidone drug. This drug is used in the treatment of heroin addiction. Apomorphine gives agonist for both D1 and D2 dopamine receptors.

Uses:

- This drug is used in the treatment of alcohol and morphine addiction.
- This drug is used in the treatment of Parkinson's diseases as early as 1951. This drug gives strong dopaminergic action. When this drug was administered by subcutaneously, then it is effective as dopamine agonist.
- When this drug was administered by intravenously, then it gives magnitude effect.
- This drug is used in the treatment of erectile dysfunction i.e. male impotence. It stimulates dopamine in the brain, dopamine increases or enhances the sexual response. This drug gives poor efficacy.

Lisuride:



Systematic (IUPAC) name

1,1-Diethyl-3-(7-methyl-4,6,6a,7,8,9-hexahydro-indolo[4,3-fg]quinolin-9-yl)-urea

Lisuride is available in the form of brand names like Dopergin, Proclacam and Revanil. This drug is used in the treatment of Parkinson's diseases. This drug is an example of iso-ergoline class. This drug is chemically related to the dopaminergic ergoline Parkinson's drug. This drug reduces the prolactin level. This drug is used in the treatment of migraine attack but at low dose.

Mechanism of action:

This drug acts as partial dopamine agonist drug and also for serotonin receptors. This drug gives antagonistic activity for the serotonin 5HT_{2B} receptors. This drug gives high affinity for the Dopamine D₂, Dopamine D₃, and Dopamine D₄ receptors. It also gives high affinity for the serotonin 5HT_{1A} receptors and serotonin 5HT_{2A}.

CONCLUSION

Parkinson's is a neurological disorder that is mainly characterized by problems with body movements. Currently, there is no known cause of Parkinson's disease. There are many theories as to the causes and it is generally thought that multiple factors are responsible. There is currently no cure for Parkinson's disease. Research is ongoing to find new treatments for Parkinson's disease. Disease-modifying anti-Parkinson agent is desirable and may be a field of interest for research in Parkinson's disease in future.

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