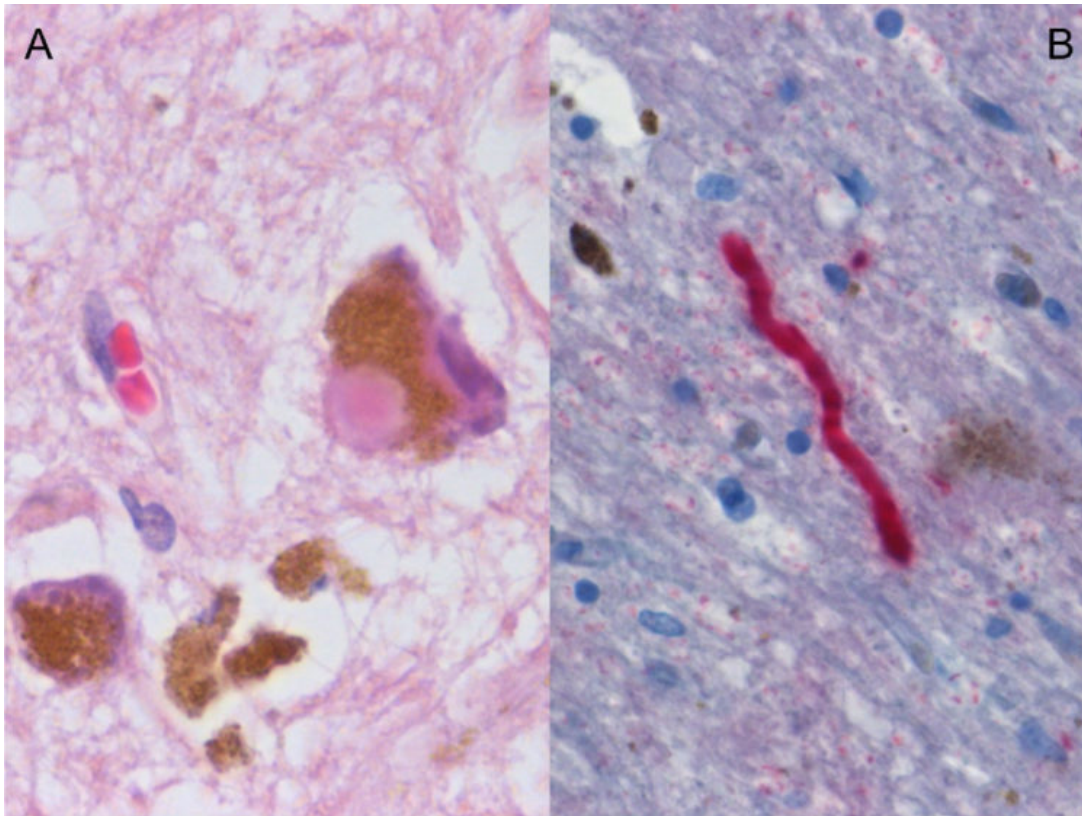


Parkinson's Disease and Other Movement Disorders

[See online here](#)

Abnormal movements can be presenting features of several neurodegenerative disorders, most commonly parkinsonism, or can occur as side effects of drugs, most commonly antipsychotics. A few other disorders can also present with abnormal movements. Drugs used in treatment of parkinsonism and other movement disorders mainly act on the central nervous system. In this article, we will study the pharmacology of these drugs.



Abnormal Movements

Tremors are rhythmic oscillatory movements around a joint. They include **resting tremors**, **postural tremors**, or **intention tremors**.

Unpredictable, irregular, and involuntary muscle jerks in different parts of the body that impair voluntary activities are known as **chorea**. Such violent abnormal movements occurring in proximal muscles of the limbs are known as **ballismus**.

Athetosis is a slow and writhing abnormal movement, while **dystonias** are sustained abnormal movements causing abnormal postures.

Tics are sudden, coordinated, repetitive abnormal movements. They are common in children and often involve the head and face.

Parkinsonism



Image: "A man with Parkinson's disease displaying a flexed walking posture." by Albert Londe (1858-1917). License: Public Domain

Rigidity, bradykinesia, tremors at rest, and postural instability are the most important clinical features seen in parkinsonism. Other features are a cognitive decline, personality changes, affective disorders, autonomic abnormalities, sleep disorders, and sensory disturbances. **Idiopathic parkinsonism** is known as Parkinson's disease or **paralysis agitans**.

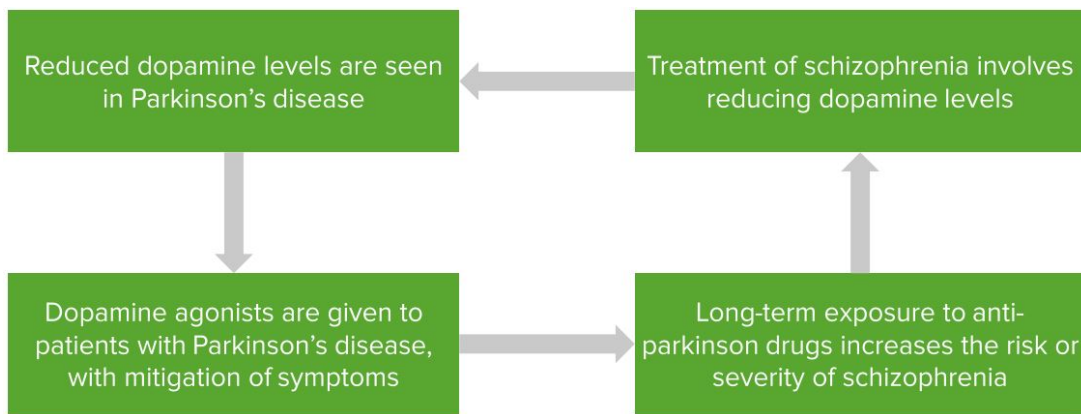
Dopamine Hypothesis

Dopamine levels are found to be reduced in the basal ganglia of the brain in parkinsonism. In idiopathic parkinsonism, **nigrostriatal dopaminergic neurons** that inhibit striatal GABAergic neurons are lost.

Most of the drugs used in treatment of parkinsonism act by increasing dopaminergic activity or restore the balance between cholinergic and dopaminergic activities. Drugs that antagonize dopamine or that damage dopaminergic nigrostriatal neurons can cause parkinsonism.

D₂ receptors are present presynaptically on axons in the **substantia nigra** and postsynaptically on striatal neurons. They are the most important subtype of dopaminergic receptors for the **antiparkinsonian effect** of drugs.

Drugs used in the treatment of parkinsonism can be broadly classified into **dopamine precursor, dopamine agonists, MAO inhibitors, COMT inhibitors, and muscarinic antagonists**.



"Circle Dopamine Hypothesis" Image created by Lecturio

Dopamine precursor – levodopa

Dopamine cannot cross the **blood-brain barrier**, and hence cannot be used in the treatment of parkinsonism.

Levodopa is a levo-isomer of dopa and a metabolic precursor of dopamine that can enter the brain via **L-amino acid transporter** and is then decarboxylated by **dopa decarboxylase** into dopamine. It is rapidly absorbed from the small intestine and its absorption is delayed by foods, hence it is best taken **30-60 minutes before meals**.

Due to decarboxylation by peripheral dopa decarboxylase, only 1-3% of the ingested levodopa reaches the brain. Hence, it is administered along with **carbidopa**, a dopa decarboxylase inhibitor that does not enter the brain; therefore, it increases the half-life of levodopa by reducing its peripheral metabolism and reduces its dose by ~75%.

Dopamine improves most of the clinical features of **parkinsonism**, but it particularly improves **bradykinesia**. However, it does not prevent the progression of parkinsonism and the clinical response usually decreases with time due to the progression of the disease.

Fluctuations in clinical response occur in relation to the timing of consumption (**end-of-dose akinesia or wearing-off reactions**) or due to an on-off phenomenon (**'off-periods'** of akinesia alternating with **'on-periods'** of improved mobility with dyskinesias).

Important side effects are **gastrointestinal** (**anorexia**, nausea, vomiting), **postural hypotension**, **cardiac** (tachycardia, asystole, **arrhythmias** such as ventricular extrasystoles or **atrial fibrillation**), **dyskinesias**, and **behavioral disturbances** (confusion, agitation, anxiety, depression, mood changes, personality changes, hallucinations, delusions, insomnia, somnolence, nightmares).



[Image](#): "Mydriasis " by Bin im Garten - Own work (own picture).
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Other possible side effects are **mydriasis** (can precipitate acute glaucoma), hot flashes, gout, smell disturbances, taste disturbances, brownish discoloration of secretions, priapism, **blood dyscrasia**, and **positive Coomb's test**.

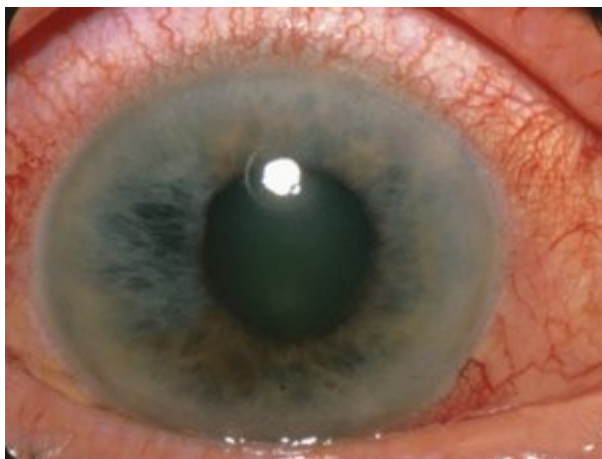
Dyskinesias can occur in up to 80% of patients after 10 or more years of duration of treatment. The most common of them is **choreoathetosis** of the face and distal extremities, others being chorea, ballismus, tremors, tics, **myoclonus**, etc. Their incidence is low with continuous drug delivery systems such as **intraduodenal or intrajejunal administration**.

Gastrointestinal side effects of levodopa can be reduced by combining the drug with **carbidopa**, by taking it in divided doses, by taking it with or immediately after meals, by very slow up-titration of the dose, or by taking antacids 30-60 minutes before the dose.

Behavioral disturbances are more common with a levodopa-carbidopa combination than with levodopa alone and can be precipitated by surgery or concurrent illness. They can be treated by **atypical antipsychotics** such as risperidone, clozapine, olanzapine, and quetiapine.

With time, tolerance can develop to lead to emetic effects and **postural hypotension**.

Drug holidays (discontinuation of levodopa for 3-21 days) are not recommended due to increased risk of **thromboembolism**, **aspiration pneumonia**, and depression in patients with severe parkinsonism, although they may improve responsiveness to levodopa and reduce some side effects.



[Image](#): "Photograph showing acute angle-closure glaucoma which

is a sudden elevation in intraocular pressure that occurs when the iris blocks the eye's drainage channel—the trabecular meshwork." by Jonathan Trobe, M.D. - The Eyes Have It. License: [CC BY 3.0](#)

In absence of carbidopa, **pyridoxine** (vitamin B₆) reduces the therapeutic effects of levodopa by enhancing its peripheral metabolism.

Psychosis and **angle-closure glaucoma** are contraindications for levodopa, while it should be used cautiously in patients with **cardiac disease**, active [peptic ulcer](#), history of melanoma or suspicious undiagnosed skin lesions.

A combination of levodopa and **monoamine A inhibitors** can precipitate **hypertensive crisis**, hence it should not be given to patients taking a MAO inhibitor or within 2 weeks of its discontinuation.

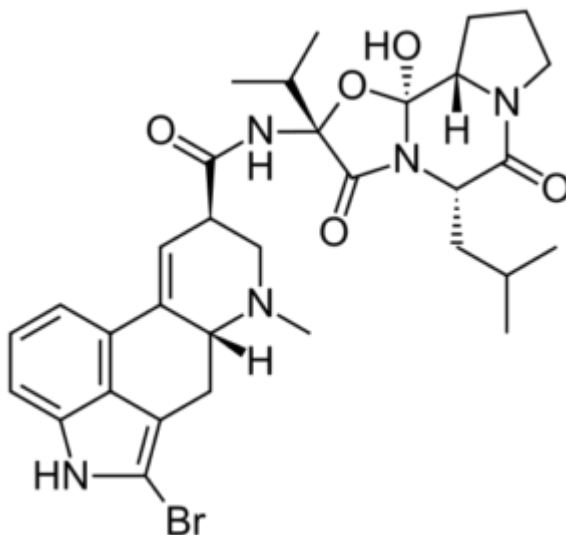
Dopamine agonists

These act directly on dopamine receptors in the brain and may be additionally beneficial over levodopa.

Response fluctuations and **dyskinesias** are less with dopamine agonists, hence they can be used as first-line therapy for parkinsonism or with low dose levodopa/carbidopa. In severe cases, they help to reduce the dose of levodopa.

Their role is important when patients taking levodopa experience end-of-dose akinesia, on-off phenomena, or are developing resistance to levodopa. General contraindications to dopamine agonists are **psychosis**, recent [myocardial infarction](#), and **active peptic ulcer**.

Ergot derivatives



[Image:](#) "Structural formula of bromocriptine" by Fvasconcellos (talk · contribs) - Own work, after ChemSpider 28858. License: [Public Domain](#)

Bromocriptine and **pergolide** are ergot derivatives that are rarely used in the treatment of parkinsonism at present.

Bromocriptine is a partial agonist at D₂ receptors and is associated with side effects like

[anorexia](#), nausea, vomiting, dyskinesias, **postural hypotension**, behavioral disturbances, headache, nasal congestion, peripheral [edema](#), **erythromelalgia**, pulmonary infiltrates, pleural fibrosis, retroperitoneal fibrosis, etc. Behavioral disturbances are more common with bromocriptine than with newer dopamine agonists.

Bromocriptine should be used cautiously in patients with **peripheral [vascular disease](#)** or **history of myocardial infarction**.

Pergolide is a D₁ and D₂ agonist and is associated with the development of **[valvular heart disease](#)**.

Ergot derivatives can also cause **painless digital vasospasm** after long-term use.

Pramipexole

This is a **non-ergot derivative** with high affinity for D₃ receptors which can be used as monotherapy in mild disease and with levodopa in advanced disease.

Its important side effects are anorexia, nausea, vomiting, **postural hypotension**, **dyskinesias**, behavioral disturbances (delusions, hallucinations, confusion, impulsivity, etc., more than those with levodopa), **narcolepsy**.

It is contraindicated in **active peptic ulcer**, psychosis, and recent **myocardial infarction**. Dose reduction is necessary for **[renal insufficiency](#)** as it is excreted mainly in the urine.

Pramipexole has a possible **neuroprotective effect** due to hydrogen peroxide scavenging action.

Ropinirole

Ropinirole is a non-ergot derivative and a **pure D₂ agonist**. It can be used as **monotherapy in mild disease** and with levodopa in advanced disease to smooth out response fluctuations.

It is metabolized by **CYP1A2**, hence **caffeine and warfarin** can reduce its clearance. Adverse effects and contraindications are similar to those of pramipexole, including **narcolepsy**.

Apomorphine

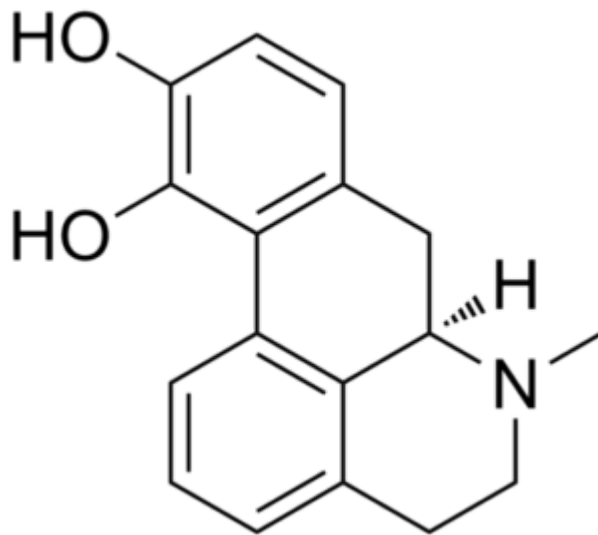


Image: "Chemical structure of apomorphine" by Edgar181 - Own work. License: Public Domain

This is a potent dopamine receptor agonist which is available in **injectable** form. Its **subcutaneous administration** is rapid, though temporarily, effective in treatment of "off-period" akinesia.

Severe nausea is an important side effect and can be prevented by pretreatment with **antiemetics trimethobenzamide** for 3 days. Other side effects are **hypotension**, drowsiness, chest pain, **perspiration**, **dyskinesias**, etc.

Rotigotine

Rotigotine is available as a **transdermal patch** which delivers even drug levels over 24 hours and is effective in **early parkinsonism**.

Advantages and adverse effects are similar to those of other **dopamine agonists**; it can also cause reactions at the application site.

Monoamine Oxidase (MAO) Inhibitors

In the brain, **norepinephrine**, **serotonin**, and **dopamine** are metabolized by MAO-A, while MAO-B selectively metabolizes dopamine. MAO inhibitors reduce the metabolism of dopamine, thus enhance the effects of levodopa.

They should not be taken by patients taking tramadol, meperidine, propoxyphene, dextromethorphan, cyclobenzaprine, or **John's wort**. Patients taking tricyclic antidepressants or serotonin reuptake inhibitors can develop **serotonin syndrome like acute reactions** if they also consume these drugs.

Selegiline

This drug selectively irreversibly inhibits MAO-B (also inhibits MAO-A at high doses). It is used as **adjunctive therapy** in parkinsonism to reduce on-off or wearing-off phenomena associated with levodopa.

An important side effect is **insomnia**, when taken later in the day.

Rasagiline

Rasagiline is a more potent MAO-B inhibitor than selegiline that can be used in the **early treatment** of symptoms of parkinsonism. It is also used as **adjunctive therapy** in parkinsonism with levodopa.

Catechol-O-Methyltransferase (COMT) Inhibitors

COMT, present in both central [nervous system](#) and peripheral tissues, is an enzyme that metabolizes levodopa to **3-O-methyldopa (3-OMD)**, which then competes with levodopa for transport across intestine and BBB, thus reducing the therapeutic effect of levodopa. COMT inhibitors reduce the peripheral metabolism of levodopa and prolong its action by increasing its bioavailability.

COMT inhibitors are used as **adjuncts** in patients taking levodopa with having **response fluctuations** as they reduce fluctuations, prolong the 'on-times,' and reduce the total dose of levodopa.

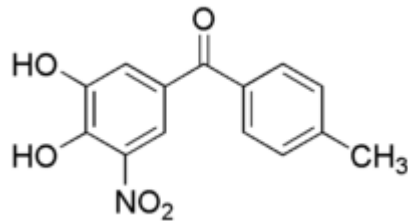


Image: "Chemical structure of tolcapone" by No machine-readable author provided. Walkerma assumed (based on copyright claims). - No machine-readable source provided. Own work assumed (based on copyright claims). License: Public Domain

Tolcapone and **entacapone** are COMT inhibitors. Tolcapone has both central and peripheral effects, while entacapone has only peripheral actions. As compared to entacapone, tolcapone is more potent and has a longer duration of action.

Important adverse effects are **nausea**, **dyskinesias**, and **confusion** (due to increased bioavailability of levodopa; reduced by lowering dose of levodopa within 48 hours of initiation), **orthostatic hypotension**, diarrhea, abdominal pain, sleep disturbances, and orange discoloration of urine.

Hepatotoxicity (increased liver enzymes and [acute liver failure](#)) is an important side effect of tolcapone and is not seen with entacapone.

Amantadine

This is an antiviral agent which is effective in parkinsonism by unknown mechanisms, possibly by potentiating the dopaminergic function by its effects on synthesis, release, or reuptake of dopamine. Other possible mechanisms are **antagonism at adenosine A_{2A} receptors** (which inhibit **D₂ receptors**), antimuscarinic effects, and inhibition of **NMDA type glutamate receptors**.

It improves **bradykinesia**, rigidity, and tremor, however, the effect lasts for a few weeks and it is less effective than levodopa. It also reduces **iatrogenic dyskinesias** seen in

patients with advanced disease.

Important side effects are **behavioral disturbances** (insomnia, irritability, excitement, confusion, hallucinations, agitation, restlessness, acute toxic psychosis), **livedo reticularis** and other dermatologic reactions, **peripheral edema** (responds to [diuretics](#)), anorexia, nausea, dry mouth, constipation, postural hypotension, urinary retention, headache, rarely **heart failure** and seizures. It is used cautiously in persons with a history of heart failure or seizures.

Antimuscarinic drugs

These decrease excitatory effects of cholinergic neurons on **striatal neurons** and help to improve the dopamine/acetylcholine ratio in the brain. They improve tremor and rigidity, but not **bradykinesia** and have only an adjuvant role.

Common drugs are benztropine, trihexyphenidyl, biperiden, orphenadrine, and procyclidine.

Important side effects are **behavioral effects** (mood changes, hallucinations, delusions, confusion, inattention, drowsiness), dry mouth, constipation, and blurring of vision. They reduce some **extrapyramidal symptoms** induced by antipsychotics drugs but exacerbate **tardive dyskinesias** caused by them.

They are contraindicated in patients with **prostatic hyperplasia**, **glaucoma**, and **pyloric stenosis**.

Overview

Drugs used to treat parkinsonism		Drugs used to treat other movement disorders	
Dopamine precursors <ul style="list-style-type: none">• Levodopa	MAO inhibitors <ul style="list-style-type: none">• Selegiline	Tremor <ul style="list-style-type: none">• Propranolol Wilson's disease <ul style="list-style-type: none">• Penicillamine	Huntington's disease <ul style="list-style-type: none">• Haloperidol
Dopamine agonists <ul style="list-style-type: none">• Bromocriptine• Pramipexole	COMT inhibitors <ul style="list-style-type: none">• Entacapone	Complex choreas <ul style="list-style-type: none">• Haloperidol	Tourette's syndrome <ul style="list-style-type: none">• Tetrabenazine• Haloperidol• Others

Other Movement Disorders

Tremor

Propranolol (β -adrenergic blocker) is used in the treatment of **physiologic postural tremor** and **essential tremor**. It should be cautiously used in patients with **asthma**, **heart failure**, heart block, and hypoglycemia.

Metoprolol (selective β_1 -blocker) can be used in the treatment of **essential tremors** when propranolol is contraindicated.

Other drugs that are used in the treatment of essential tremor are gabapentin, topiramate, primidone, alprazolam, and botulinum toxin.

Huntington's disease

This is a genetic disorder resulting from reduced **GABAergic and cholinergic functions** and enhanced dopaminergic functions in the brain presenting with **progressive chorea and dementia**.

Reserpine depletes cerebral dopamine and reduces abnormal movements. Common side effects are sedation, depression, hypotension, nasal congestion, and diarrhea.

Tetrabenazine has similar action but has less side effects.

Antipsychotics (haloperidol, perphenazine, olanzapine) and antiepileptics (gabapentin, primidone, topiramate) may also be useful.

Gilles de la Tourette's syndrome

Haloperidol and **pimozide**, D₂ receptor antagonists, are commonly used in treatment.

Other less effective drugs are carbamazepine, clonazepam, clonidine, guanfacine, fluphenazine, risperidone, and aripiprazole.

Restless legs syndrome

This condition is characterized by unpleasant discomfort in the legs, especially at rest at night. The exact cause is unknown, but it is more common in **pregnant women** and patients with **diabetes mellitus or uremia**.

The dopamine agonists **pramipexole** and **ropinirole** are approved for its treatment. Other drugs that can be used are carbamazepine, benzodiazepines, gabapentin, and opioid analgesics.

Wilson's disease

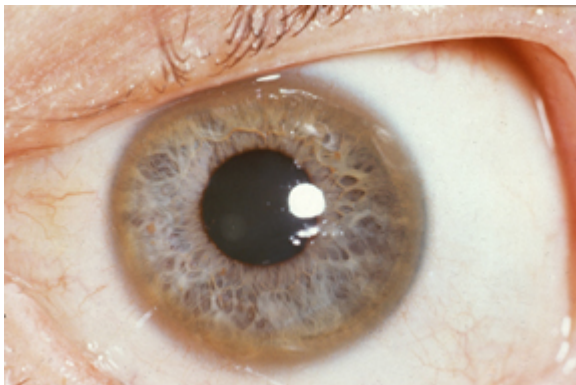


Image: "Kayser-Fleischer ring: copper deposition in Descemet's membrane of the cornea. These rings can be either dark brown, golden, or reddish-green, are 1 to 3 mm wide, and appear at the corneal limbus. With rare exceptions, they are diagnostic of inherited hepatolenticular degeneration - Wilson's disease. This 32-year-old patient complained of longstanding difficulty speaking. He also had a tremor." by Herbert L. Fred, MD, Hendrik A. van Dijk - <http://cnx.org/content/m15007/latest/>, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

This is a genetic disorder characterized by the deposition of copper salts in hepatic and brain tissues. **Penicillamine**, a chelating agent, is a mainstay of its treatment.

Drug-induced dyskinesias

Butyrophenone and phenothiazine groups of antipsychotic drugs cause parkinsonism by D₂ antagonism, which can be treated by reducing the dose, changing the drug, or by adding an antimuscarinic agent.

Reserpine and **tetrabenazine** cause parkinsonism by depleting brain dopamine, while **MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)** causes destruction of dopaminergic neurons in the nigrostriatal tract producing irreversible parkinsonism.

Parenteral benztropine or **diphenhydramine** can be used in the treatment of **acute dystonias** caused by antipsychotics. No specific drug is available for the treatment of **tardive dyskinesias**, although clonazepam, clozapine, risperidone have been used with limited success.

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