

# [The cholinergic drug](https://assignbuster.com/the-cholinergic-drug/)

A cholinergic drug is a drug that acts on the peripheral nervous system, the central nervous system, or both and enhances the effects that are mediated by acetylcholine. It is also known as cholinergic agent, parasympathomimetic drug or cholinergic agonist. [1][2] It can work in two ways; either acting directly by mimicking the effects of acetylcholine at one or more acetylcholine receptors present in the body, or acting indirectly by blocking/inhibiting the enzyme acetylcholine that is responsible for the degradation/ hydrolysis of acetylcholine. [1][2]

Depending on the type of receptor to act on, cholinergic drugs are either classified as muscarinic agonists or nicotinic agonists. [6]

### Anticholinergic drugs:

An anticholinergic drug is a drug or an agent that competes with the neurotransmitter “ acetylcholine” for its binding sites at synaptic junctions thereby suppressing or inhibiting its activity and thus preventing the transmission of parasympathetic nerve impulses. [3][4]

Depending on the type of receptor to act on, anticholinergic drugs are either classified as muscarinic antagonists or nicotinic antagonists. [6]

### Pilocarpine: (Chemical formula= C11H16N2O2)

### Introduction:

Pilocarpine is a naturally occurring alkaloid which is extracted from the South American shrub named “ Pilocarpus jaborandi”. It is a non-selective cholinergic parasympathomimetic agonist that binds to muscarinic-M3 receptors and results in contraction of smooth muscles and stimulation of various exocrine glands. [5]

The drug is available in the form of eye drops, tablets, suspensions and gel. It has a slow onset of action which is about 10 to 15 minutes but has a longer duration of action of about 6 to 8 hours, and therefore can be given thrice a day. It is inactivated at neuronal synapses and in plasma and is excreted in urine.

“ Pilocarpine can be used in combination with other sympathomimetics, carbonic anhydrase inhibitors, miotics, beta-blockers, or hyperosmotic agents”. [8]

### History:

* In 1875, Mr. Gerrard discovered pilocarpine from the leaves of Pilocarpus jaborandi. At that time, he believed that there were at least two alkaloids present in this plant. At the same time, M. Hardy isolated pilocarpine.
* “ In 1876, the isolated pilocarpine alkaloid was introduced to conventional ophthalmology for the treatment of glaucoma”.
* 1879, Straws, while doing an active research concerning the sudoriferous secretion in cases of facial paralysis, was the first to employ local medication with pilocarpine and published relevant results.

### Chemical synthesis of pilocarpine:

Although pilocarpine looks like a simple molecule but it has a complex chemical synthesis. This is because of the stereospecific construction of the imidazole moiety that is cis to the ethyl group on the butyrolactone ring which makes its synthesis difficult and challenging. The starting reagent for its synthesis is 2-acetylbutyrolactone which undergoes selenenylation by reacting with phenylaelenenyl chloride to produce a seleno lactone “ 2-acetyl-2-(phenylselenyl) butyrolactone” with a yield of 94%. This is then subjected to oxidative elimination of selenoxide in the presence of cyclo-pentadiene and hydrogen peroxide to produce a mixture of endo and exo bicycle ketones in a ratio of 2. 3: 1. Pyrolysis (flash vacuum thermolysis) of these ketones produces a white solid “ 3-acetyl-2(5H)-furanone” with a yield of 95%. This ketone is then reduced under mild conditions by treating it with an asymmetric reducing agent “(+)-?-chlorodiisopinocamphenylborane”, which is used particularly for chiral reductions, to produce (3R)-3-(1-hydroxyethyl)-2(5H)-furanone in 60% chemical yield and an optical purity of > 92% that was determined by NMR analysis. Next, a stereocentre is introduced at C4 of the (3R)-3-(1-hydroxyethyl)-2(5H)-furanone by the Claisen rearrangement at its vinyl ether which produces an exocyclic double bond and the (4R)-acetaldehyde side chain. Both of them are necessary for the formation of the imidazole ring. This will result in a 2: 1 mixture of (4R)-(Z)-dehydrohomopilopic aldehyde and (4S)-E-diastereomer in 71% yield. Hydrogenation of (4R)-(Z)-dehydrohomopilopic aldehyde in the presence of pyridine/benzene (1: 1) solution at 25? C at 1atm for 1 hour produces (3s, cis)-Homopilopic aldehyde. Finally, when (3s, cis)-Homopilopic aldehyde is reacted with 1, 5-disubstituted imidazole under aprotic conditions, it results in the formation of pilocarpine in 61% yield. [9]

### Structure-activity relationship (SAR):

The nitrogen on the imidazole ring is protonated before interacting with the muscarinic receptor. There is a strong ionic interaction between the charged nitrogen atom and an anionic side group of an aspartate residue in the receptor. The methyl substitute on the nitrogen is positioned in an open region of the binding site. Hydrogen bonding interactions exist between the ester group of pilocarpine and an asparagines residue of the cholinergic receptor. A small hydrophobic pocket exists in the receptor site which can accommodate the methyl group of pilocarpine. The drug has a correct pharmacophore for the muscarinic receptor with a separation between nitrogen and oxygen being 4. 4? A. [6]

### Mechanism of action:

Pilocarpine is a direct acting cholinergic agent that resembles acetylcholine and therefore binds to the same muscarinic neuroreceptor and results in its stimulation. In eye, it causes contraction of the iris sphincter muscle and therefore results in miosis (pupil constriction).

### Clinical uses:

Pilocarpine has been used in the treatment of both acute closed-angle and chronic open-angle glaucoma. [8] Glaucoma is a condition when the aqueous contents of the eye cannot be drained. This result in increased intraocular pressure which causes optic nerve damage and can lead to side vision damage (peripheral vision damage) and if not treated, can result in central vision damage and leads to irreversible blindness. [6]

Pilocarpine is also used to treat xerostomia which is a condition characterised by dryness of the oral mucosa. The drug acts on cholinergic receptors in the glandular parenchyma thereby increasing the salivary secretion. [7]

Pilocarpine hydrochloride (Salagen) tablets are prescribed to the patients suffering from Sjögren syndrome (SS) in order to treat their symptoms of xerostomia (dry mouth) and xerophthalmia (dry eyes). “ Sjögren syndrome (SS) is a chronic, autoimmune, rheumatic disorder” in which immune cells attack and destroy the exocrine glands that produce tears and saliva. This in turn makes the individual susceptible to various infections and if untreated may also lead to other complications like “ bacterial sialadenitis, bacterial conjunctivitis, stomatopyrosis (burning mouth), oral candidiasis, oral ulcers, periodontal disease, accelerated dental caries, corneal ulceration or perforation, malnutrition, weight loss and sleep disruption”. [5]

Pilocarpine is also used to diagnose cystic fibrosis (CF). [8] Cystic fibrosis is a common hereditary disease which is characterised by scarring (fibrosis) and formation of cyst within the pancreas. The disease is characterised by shortness of breath, frequent chest infections, sinus infections, salty tasting skin, normal appetite but poor growth and poor weight gain, excess mucus production, diarrhea and infertility in males. [14] Sweat test method is used to diagnose of disease in which the drug stimulates sweat glands in order to measure the concentration of chloride and sodium that is excreted in the sweat.

“ Pilocarpine is often used as an antidote for Atropine, Hyoscyamine and Scopolamine poisoning”. [8]

### Adverse effects:

Since pilocarpine is a non-selective muscarinic receptor anonist, its use can result in a wide variety of side-effects which can include lacrimation, excessive perspiration, excessive salivation, bronchospasm, increased bronchial mucus secretion, muscle tremors, tachycardia, hypertension, diarrhea, blurred vision and eye pain, browache and miosis when used chronically as an eye drop.

When pilocarpine is used in the form systemic injection, it can cross the blood-brain barrier and reach the brain where it can lead to chronic epilepsy. [13]

### Suggestions for design of new drugs:

Pilocarpine has significant delivery problems associated with its low lipophilicity. Its bioavailability in the eye is low, duration of action is fast due to its rapid elimination from the eye and above all, it has serious side effects like miosis and myopia. Based on the knowledge of dependence of drug delivery with physicochemical properties of the drug, a prodrug approach can be used to improve the delivery characteristics of pilocarpine. A prodrug should be designed such that it has a higher lipophilicity than pilocarpine which would enable it to cross the corneal membrane with ease, should have sufficient aqueous solubility so that it could be formulated as eyedrops, should be able to convert back to the active parent drug within the cornea, should have a controlled release and a prolonged duration of action. [10]

### Curare:

### Introduction:

Curare is a nicotinic antagonist. It is a crude, dried extract from a plant called Chondrodendron tomentosum. [6] It is a mixture of 70 alkaloids. [11] The active principle in curare is tubocurarine (C37H41N2O6). [6]The antidote for curare poisoning is an acetylcholinesterase (AChE) inhibitor (anti-cholinesterase), such as physostigmine or neostigmine. [15]

The drug is available in the form of solutions and intravenous injections. It has an onset of action of about 4 to 6 minutes and duration of action of about 80 to 120 minutes. It is eliminated through kidney and liver.

### History of curare:

During the sixteenth century, the South American indigenous people used curare as a paralyzing poison where they killed the prey by dipping the arrows or blowgun darts in curare. [16]The prey is killed due to asphyxia in which the respiratory muscles fail to contract. [16]

In 1780, Abbe Felix Fontana studied the effects of curare on heart, voluntary muscles and nerves and found that it affects the voluntary muscles of the body as compared to the other two. [15]

In 1800, Alexander von Humboldt reported the method used by the Orinoco River natives to prepare the curare toxin from its plant source.[16]

During 1811-1812 Benjamin Collins Brodie (1783-1862), a leading English surgeon, experimented with curare. [16]He found that curare paralysed the respiratory muscles but the heart continued to beat for a while. [16]He was the first to show that if the animal’s respiration is maintained artificially, recovery is complete. [16]

In 1850, George Harley found that tetanus or strychnine poisoning can be cured by using curare. [15]

“ From 1887 the Burroughs Wellcome catalogue listed under its ‘ Tabloids’ brand name, tablets of curare at 1/12 grain (price 8 shillings) for use in preparing a solution for hypodermic injection”. [15]

In 1939, Henry Hallett Dale reported the antagonistic effect of curare on acetylcholine. [15]

### Mechanism of action:

Curare is a non-depolarizing muscle relaxant that blocks the nicotinic acetylcholine receptor. The main toxin of curare, d-tubocurarine, is a competitive antagonist of acetylcholine and so occupies the same position on the receptor as the neurotransmitter but does not switch it on. The overall effect on the body is the same as it would be in the absence of acetylcholine. [15]

### History of tubocurarine:

In 1935, Harold King of London was experimenting on a sample of curare in Sir Henry Dale’s laboratory and was not only able to isolate tubocurarine in its pure form from the crude drug but also discovered its chemical structure. [16]

In 1912, tubocurarine was used for the first time in medicine. [15]

In 1942, tubocurarine was used along with anaesthetics in surgical procedures to relax muscles. [15]

### Structure-activity relationship:

The structure of tubocurarine is shown in fig. Although the molecule does not have an ester group to bind to the nicotinic receptor, but it has two positively charged nitrogen atoms, one of which is a tertiary nitrogen atom while the other is a quaternary nitrogen. One of them binds to the anionic binding region of the nicotinic receptor while the other binds to a nearby cysteine residue that is 0. 9-1. 2nm away. Such an intreraction is so strong that it makes up for the lack of the ester binding interaction. Also, the distance between the two positive centres is 1. 15nm which is also important for the activity of the drug. [6]

### Indication

Curare is used in the diagnosis of myasthenia gravis, [17]which is an autoimmune disease in which antibodies are produced against acetylcholine nicotinic post synaptic receptors at the neuro-muscular junction. [18]

Curare is also used in surgical procedures in association with general anesthesia in order to facilitate in the relaxation of abdominal muscles when it is not possible with inhalation anesthesia. [12]

### Adverse effects:

Curare has undesirable side-effects, the most common of which include hypotension (by ganglion-block and histamine release), bronchoconstriction (by histamine release), skeletal muscles paralysis and asphyxia (impaired breathing). [15]

### Suggestions for design of new drugs:

Tubocurarine has undesirable side effects because it also acts as an antagonist at the nicotinic receptors of the autonomic nervous system. Also, its deactivation depends on metabolic mechanisms involving enzymatic deactivation and/or excretion, the efficiency of which varies from patient to patient and is particularly poor for patients with low levels of plasma esterases or kidney failure. Therefore, a self-destruct mechanism can be introduced into the design of a new drug for its sufficiently rapid breakdown. If a good electron withdrawing group is introduced on to a carbon that is beta to the quaternary nitrogen centre, Hofmann elimination is possible under the slightly alkaline pH of blood (pH = 7. 4) and body temperature. The electron-withdrawing groups will function to increase the acidity of the hydrogen on the beta-carbon such that it is easily lost. Thus by introducing such a group, the drug is inactivated and is unable to bind to its receptor due to the loss of the positive charge on the quaternary centre and is split into two molecules. Thus deactivation occurs at a constant rate between patients. [6]