Pharmacology

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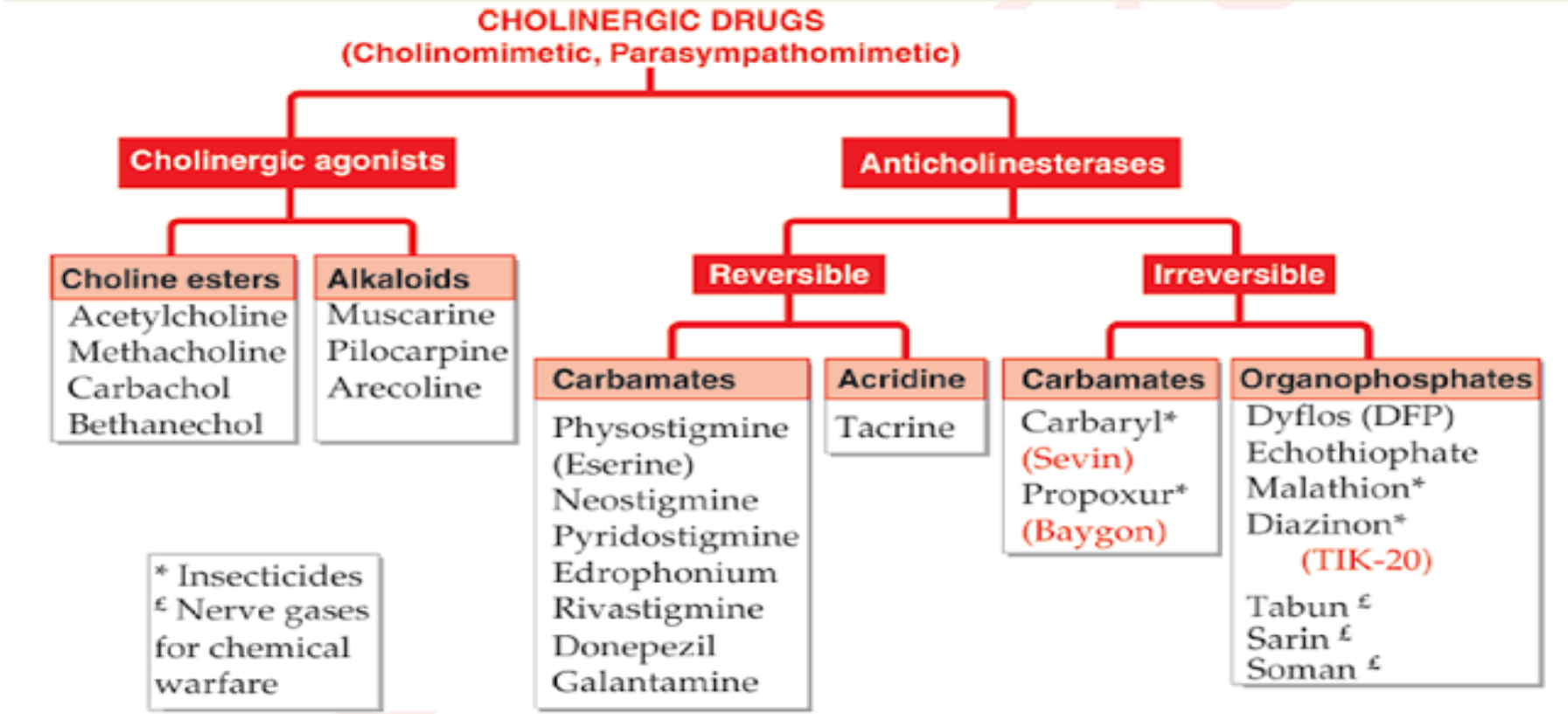
MSc. Pharmacology

Basic science department/collage of dentistry

Al-Mustansiriyah University

Clinical application of Cholinergic drugs

Drug Acting on Autonomic Nervous system



Clinical application of Cholinergic drugs

1.Myasthenia gravis: The initial first-line therapy for most patients is anticholinesterase medication, usually pyridostigmine. Neostigmine is also available but not commonly used.

2.Dementia: Cholinesterase inhibitors like rivastigmine, donepezil, galantamine are the available medications for cognition and global functioning in patients with dementia of all causes. Their primary use is in mild to moderate Alzheimer disease.

3.Ophthalmology: Pilocarpine work by increasing the aqueous outflow and hence decrease the intra-ocular tension in open-angle glaucoma. Miotics are used as an add on therapy and are now third-choice drugs.

4.Reversal of non-depolarizing neuromuscular blockade after surgery: Neostigmine preceded by atropine to block muscarinic effects, rapidly reverses muscle paralysis induced by non-depolarizing neuromuscular blockers .

Clinical application of Cholinergic drugs

5.Postoperative urinary retention: For both prevention and treatment of urinary distention and retention, neostigmine is a common option. Bethanechol is the indicated pharmaceutical treatment of acute postoperative and postpartum non-obstructive urinary retention.

6.Xerostomia: Use of muscarinic agonists in patients with an inadequate response to artificial saliva and mechanical stimulation in Sjogren syndrome or patients post-radiation treatment associated with head and neck cancer.

Sjogren's Syndrome: Pilocarpine is used to stimulate salivary secretions in patients with reduced saliva production caused by autoimmune disease (Sjogren's Syndrome) or damage to saliva glands due to radiation therapy.

7.Anticholinergic overdose: Physostigmine is the specific antidote for poisoning with atropine or other anticholinergics. It should only be used to reverse toxic, life-threatening delirium caused by an anticholinergic agent (atropine, scopolamine, diphenhydramine).

Administration

Pilocarpine (Isopto carpine®)eye drop,(Salagen®) tab

physostigmine intravenous, intramuscular, ophthalmic

For the treatment of myasthenia gravis, pyridostigmine(mestinon®) dosing is oral. It can be given parenterally to patients who cannot take it orally.

Neostigmen (prostigmin®) tab,injection

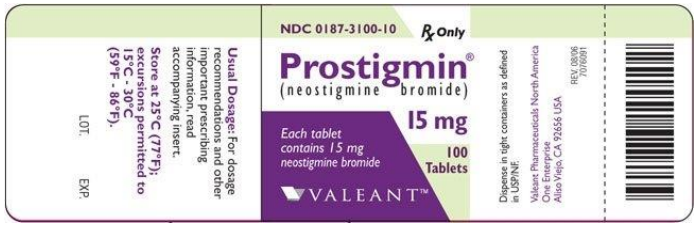
Rivastigmine(Exelon®)oral,cap.,patch, donepezil(Aricept®)tab, and galantamine (Reminyl®)are administered orally in Alzheimer disease.













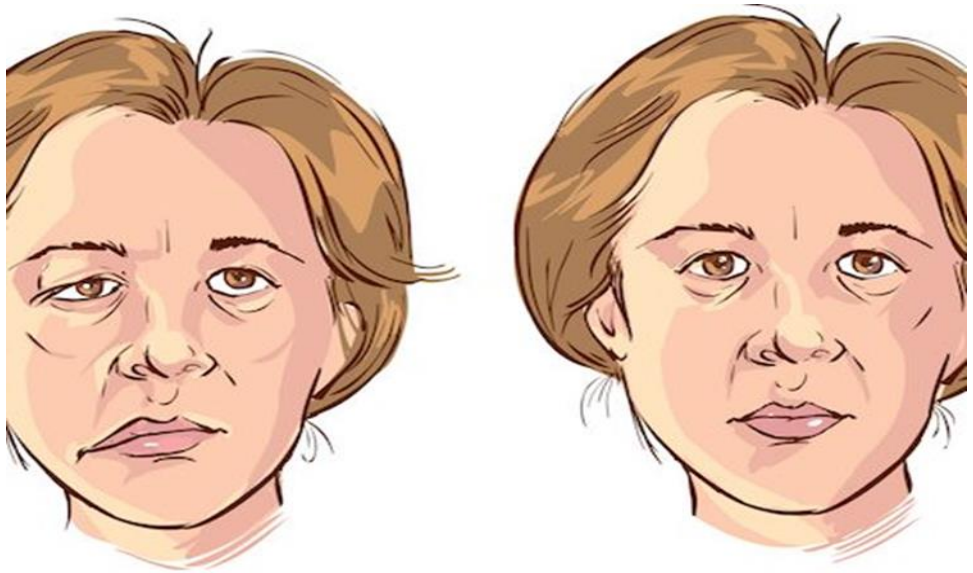






Myasthenia gravis (MG):

Myasthenia gravis: from Greek (muscle weakness) is an autoimmune neuromuscular disease. Muscle weakness is caused by circulating antibodies that block acetylcholine receptors at postsynaptic neuromuscular junction, inhibiting the excitatory effects of the neurotransmitter acetylcholine on nicotinic receptors at neuromuscular junctions.





Signs and symptoms:

- **Fatigability.** Muscles become progressively weaker during periods of activity and improve after periods of rest.

Muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing are especially susceptible. The muscles that control breathing and neck and limb movements can also be affected.

- The weakness of the muscles involved in swallowing may lead to swallowing difficulty (**dysphagia**).
- First noticeable symptom is weakness of the eye muscles, difficulty in swallowing and **slurred speech** may be the first signs.
- Due to weakness of the muscles of facial expression and muscles of mastication, facial weakness may manifest as the inability to hold the mouth closed (the "**hanging jaw** sign") and as a snarling expression when attempting to smile. With **drooping eyelids**, facial weakness may make the individual **appear sleepy or sad**. Difficulty in holding the head upright may occur.

- The muscles that control breathing and limb movements can also be affected; rarely do these present as the first symptoms of MG, but develop over months to years. In a myasthenic crisis, a **paralysis of the respiratory muscles** occurs, necessitating assisted ventilation to sustain life.
- The thymus gland cells form part of the body's immune system. In those with myasthenia gravis, the thymus gland is large and abnormal. It sometimes contains clusters of immune cells that indicate lymphoid hyperplasia, and the thymus gland may give wrong instructions to immune cells.

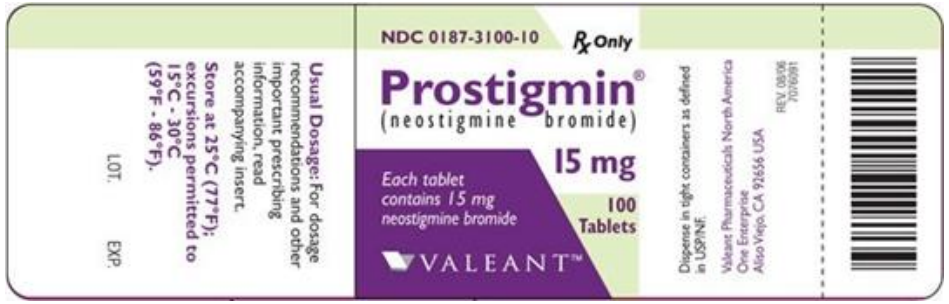
Medication:

1) Acetylcholinesterase inhibitors: neostigmine and pyridostigmine can improve muscle function by slowing the natural enzyme cholinesterase that degrades acetylcholine in the motor end plate. The first medicine used for myasthenia gravis is usually a tablet called pyridostigmine, which helps electrical signals travel between the nerves and muscles. It can reduce muscle weakness.

2) Immunosuppressive drugs: prednisone, azathioprine may be used. These work by reducing the activity of immune system to stop it attacking the communication system between the nerves and muscles.

3)In selected cases, **thymectomy** may be considered.





Diagnosis

-Edrophonium(Enlon®) test **(Tensilon test)**: short acting acetylcholinesterase inhibitor, improvement seen in 5 minute and last 10 minute

-Antibodies detected in serum

-A chest CT-scan showing a thymoma

Tensilon test (edrophonium test) is a pharmacological test used for the diagnosis of certain neural diseases, especially myasthenia gravis .It is also used to distinguish a myasthenic crisis from a cholinergic crisis in individuals undergoing treatment for myasthenia gravis.

Edrophonium is used for the diagnosis of myasthenia and in differentiating myasthenic crisis from cholinergic crisis in patient with this disease . Because cholinergic crisis can result in muscle weakness like that of myasthenic crisis short acting cholinomimetic as edrophonium will improve muscle strength in myasthenic crisis but weaken it in cholinergic crisis

What is cholinergic crisis?

- Cholinergic crisis results from an excess of acetylcholine at nicotinic and muscarinic receptor sites and usually occurs as a result of excess anticholinesterase administration. a cholinergic crisis include
- weakness, wheezing, increased secretions, fasciculations, nausea, vomiting, diarrhea, lacrimation, bradycardia, and hypotension. Respiratory muscle weakness may progress rapidly to respiratory failure.
- **Cholinergic crisis** and **myasthenic crisis** can both present with muscle weakness and may be hard to differentiate .

Cholinergic crisis and **myasthenic crisis**

- The edrophonium test usually helps to distinguish between the two entities. A small dose of edrophonium (2–10 mg) is administered.

Myasthenic crisis (a relative dearth of acetylcholine) should show improved strength while a cholinergic crisis (a relative excess of acetyl-choline) will demonstrate no change in strength or exacerbation of symptoms. Rapid progression to respiratory failure may necessitate emergent intubation and controlled ventilation. The muscarinic side-effects of a cholinergic crisis may be treated with atropine or glycopyrrolate.

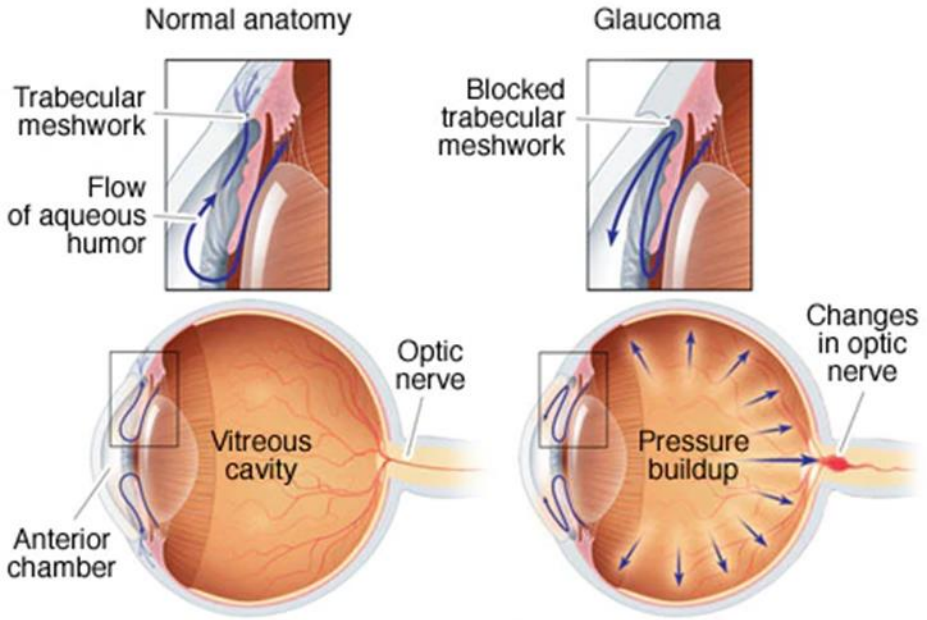


Glaucoma

Is a disease that damages the eye's optic nerve. It usually happens when fluid builds up in the front part of the eye. That extra fluid increases the pressure in the eye, damaging the optic nerve.

Glaucoma is a leading cause of blindness for people over 60 years old. But blindness from glaucoma can often be prevented with early treatment.

In a healthy eye, excess fluid leaves the eye through the drainage angle, keeping pressure stable.



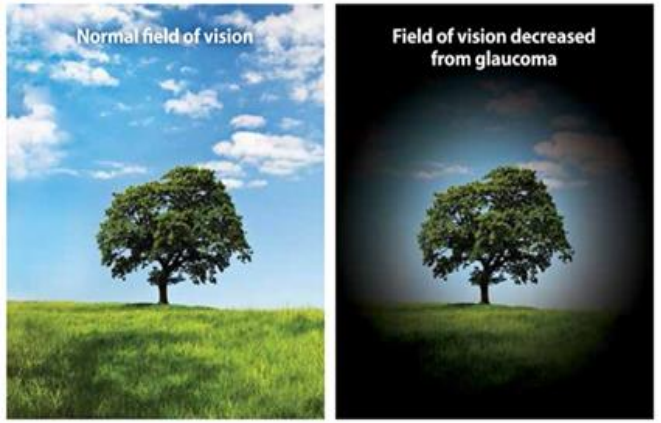
Types of glaucoma

There are two major types of glaucoma. (The angle refers to the area between the iris and cornea, through which fluid must flow to escape via the trabecular meshwork):

1.Primary open-angle glaucoma

This is the most common type of glaucoma. It happens gradually, where the eye does not drain fluid as well as it should .As a result, eye pressure builds and starts to damage the optic nerve. This type of glaucoma is painless and causes no vision changes at first.

- As the disease progresses, blind spots develop in peripheral (side) vision.
- Most people with open-angle glaucoma do not notice any change in their vision until the damage is quite severe.

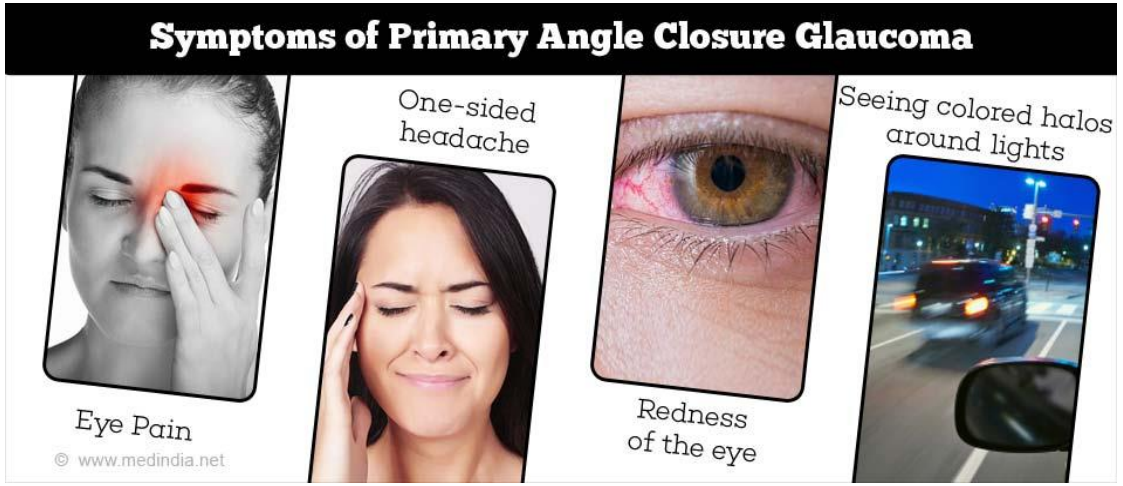


2.Angle-closure glaucoma “closed-angle glaucoma” or “narrow-angle glaucoma”

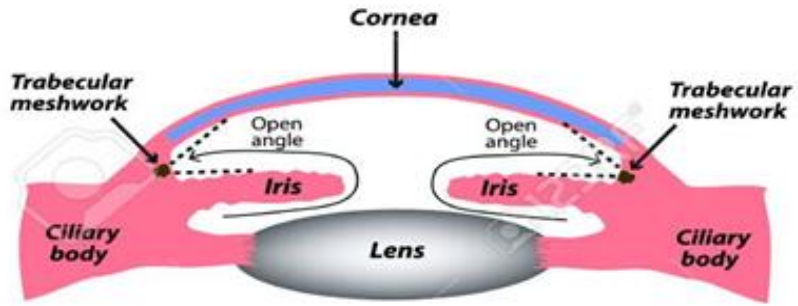
When someone’s iris is very close to the drainage angle in their eye. The iris can end up blocking the drainage angle. When the drainage angle gets completely blocked, eye pressure rises very quickly. This is called an acute attack. It is a true eye emergency, or might go blind.

Signs of an acute angle-closure glaucoma attack:

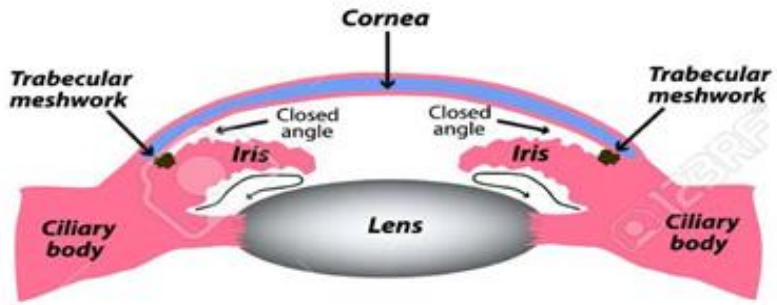
- vision is suddenly blurry, severe eye pain, a headache, nausea, vomit, see rainbow-colored rings or halos around lights



TYPES OF GLAUCOMA



OPEN-ANGLE GLAUCOMA



ANGLE-CLOSURE GLAUCOMA

Causes of Glaucoma

Eye constantly makes aqueous humor. As new aqueous flows into the eye, the same amount should drain out. The fluid drains out through an area called the drainage angle.
This process keeps pressure in the eye (called intraocular pressure or IOP) stable.
But if the drainage angle is not working properly, fluid builds up. Pressure inside the eye rises, damaging the optic nerve.

Who Is at **Risk for Glaucoma**?

people who: are over age 40, have family members with glaucoma, have high eye pressure

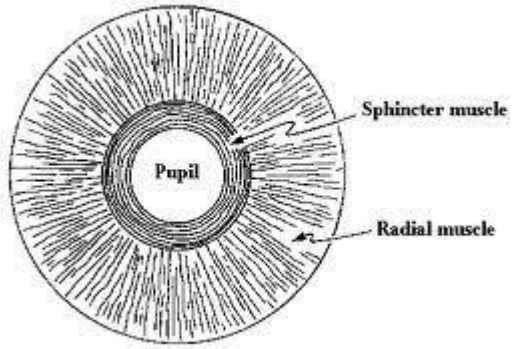
use long-term steroid medications, have corneas that are thin in the center, have thinning of the optic nerve, have diabetes, migraines, high blood pressure

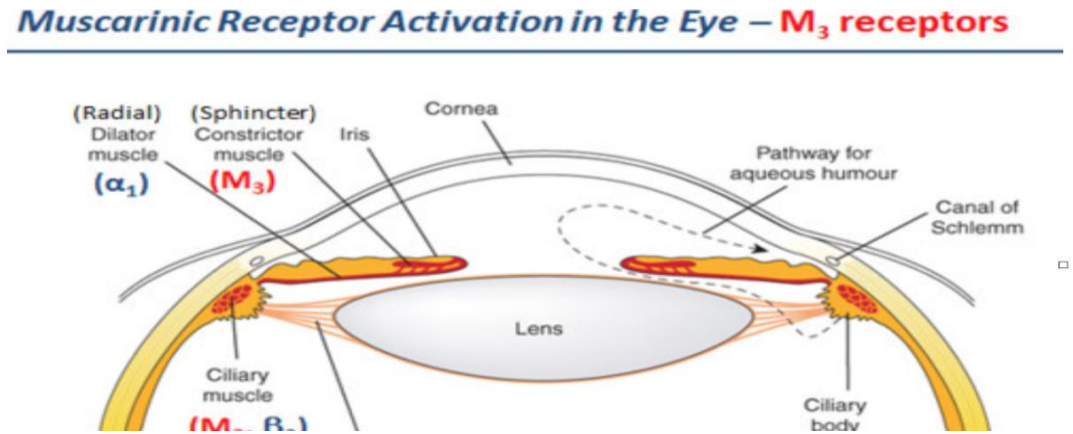
Treatment

In acute glaucoma: drainage of aqueous humor become impeded when the pupil is dilated because folding of the iris tissue occludes the drainage angle, causing the intraocular pressure to rise.

Activation of the constrictor pupillae muscle by muscarinic agonists in these circumstances lower the intraocular pressure.

Target		Receptor	Response
Eye	Sphincter	M_3	Contraction—miosis
	Ciliary muscle	M_3	Contraction—accommodation for near vision





Treatment

Glaucoma treatment often starts with prescription eyedrops. These can help decrease eye pressure by improving how fluid drains from the eye or by decreasing the amount of fluid the eye .

Prescription eyedrop medications include:

- **Prostaglandins.** These **increase the outflow** of the fluid in the eye (aqueous humor), thereby reducing eye pressure. **latanoprost** (Xalatan), **travoprost** (Travatan)
- **Beta blockers.** These **reduce the production** of fluid in eye, thereby lowering the pressure in the eye (intraocular pressure). Examples include **timolol** (Timoptol), **Betaxalol** HCl (Betoptic)
- **Alpha-adrenergic agonists.** These **reduce the production** of aqueous humor and increase outflow of the fluid in the eye. Examples include **apraclonidine** and **brimonidine** (Alphagan).
- **Carbonic anhydrase inhibitors.** The carbonic anhydrase inhibitors **Acetazolamide** (systemic administration), **Brinzolamide** (Topical), and **dorzolamide**(Topical Trusept)These medicines **reduce the production** of fluid in the eye

Treatment

- **<u>Miotic or cholinergic agents</u>.** These increase the outflow of fluid from eye. An example is **pilocarpine** (Isopto Carpine). Side effects include headache, eye ache, smaller pupils, possible blurred vision
- Acute Angle Closure Glaucoma: Muscarinic agonists produce contraction of the iris sphincter muscle, producing a small pupil diameter (miosis), and contraction of the ciliary muscle, which opens the trabecular network to allow increased outflow of aqueous humor through the canal of Schlemm. Eye drops used to reduce intraocular pressure in the setting of acute angle-closure glaucoma, prior to surgery which is required to produce a permanent correction.

Antiglaucoma drugs (combined preparations)

- Dorzolamide +timolol Eye drop
- Latanoprost + timolol Eye drop

Oral medications

If eyedrops alone don't bring the eye pressure down to the desired level, may also prescribe an oral medication, usually a carbonic anhydrase inhibitor.

Surgery and other therapies

Other treatment options include laser therapy and various surgical procedures. Many techniques are intended to improve the drainage of fluid within the eye, thereby lowering pressure

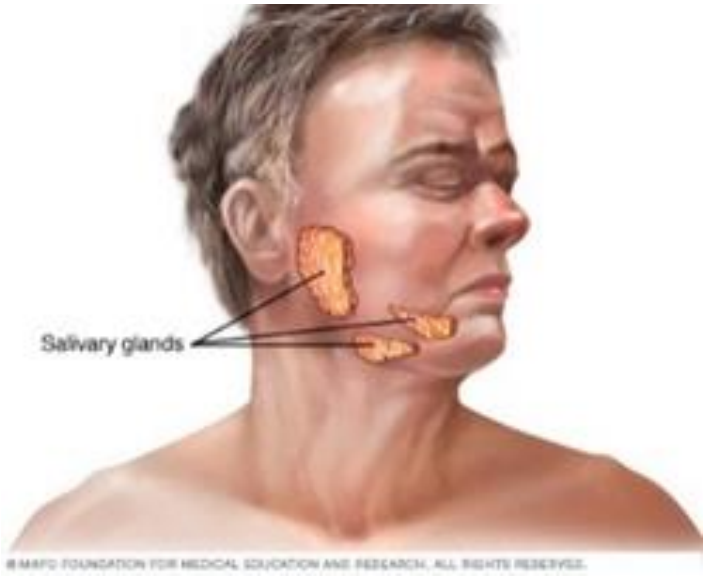
Sjogren's Syndrome:

- Sjogren's (SHOW-grins) syndrome is a disorder of immune system identified by its two most common symptoms dry eyes and a dry mouth.

- The condition often accompanies other immune system disorders, such as rheumatoid arthritis . In Sjogren's syndrome, the mucous membranes and moisture-secreting glands of eyes and mouth are usually affected first resulting in decreased tears and saliva.

- Although develops of Sjogren's syndrome at any age, most people are older than 40 . The condition is much more common in women. Treatment focuses on relieving symptoms.







The main symptoms of Sjogren's syndrome are:

Dry eyes. The eyes might burn, itch or feel gritty as if there's sand in them.
Dry mouth. the mouth might feel like it's full of cotton, making it difficult to swallow or speak.

Some people with Sjogren's syndrome also have one or more of the following:

- Joint pain, swelling and stiffness
- Swollen salivary glands particularly the set located behind jaw and in front of ears
- Skin rashes or dry skin
- Persistent dry cough
- Prolonged fatigue



Causes

Sjogren's syndrome is an autoimmune disorder. immune system mistakenly attacks body's own cells and tissues.

Scientists aren't certain why some people develop Sjogren's syndrome. Certain genes put people at higher risk of the disorder, but it appears that a triggering mechanism such as infection with a particular virus or strain of bacteria is also necessary.

In Sjogren's syndrome, immune system first targets the glands that make tears and saliva. But it can also damage other parts of your body, such as:

Joints, Thyroid , Kidneys, Liver, Lungs, Skin, Nerves.

Risk factors

Sjogren's syndrome typically occurs in people with one or more known risk factors, including:

- **Age.** Sjogren's syndrome is usually diagnosed in people older than 40.
- **Sex.** Women are much more likely to have Sjogren's syndrome.
- **Rheumatic disease.** It's common for people who have Sjogren's syndrome to also have a rheumatic disease — such as rheumatoid arthritis or lupus.

Complications

The most common complications of Sjogren's syndrome involve eyes and mouth.

- **Dental cavities.** Because saliva helps protect the teeth from the bacteria that cause cavities, more prone to developing cavities if mouth is dry.
- **Yeast infections.** People with Sjogren's syndrome are much more likely to develop oral thrush, a yeast infection in the mouth.
- **Vision problems.** Dry eyes can lead to light sensitivity, blurred vision and corneal damage.

Less common complications might affect:

- **Lungs, kidneys or liver.** Inflammation can cause pneumonia, bronchitis or other problems in lungs; lead to problems with kidney function; and cause hepatitis or cirrhosis in liver.
- **Lymph nodes.** A small percentage of people with Sjogren's syndrome develop cancer of the lymph nodes (lymphoma).
- **Nerves.** might develop numbness, tingling and burning in hands and feet (peripheral neuropathy).

Diagnosis

Sjogren's syndrome can be difficult to diagnose because the signs and symptoms vary from person to person and can be similar to those caused by other diseases. Side effects of a number of medications also mimic some signs and symptoms of Sjogren's syndrome.

Tests can help rule out other conditions and help pinpoint a diagnosis of Sjogren's syndrome.

Blood tests

- Levels of different types of blood cells
- Presence of antibodies common in Sjogren's syndrome
- Evidence of inflammatory conditions
- Indications of problems with liver and kidneys

Eye tests :measure the dryness of eyes , examine the surface of eyes, see damage to cornea.

Sialogram. This special X-ray can detect dye that's injected into the salivary glands in front of ears. This procedure shows how much saliva flows into mouth, can check the function of salivary glands.

Biopsy : a lip biopsy to detect the presence of clusters of inflammatory cells, which can indicate Sjogren's syndrome. For this test, a sliver of tissue is removed from salivary glands and examined under a microscope.

Treatment

Treatment for Sjogren's syndrome depends on the parts of the body affected

Decrease eye inflammation. Prescription eyedrops such as cyclosporine (Restasis) moderate to severe dry eyes.

Increase production of saliva. Drugs such as **pilocarpine** (Salagen) and cevimeline (cholinergic agonists)(Evoxac) can increase the production of saliva, and sometimes tears. Side effects can include sweating, abdominal pain, flushing and increased urination.

Pilocarpine is used to stimulate salivary secretions in patients with reduced saliva production caused by autoimmune disease (Sjogren's Syndrome) or damage to saliva glands due to radiation therapy.

- If develop arthritis symptoms, might benefit from nonsteroidal anti-inflammatory drugs (NSAIDs) or other arthritis medications.
- Yeast infections in the mouth should be treated with antifungal medications.(topical nystatin)
- Drugs that suppress the immune system, also might be prescribed

Increase production of saliva





Lifestyle and home remedies

Many Sjogren's syndrome symptoms respond well to self-care measures.

Use artificial tears,

-Drugs for dry eye (tear deficiency) (artificial tear preparations). eye drops

1-They act by stabilizing the tear film (by increasing the viscosity of tear decrease evaporation)

2-Examples are : Hypromellose (hydroxypropyl methylcellulose).

Increase humidity. Increasing the indoor humidity and reducing exposure to blowing air can help keep eyes and mouth from getting uncomfortably dry.

Don't smoke. Smoking can irritate and dry out mouth.

Increase fluid intake.

Stimulate saliva flow. Sugarless gum or citrus-flavored hard candies can boost saliva flow. Because Sjogren's syndrome increases risk of dental cavities, limit sweets, especially between meals.

Try artificial saliva. Saliva replacement products often work better than plain water because they contain a lubricant that helps mouth stay moist longer. These products come as a spray or lozenge.

Use nasal saline spray. A nasal **saline spray** can help moisturize and clear nasal passages so that patient can breathe freely through the nose. A dry, stuffy nose can increase mouth breathing.

Oral health

Schedule regular dental appointments, at least every six months

Use daily topical fluoride treatments and antimicrobial mouthwashes

Alzheimer's disease

Is a progressive disorder that causes **brain cells** to waste away (**degenerate**) and die. Alzheimer's disease is the most common cause of **dementia** — a continuous **decline in thinking**, behavioral and social skills that disrupts a person's ability to function independently.

The early signs of the disease may be **forgetting recent events** or **conversations**. As the disease progresses, a person with Alzheimer's disease will develop severe **memory impairment** and **lose the ability to carry out everyday tasks.**

Current Alzheimer's disease medications may temporarily improve symptoms or slow the rate of decline.

There is no treatment that cures Alzheimer's disease or alters the disease process in the brain. In advanced stages of the disease, **complications** from severe loss of brain function — such as **dehydration**, **malnutrition** or **infection** — result in **death.**



Symptoms

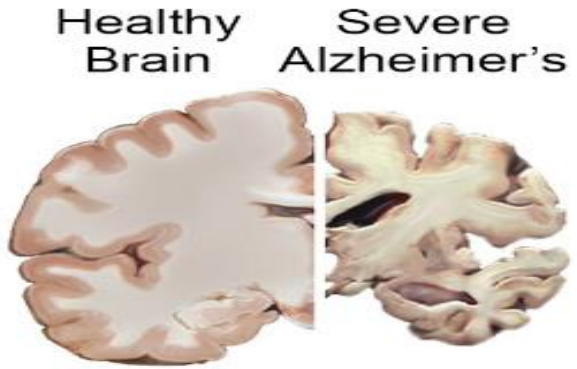
Memory loss is the key symptom of Alzheimer's disease. An early sign of the disease is usually difficulty remembering recent events or conversations. As the disease progresses, memory impairments worsen and other symptoms develop.

Brain changes associated with Alzheimer's disease lead to growing trouble with:

Memory, Thinking and reasoning, Making judgments and decisions, Planning and performing familiar tasks ,Changes in personality and behavior(Depression**,** Apathy**,** Social withdrawal **,**Mood swings **,**Irritability and aggressiveness **)**

As Alzheimer's disease progresses to its last stages, brain changes begin to affect physical functions, such as swallowing, balance, and bowel and bladder control. These effects can increase vulnerability to additional health problems such as:

Inhaling food or liquid into the lungs (aspiration), Pneumonia and other infections, Falls, Fractures, Malnutrition or dehydration



Causes

Alzheimer's disease is caused by a combination of genetic, lifestyle and environmental factors that affect the brain over time.

1) Accumulation of senile plaques (β-amyloid accumulations) Aβ hypothesis

2) Formation of numerous neurofibrillary tangles. Neurofibrillary tangles, are composed of tau. Tau is a microtubule-associated protein working as scaffolding proteins that are enriched in axons. In pathological conditions, tau aggregation will impair axons of neurons and thus cause neurodegeneration. (Tau hypothesis)

3) loss of cortical neurons ,particularly cholinergic neurons. (cholinergic hypothesis)

- Current therapies are aimed at either improving cholinergic transmission within the CNS **or** preventing excitotoxic actions resulting from overstimulation of N-methyl-D-aspartic acid (NMDA)-glutamate receptors in selected brain areas.

Treatment

Pharmacologic intervention for Alzheimer's disease is only palliative and provides modest short-term benefit. None of the currently available therapeutic agents have been shown to alter the underlying neurodegenerative process

- **Cholinesterase inhibitors.** These drugs work by boosting levels of cell-to-cell communication by preserving a chemical messenger that is depleted in the brain by Alzheimer's disease. The improvement is modest. have produced modest improvement in patients with mild to moderately severe disease

Cholinesterase inhibitors may also improve neuropsychiatric symptoms, such as agitation or depression. Commonly prescribed cholinesterase inhibitors include **donepezil** (Aricept), **galantamine (Reminyl)** and **rivastigmine** (Exelon).









Treatment

- **Memantine** is a glutamate receptor antagonist (NMDA-receptor antagonist) it is licensed for treating moderate to severe Alzheimer’s disease.

This drug works in another brain cell communication network and slows the progression of symptoms with moderate to severe Alzheimer's disease.

It's sometimes used in combination with a cholinesterase inhibitor

- Stimulation of glutamate receptors in the CNS appears to be critical for the formation of certain memories; however, overstimulation of glutamate receptors, particularly of the NMDA type, has been shown to result in excitotoxic effects on neurons and is suggested as a mechanism for neurodegenerative or apoptotic (programmed cell death) processes.

Thank you