Drugs for Alzheimer's disease:

cholinergic agonists and acetylcholine esterase inhibitors.

It is the most common type of dementia, accounting for 60 to 80 percent of cases of dementia. Increasing age is the most important known risk factor for Alzheimer's.

Alzheimer's is caused by **brain cell death**.

It is a **neurodegenerative** disease, which means there is progressive **brain cell death** that happens over time.

In a person with Alzheimer's, the tissue has fewer and fewer **nerve cells** and connections.

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Alzheimer's is a progressive disease, where dementia symptoms gradually worsen over a number of years. As symptoms worsen, it becomes harder for people to remember recent events, to reason, and to recognize people they know. Eventually, a person with Alzheimer's is likely to need full-time assistance.

Types of Dementia

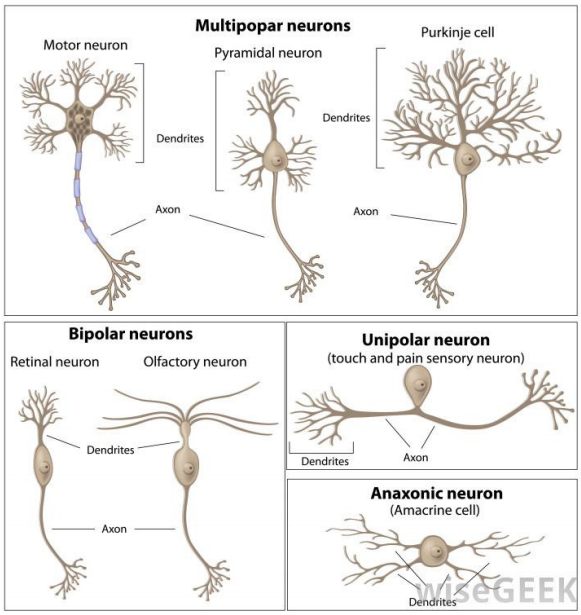
Alzheimer's disease
Vascular dementia
Dementia with Lewy bodies (DLB)
Mixed dementia
Parkinson's disease
Frontotemporal dementia
Creutzfeldt-Jakob disease
Normal pressure hydrocephalus
Huntington's disease
Wernicke-Korsakoff Syndrome

Alzheimer's disease is caused by parts of the brain shrinking (atrophy), which affects the structure and function of particular brain areas.

It happens when plaques containing beta amyloid form in the brain.

This includes the extracellular deposits of β-amyloid (derived from amyloid precursor protein; APP) in senile plaques, intracellular formation of neurofibrillary tangles and the loss of neuronal synapses and pyramidal neurons. (**Pyramidal neurons** are the primary excitation units of the mammalian prefrontal cortex and the corticospinal tract.)

Types of Neurons



Symptoms: Difficulty remembering recent conversations, names or events is often an early clinical symptom; apathy and depression are also often early symptoms. Later symptoms include impaired communication, poor judgment, disorientation, confusion, behavior changes and difficulty speaking, swallowing and walking.

Revised guidelines for diagnosing Alzheimer's were published in 2011 recommending that Alzheimer's be considered a slowly progressive brain disease that begins well before symptoms emerge.

Brain changes: Hallmark abnormalities are deposits of the protein fragment beta-amyloid (plaques) and twisted strands of the protein tau (tangles) as well as evidence of nerve cell damage and death in the brain.

Stages

The progression of Alzheimer's can be broken down into three main stages: **Alzheimer's disease** typically progresses slowly in

- mild (early-**stage**),
- **moderate** (middle-**stage**)
- severe (late-**stage**).

Since **Alzheimer's** affects people in different ways, each person will experience symptoms - or progress through **Alzheimer's stages** - differently.

The cognitive decline must be seen in at least two of the five symptom areas listed below:

1. Reduced ability to take in and remember new information, which can lead, for
2. Impairments to reasoning, complex tasking, and exercising judgment,
3. Impaired visuospatial abilities that are not, for example, due to eye sight problems.
4. Impaired speaking, reading and writing,
5. Changes in personality and behavior,

Alzheimer's Disease Genetics

There are two types of Alzheimer's—early-onset and late-onset. Both types have a genetic component.

Some Differences Between Late-Onset and Early-Onset Alzheimer's Disease	
Late-Onset Alzheimer's	Early-Onset Alzheimer's
Signs first appear in a person's mid-60s	Signs first appear between a person's 30s and mid-60s
Most common type	Very rare
May involve a gene called APOE ε4	Usually caused by gene changes passed down from parent to child

Cholinergic agonists in **Alzheimer's disease**

Considerable effort was focused on the development of (cholinergic agonists) muscarinic and nicotinic agonists for the treatment of Alzheimer's disease.

The rationale for developing cholinergic agonists was based on the role of acetylcholine in learning and memory function and the consistent neurochemical finding that cholinergic neurons degenerated in Alzheimer's patients.

Cholinergic agonists is useful in treating not only memory deficits, but also psychiatric disturbances and some of the underlying causes of Alzheimer's disease.

Emerging role of ACh in learning and memory, led to the "cholinergic hypothesis of Alzheimers disease"

Acetylcholine esterase inhibitors **in Alzheimer's disease**

There are a number of approaches to the treatment of the cholinergic deficit in Alzheimer's disease, most of which have initially focused on the replacement of ACh precursors (choline or lecithin) but these agents failed to increase central cholinergic activity.

Other studies have investigated the use of ChE inhibitors that reduce the hydrolysis of Ach

First generation cholinesterase inhibitors

Tacrine has been approved for use in some, but not all, countries.

Tacrine (Cognex), the first FDA-approved cholinesterase inhibitor, works in only about 20 to 40% of people with Alzheimer's disease and causes **liver damage** in some individuals. It is **rarely used** now that a second generation of cholinesterase inhibitors is available.

Unfortunately, potentially serious adverse side effects have limited the use of this compound.

These side effects are manifested predominantly by gastrointestinal tract discomfort and overactivity, resulting in nausea, vomiting, abdominal pain, and diarrhoea.

Tacrine is a centrally acting anticholinesterase and indirect cholinergic agonist. It was the first centrally acting cholinesterase inhibitor approved for the treatment of Alzheimer's disease, and was marketed under the trade name Cognex

Despite these limitations, a substantial number of patients, some 250 000–300 000 worldwide, have been exposed to tacrine. Consequently, although tacrine produces a meaningful benefit in a significant proportion of patients with Alzheimer's disease, the question has been raised as to whether this approach represents a fair test of the cholinergic hypothesis.

This issue has been considered in the development of "second generation" ChE inhibitors. Such ChE inhibitors have been designed to limit side effect problems, and the maximum tolerated dose that can be achieved may be determined more by the effects of ChE inhibition itself.

Second generation cholinesterase inhibitors

The newer second generation ChE inhibitors including donepezil, rivastigmine, metrifonate, galantamine and several other compounds.

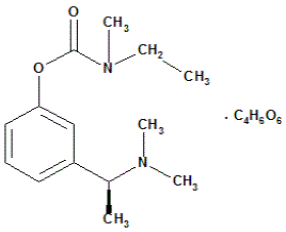
Such compounds show an effect and magnitude of benefit of at least that reported for tacrine, but with a more favorable clinical profile.

For example, donepezil has a once daily dosage schedule and produces dose related significant improvements in cognition and global function, with over 80% of patients experiencing an improvement or no deterioration in cognition. with no evidence of hepatotoxicity.

This general thesis that ChE inhibitors will delay the progression of symptoms of Alzheimer's disease and improve patients, on average, by the equivalent of 6–12 months deterioration, is now receiving further support with the publication of results from the trials of rivastigmine and metrifonate.

The second of these drugs to be approved was Rivastigmine (Exelon), which is for mild to moderate Alzheimer's.

Is a reversible cholinesterase inhibitor.



Side effects: Rivastigmine and call your doctor at once if you have any of these serious side effects:

stomach pain, nausea and vomiting, loss of appetite;
black, bloody, or tarry stools;

coughing up blood or vomit that looks like blood or coffee grounds;

feeling light-headed, fainting;

chest pain;

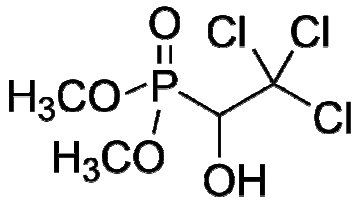
confusion, agitation, extreme fear; or pain or burning

Metrifonate is a long-acting irreversible cholinesterase inhibitor, originally used to treat schistosomiasis.

Its potential to enhance central nervous system cholinergic neurotransmission led to clinical trials for the treatment of people with Alzheimer's disease (AD).

Although low incidence of serious side effects occurred during short-term use as an antihelmintic, in studies of the treatment of AD extending over 6 months, 20 patients experienced respiratory paralysis and problems with neuromuscular transmission.

These findings have led to a halt to trials of metrifonate for AD and Bayer, the pharmaceutical company, has withdrawn its FDA application.



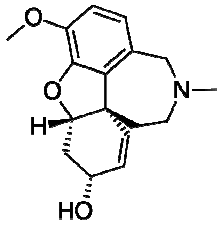
Metrifonate (INN) or trichlorfon (USAN) is an irreversible organophosphate acetylcholinesterase inhibitor. It is a prodrug which is activated non-enzymatically into 2,2-dichlorovinyl dimethyl phosphate (DDVP).

Galantamine

The newest cholinesterase inhibitor to be approved is galantamine (Razadyne), which is approved to treat mild to moderate Alzheimer's.

It is an alkaloid that has been isolated from the bulbs and flowers of *Galanthus caucasicus*

Patients taking Razadyne scored better on measures of cognitive performance and daily functioning.



Galantamine inhibits acetylcholinesterase, an enzyme which hydrolyzes acetylcholine.

As a result of competitive inhibition acetylcholinesterase, galantamine increases the availability of acetylcholine for synaptic transmission.

Additionally, galantamine binds to the allosteric sites of nicotinic receptors, which causes a conformational change. This allosteric modulation increases the nicotinic receptor's response to acetylcholine. The activation of presynaptic nicotinic receptors increases the release of acetylcholine, further increasing the availability of acetylcholine.

The most common **adverse effects of cholinesterase inhibitors** are nausea, vomiting, loss of appetite, diarrhea, and weight loss.