

## Overdose and Side Effects of Cholinomimetic Agents – ANS Pharmacology

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**Toxicology of cholinomimetics, especially nicotine and cholinesterase inhibitors, is important for clinical implications. In this article, clinical features of adverse effects, resulting from acute and chronic exposures to cholinomimetics, are described. Management of poisoning, including the role of atropine and cholinesterase reactivators, is also discussed.**



### Overview of Toxicity of Cholinomimetic Activators

Cholinomimetics, especially some **organophosphates**, are used as **insecticides in agriculture** and accidental poisoning with them is not uncommon. They are also used for purposes of homicide, suicide, warfare or chemical terrorism. Hence, it is important to understand their toxicology, to learn to suspect, diagnose and manage the poisoning with these agents.

**Here is a quick review of Cholinergic Agents: (See also [Cholinomimetic Agents – ANS Pharmacology](#))**

Direct-acting cholinomimetics directly stimulate the receptors, while indirect-acting cholinomimetics block the action of cholinesterase thus allowing persistence of acetylcholine on the receptor.

## Direct-acting nicotinic or muscarinic stimulants

These act by stimulating the **nicotinic or muscarinic** receptors.

### Choline esters

- Acetylcholine (all acetylcholine receptors)
- Bethanechol (M3 receptors)
- Carbachol (all muscarinic receptors and some nicotinic receptors)
- Methacholine (all muscarinic receptors)

### Plant alkaloids

- Arecoline
- Nicotine
- Muscarine
- Pilocarpine (M3 receptors)

A mnemonic for signs and symptoms of acute organophosphate poisoning:

### **DUMBBELSS: Diarrhea, Urination, Miosis, Bronchospasm, Bradycardia, Excitation of skeletal muscles and CNS, Lacrimation, Salivation, Sweating**

If that's too long, another commonly used mnemonic is **SLUDGE** (or SLUDGEM, where M stands for miosis) for salivation, lacrimation, urination, defecation, gastrointestinal distress, emesis. These mnemonics help to remember that:

- Poisoning with organophosphates presents with signs of muscarinic excess such as **nausea, vomiting, excessive salivation, excessive perspiration, diarrhea, urinary urgency, bronchospasm, flushing**, etc.
- **Miosis** (or even **pin-point pupils**) is a very important clinical sign to suspect poisoning with cholinomimetics.
- Severe poisoning can lead to **convulsions, coma**, and even **death**.
- Similar signs can also be seen in poisoning due to certain mushrooms (e.g., genus *Inocybe*) containing muscarinic alkaloids. Signs of **mushroom poisoning** usually appear within 15-30 minutes of their consumption.
- **Atropine** is the antidote of choice.
- **Topical pilocarpine** can cause **adverse effects** like blurred vision, night blindness, and brow ache.

## Nicotine toxicity

Acute nicotine toxicity can occur due to **ingestion of nicotine insecticides or tobacco**. Most of the nicotine in a cigarette is destroyed by burning or escapes via smoke, reducing chances of nicotine poisoning among cigarette smokers.

Symptoms of acute toxicity include **nausea, vomiting, hypertension, cardiac arrhythmias, central nervous system stimulation** (convulsions, coma, death due to respiratory arrest), **skeletal muscle end-plate depolarization blockade** (skeletal and respiratory muscle paralysis) and **symptoms of muscarinic excess** (due to parasympathetic ganglion stimulation). In acute poisoning, fatal dose of nicotine is ~40 mg or 1 drop of pure liquid.

Treatment of acute nicotine toxicity is mainly symptomatic, i.e., **atropine** for symptoms of muscarinic excess, **diazepam** for central nervous system stimulation, **mechanical ventilation** for neuromuscular paralysis, etc.

**Chronic nicotine toxicity** in smokers is known to be associated with increased risk of **vascular disease, coronary artery disease, sudden coronary death, peptic ulcer, certain pulmonary diseases**, etc. **Smoking cessation** is the most important step, which requires counseling and motivation.

For motivated patients, nicotine in forms with low abuse potential (gum, transdermal patch, nasal spray, inhaler, etc.) is used as **replacement therapy**. Slowly absorbed nicotine from these forms occupies the  $\alpha 4\beta 2$  receptors in the central nervous system and reduces craving.

**Varenicline**, a partial agonist at the  $\alpha 4\beta 2$  receptors, is also effective for smoking cessation.

## Varenicline

Important side effects of varenicline are **nausea, insomnia, exacerbation of anxiety and depression** and, possibly, **suicidal ideation**.

## Muscarine Intoxication

The symptoms of intoxication with mushrooms rich in muscarine, especially *Inocybe*, are very typical: The symptoms start early, after one-quarter to two hours, with a headache, nausea, vomiting, and constriction of the pharynx. Then salivation, lacrimation, and diffuse perspiration set in, combined with miosis, disturbed accommodation, and reduced vision.

Gastric and small bowel colic leads to diarrhea, and there is a painful urge for urination. Bronchoconstriction leads to asthmatic attacks and severe dyspnea, and bradycardia combined with marked hypotension and vasodilation results in circulatory shock. Death after 8 to 9 hours has been reported in about 5% of the cases but **can be avoided completely by prompt diagnosis and treatment with atropine**.

## Pilocarpine

Pilocarpine is a medication used to treat increased pressure inside the eye. As eye drops it is used for angle-closure glaucoma until surgery can be performed, ocular hypertension, open-angle glaucoma, and to bring about constriction of the pupil following their dilation. By mouth, it is used for the dry mouth as a result of Sjogren's syndrome or radiation therapy. The  $M_3$  receptor is found on the iris sphincter muscle, where pilocarpine causes the muscle to contract (miosis). Pilocarpine also acts on the ciliary muscle and causes it to contract.

When the ciliary muscle contracts, it opens the trabecular meshwork. This action facilitates drainage of aqueous humor to decrease intraocular pressure.

Another important use of Pilocarpine is the diagnosis of cystic fibrosis by stimulation of the sweat glands in the sweat test to measure the concentration of chloride and sodium that is excreted in sweat.

## Indirect-acting

Indirect acting parasympathomimetic drugs may be either reversible cholinesterase inhibitors, irreversible cholinesterase inhibitors or drugs that promote ACh release or anti-adrenergic. The latter inhibits the antagonistic system, the sympathetic nervous system.

Reversible cholinesterase inhibitors	Irreversible cholinesterase inhibitors	ACh release promoters	Anti-adrenergics
<ul style="list-style-type: none"> <li>• Donepezil</li> <li>• Edrophonium</li> <li>• Neostigmine</li> <li>• Physostigmine</li> <li>• Pyridostigmine</li> <li>• Rivastigmine</li> <li>• Tacrine</li> <li>• Caffeine (non-competitive)</li> <li>• Huperzine A</li> </ul>	<ul style="list-style-type: none"> <li>• Echothiophate</li> <li>• Isoflurophate</li> <li>• Malathion</li> </ul>	<ul style="list-style-type: none"> <li>• Cisapride</li> <li>• Domperidone</li> <li>• Metoclopramide</li> <li>• Risperidone</li> <li>• Paliperidone</li> <li>• Trazodone – via blockade of the <math>\alpha</math> adrenergic receptors</li> </ul>	

## Toxicity of Cholinesterase Inhibitors

Cholinesterase inhibitors (organophosphates and carbamates) are widely available as pesticides and veterinary vermifuges, which can cause **poisoning by acute or chronic exposure**.

Acute intoxication presents with signs of **muscarinic excess** (nausea, vomiting, excessive salivation, excessive perspiration, diarrhea, urinary urgency, bronchospasm, excessive tracheobronchial secretions, and miosis), **central nervous system signs** (cognitive disturbances, convulsions, coma) and **peripheral nicotinic effects** (depolarizing neuromuscular blockade).



[Image](#): "A 25 year old Caucasian male with miosis due to opiate (i.e., codeine) use." by Anonymous. License: [CC0 1.0](#)

Central nervous system side effects are more common with physostigmine than with neostigmine or pyridostigmine as **physostigmine enters the CNS** while the others cannot.

Compared to direct-acting cholinomimetics, poisoning with cholinesterase inhibitors has the following differences: vasodilation is uncommon and bradycardia is more common than tachycardia.

The most common organophosphate is malathion. **Malathion** is a cholinesterase inhibitor, a diverse family of chemicals that includes **sarin and carbaryl**. Carbaryl **enters the CNS** where it irreversibly oxidizes acetylcholinesterase. All organophosphates interfere with the cholinergic nervous system and cause death because the effects of the neurotransmitter acetylcholine cannot be terminated by carbamoylated acetylcholinesterase. Upon uptake into the target organism, it binds

irreversibly to several random serine residues on the cholinesterase enzyme, with peroxide as the leaving group.

The resultant phosphoester group is strongly bound to the cholinesterase, and **irreversibly deactivates the enzyme** which leads to rapid build-up of acetylcholine at the synapse.

**Parathion** is a cholinesterase inhibitor. It generally disrupts the nervous system by inhibiting acetylcholinesterase. Parathion acts on the enzyme acetylcholinesterase indirectly. After an insect (or a human) ingests parathion, an oxidase replaces the double-bonded sulfur with oxygen to give paraoxon. Parathion and related organophosphorus pesticides are used in hundreds of thousands of poisonings annually, especially suicides. It is known as “Schwiegermuttergift” (mother-in-law poison) in Germany. For this reason, most formulations contain a blue dye providing warning.

Nerve toxicity can also develop 1-4 days after exposure to organophosphate insecticides, which is known as an intermediate syndrome. It is also characterized by muscular weakness; the mechanism of toxicity is thought to be related to cholinesterase inhibition, but there is no proof.

As cholinesterase inhibitors are used as chemical weapons in wars, soldiers and civilians are provided with autoinjection syringes containing carbamate, pyridostigmine, and atropine. **Pyridostigmine** prevents prolonged inhibition of cholinesterase by impeding the binding of the chemical agent; however, it does not enter the central nervous system.

**Tacrine**, an anticholinesterase used in the treatment of Alzheimer’s disease, is replaced by other drugs due to its **hepatotoxicity**.

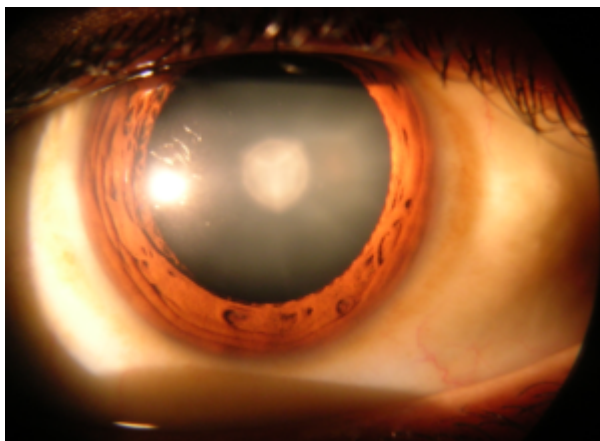


Image: “Cataract in the human eye” by Rakesh Ahuja, MD - Own work, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Important adverse effect of **donepezil, rivastigmine and galantamine**, anticholinesterase drugs used in the treatment of Alzheimer’s disease, is **gastrointestinal distress**.

Chronic exposure to **triorthocresyl phosphate**, used as an additive in lubricating oils, can cause delayed demyelinating neuropathy 1-2 weeks after exposure by inhibiting **neuropathy target esterase (NTE)**. Clinical presentation includes weakness of limbs and unsteadiness of gait.

Important adverse effects associated with **echothiophate** (previously used topically in the treatment of glaucoma) are brow ache, uveitis, blurred vision, and cataract formation.

# Treatment of Cholinomimetic Toxicity

## Management of acute anticholinesterase poisoning

- Maintenance of vital signs, with special importance to respiration.
- Prevention of further absorption of the agent (removal of clothing and washing of skin when exposure is through the skin, etc.).
- Management of other symptoms (control of seizures by benzodiazepines, etc.).
- Specific antidotes: atropine & cholinesterase reactivators.

## Atropine

- Very effective for the treatment of **muscarinic symptoms**;
- Higher doses are necessary to counteract central actions;
- **Peripheral muscular paralysis cannot be reversed by atropine as it is a nicotinic effect.**

## Cholinesterase reactivators

Cholinesterase reactivators are composed of substituted oximes that regenerate active cholinesterase from the **organophosphorus-cholinesterase complex**. They attach to the anionic site of cholinesterase, which is unoccupied by organophosphates. **The anionic site is not free in case of carbamates**—cholinesterase reactivators are ineffective and contraindicated in carbamate poisoning as they also have a weak anti-cholinesterase activity.

Cholinesterase reactivators are most effective when administered as early as possible before the phosphorylated cholinesterase has undergone aging.

**Pralidoxime** can reverse both muscarinic and nicotinic peripheral effects but cannot reverse CNS effects as it **cannot penetrate the CNS**.

Other important cholinesterase reactivators are **obidoxime** (more potent than pralidoxime) and **diacetyl-monoxime (DAM)** (a lipophilic cholinesterase reactivator).

## Myasthenic Crisis versus Cholinergic Crisis

<b>Myasthenic Crisis</b>	<b>Cholinergic Crisis</b>
The pathophysiologic cause is insufficient cholinesterase inhibitors in presence of reduced number of acetylcholine receptors	The pathophysiologic cause is excess of acetylcholine due to excessive cholinesterase inhibitors
External ophthalmoplegia present	External ophthalmoplegia absent
Pupils normal and reactive to light	Pupils reactive to light but miosis present
Ptosis usually present	Ptosis usually absent
Fasciculations absent in skeletal muscles	Fasciculations present in skeletal muscles
Increased blood pressure	Decreased blood pressure
Bowel and bladder incontinence	Abdominal cramps, nausea, vomiting, diarrhea
Edrophonium gives temporary relief	Edrophonium has no effect but may worsen symptoms
Atropine does not improve symptoms	Atropine improves symptoms

# Review Questions

The correct answers can be found below the references.

**1. Which of the following clinical features of acute cholinomimetic poisoning cannot be effectively treated by the administration of parenteral atropine?**

- A. Muscular paralysis
- B. Hyperlacrimation
- C. Miosis
- D. Hypersalivation
- E. Diarrhea

**2. Due to which of the following adverse effects has tacrine been replaced by other cholinesterase inhibitors for management of Alzheimer's disease?**

- A. Nephrotoxicity
- B. Retinal damage
- C. Neurotoxicity
- D. Hepatotoxicity
- E. Cardiotoxicity

**3. In acute poisoning due to which of the following compounds will pralidoxime not be effective?**

- A. Malathion
- B. Parathion
- C. Carbaryl
- D. Sarin
- E. Metrifonate

## References

Pappano AJ. Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs. Ed: Katzung BG, Masters SB, Trevor AJ. In: Basic & Clinical Pharmacology, 12<sup>th</sup> Edition. The McGraw-Hill Companies, Inc. (2012). pp 97-114.

Pappano AJ. Cholinoceptor-Blocking Drugs. Ed: Katzung BG, Masters SB, Trevor AJ. In: Basic & Clinical Pharmacology, 12<sup>th</sup> Edition. The McGraw-Hill Companies, Inc. (2012). pp 115-128.

Trevor AJ, Katzung BG, Kruidering-Hall K, Masters SB. Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs. In: Pharmacology Examination & Board Review, 10<sup>th</sup> Edition. The McGraw-Hill Companies, Inc. (2013). pp 61-9.

Radhakrishnan R. Cholinergic Agonists. Ed: Whalen K, Finkel R, Panavelil TA. In: Lippincott Illustrated Reviews Pharmacology, 6<sup>th</sup> Edition. Wolters Kluwer. (2015). pp 51-64.

Tripathi KD. Cholinergic System and Drugs. In: Essentials of Medical Pharmacology, 6<sup>th</sup> Edition. Jaypee Brothers Medical Publishers (P) Ltd. (2008). pp 93-105.

Chaudhuri A, Behan PO. Myasthenic Crisis. *Q J Med* 2009; 102 (2): 97-107. doi: 10.1093/qjmed/hcn152.

**Correct answers:** 1A, 2D, 3C

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