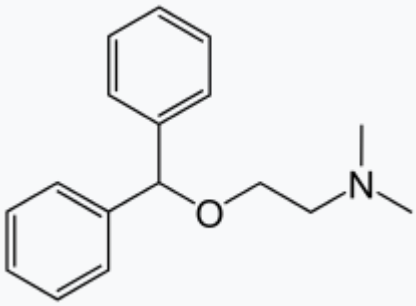
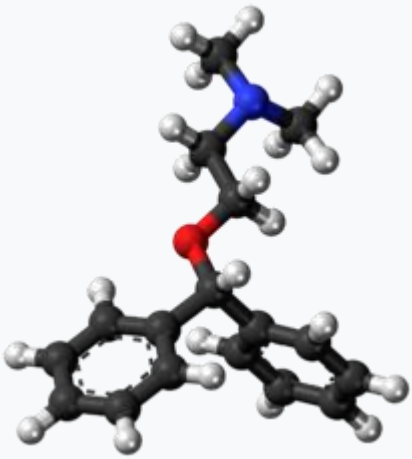
Wikipedia - Diphenhydramine

For United Nations Operation in Somalia, see UNOSOM.

Diphenhydramine





Clinical data	
Pronunciation	/ˌdaɪfɛnˈhaɪdrəmiːn/
Trade names	Benadryl, Unisom, Sominex, others
AHFS/Drugs.com	Monograph
MedlinePlus	a682539
Pregnancy	AU: A

category	US: B (No risk in non-human studies)
Dependence liability	Very low
Routes of administration	By mouth, IM, IV, topical and rectal
ATC code	D04AA32 (WHO) D04AA33 (WHO), R06AA02 (WHO)
Legal status	
Legal status	AU: S2 (Pharmacy only) US: OTC
Pharmacokinetic data	
Bioavailability	40–60%[1]
Protein binding	98–99%
Metabolism	Various cytochrome P450 liver enzymes: CYP2D6 (80%), 3A4 (10%)[4]
Biological half-life	7 hours (children)[2] 12 hours (adults)[2] 17 hours (elderly)[2]
Excretion	94% through the urine, 6% through feces[3]
Identifiers	
IUPAC name[show]	
CAS Number	58-73-1✓
PubChem CID	3100
IUPHAR/BPS	1224
DrugBank	DB01075✓
ChemSpider	2989✓

UNII	8GTS82S83M
KEGG	D00669✗
ChEBI	CHEBI:4636✓
ChEMBL	CHEMBL657✓
ECHA InfoCard	100.000.360
Chemical and physical data	
Formula	$C_{17}H_{21}NO$
Molar mass	255.355 g/mol
3D model (Jmol)	Interactive image
SMILES[show]	
InChI[show]	
✗✓ (what is this?) (verify)	

Diphenhydramine is an antihistamine mainly used to treat allergies.[5] It is also used for insomnia, symptoms of the common cold, tremor in parkinsonism, and nausea.[5] It is used by mouth, injection into a vein, and injection into a muscle.[5] Maximal effect is typically around two hours after a dose and effects can last for up to seven hours.[5]

Common side effects include sleepiness, poor coordination, and an upset stomach.[5] Its use is not recommended in babies.[5] There is no clear risk of harm when used during pregnancy; however, use during breastfeeding is not recommended.[6] It is a first generation H1-antihistamine and works by blocking certain effects of histamine.[5]

Diphenhydramine was made by George Rieveschl and came into commercial use in 1946.[7][8] It is available as a generic medication.[5] The wholesale price in the developing world as of 2014 is about US$0.01 per dose.[9] In the United States, it costs less than US$25 for a typical month supply.[10] It is sold under the trade name Benadryl among others.[5]

Medical uses[edit]

Diphenhydramine is a first-generation antihistamine used to treat a number of conditions including allergic symptoms and itchiness, the common cold, insomnia, motion sickness, and extrapyramidal symptoms.[11][12] Diphenhydramine also has local anesthetic properties, and has been used as such in people allergic to common local anesthetics such as lidocaine.[13]

Allergies[edit]

Diphenhydramine is effective in treatment of allergies.[14] As of 2007 it was the most commonly used antihistamine for acute allergic reactions in the emergency department.[15]

By injection it is often used in addition to epinephrine for anaphylaxis.[16] Its use for this purpose had not been properly studied as of 2007.[17] Its use is only recommended once acute symptoms have improved.[14]

Topical formulations of diphenhydramine are available, including creams, lotions, gels, and sprays. These are used to relieve itching, and have the advantage of causing fewer systemic effects (e.g., drowsiness) than oral forms.[18]

Movement disorders[edit]

Diphenhydramine is used to treat Parkinson's disease-like extrapyramidal symptoms caused by antipsychotics.[19]

Sleep[edit]

Because of its sedative properties, diphenhydramine is widely used in nonprescription sleep aids for insomnia. The drug is an ingredient in several products sold as sleep aids, either alone or in combination with other ingredients such as acetaminophen (paracetamol). An example of the latter is Tylenol PM. Diphenhydramine can cause minor psychological dependence.[20] Diphenhydramine can cause sedation and has also been used as an anxiolytic.[21]

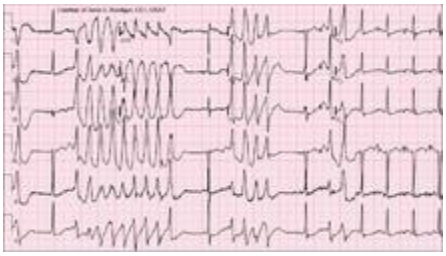
Nausea[edit]

Diphenhydramine also has antiemetic properties, which make it useful in treating the nausea that occurs in vertigo and motion sickness.[22]

Adverse effects[edit]

The most prominent side effect is sedation. A typical dose creates driving impairment equivalent to a blood-alcohol level of 0.1 which is higher than the 0.08 limit of most drunk driving laws.[15]

Diphenhydramine is a potent anticholinergic agent. This activity is responsible for the side effects of dry mouth and throat, increased heart rate, pupil dilation, urinary retention, constipation, and, at high doses, hallucinations or delirium. Other side effects include motor impairment (ataxia), flushed skin, blurred vision at nearpoint owing to lack of accommodation (cycloplegia), abnormal sensitivity to bright light (photophobia), sedation, difficulty concentrating, short-term memory loss, visual disturbances, irregular breathing, dizziness, irritability, itchy skin, confusion, increased body temperature (in general, in the hands and/or feet), temporary erectile dysfunction, and excitability, and although it can be used to treat nausea, higher doses may cause vomiting.[23] Some side effects, such as twitching, may be delayed until the drowsiness begins to cease and the person is in more of an awakening mode.



Torsades de pointes can occur as a side effect of diphenhydramine

Acute poisoning can be fatal, leading to cardiovascular collapse and death in 2–18 hours, and in general is treated using a symptomatic and supportive approach.[24] Diagnosis of toxicity is based on history and clinical presentation, and in general specific levels are not useful.[25] Several levels of evidence strongly indicate diphenhydramine (similar to chlorpheniramine) can block the delayed rectifier potassium channel and, as a consequence, prolong the QT interval, leading to cardiac arrhythmias such as *torsades de pointes*.[26] No specific antidote for diphenhydramine toxicity is known, but the anticholinergic syndrome has been treated with physostigmine for severe delirium or tachycardia.[25] Benzodiazepines may be administered to decrease the likelihood of psychosis, agitation, and seizures in patients who are prone to these symptoms.[27]

Some patients have an allergic reaction to diphenhydramine in the form of hives.[28][29] However, restlessness or akathisia can also be a side effect made worse by increased levels of diphenhydramine, especially with recreational dosages.[30] As diphenhydramine is extensively metabolized by the liver, caution should be exercised when giving the drug to individuals with hepatic impairment.

Long term anticholinergic use is associated with an increased risk for cognitive decline and dementia among older people.[31]

Special populations[edit]

Diphenhydramine is not recommended for patients older than 60 or children under the age of six, unless a physician is consulted.[32][33] These populations should be treated with second-generation antihistamines such as loratadine, desloratadine, fexofenadine, cetirizine, levocetirizine, and azelastine.[24] Due to its strong anticholinergic effects, diphenhydramine is on the "Beers list" of drugs to avoid in the elderly.[34][35]

Diphenhydramine is category B in the FDA Classification of Drug Safety During Pregnancy.[36] It is also excreted in breast milk.[37] Paradoxical reactions to diphenhydramine have been documented, in particular among children, and it may cause excitation instead of sedation.[30]

Topical diphenhydramine is sometimes used especially on patients in hospice. This use is without indication and topical diphenhydramine should not be used as treatment for nausea because research does not indicate this therapy is more effective than alternatives.[38]

Measurement in body fluids[edit]

Diphenhydramine can be quantified in blood, plasma, or serum.[39] Gas chromatography with mass spectrometry (GC-MS) can be used with electron ionization on full scan mode as a screening test. GC-MS or GC-NDP can be used for quantification.[39] Rapid urine drug screens using immunoassays based on the principle of competitive binding may show false-positive methadone results for patients having ingested diphenhydramine.[40] Quantification can be used to monitor therapy, confirm a diagnosis of poisoning in hospitalized patients, provide evidence in an impaired driving arrest, or assist in a death investigation.[39]

Mechanism of action[edit]

Overview of diphenhydramine targets and effects

Biological target	Mode of action	Effect
H_1 receptor (Peripheral)	Inverse agonist	Allergy reduction
H_1 receptor (Central)	Antagonist	Sedation
mAChR Receptors	Competitive antagonist	Anticholinergic Antiparkinson
Na channel	Blocker	Local anesthetic
SERT	Inhibitor	Mood alteration

Diphenhydramine is an inverse agonist of the histamine H_1 receptor.[41] It is a member of the ethanolamine class of antihistaminergic agents.[24] By reversing the effects of histamine on the capillaries, it can reduce the intensity of allergic symptoms. It also crosses the blood–brain barrier and inversely agonizes the H_1 receptors centrally.[41] Its effects on central H_1 receptors cause drowsiness.

Like many other first-generation antihistamines, diphenhydramine is also a potent antimuscarinic (a competitive antagonist of muscarinic acetylcholine receptors) and, as such, at high doses can cause anticholinergic syndrome.[42] The utility of diphenhydramine as an antiparkinson agent is the result of its blocking properties on the muscarinic acetylcholine receptors in the brain.

Diphenhydramine also acts as an intracellular sodium channel blocker, which is responsible for its actions as a local anesthetic.[43] Diphenhydramine has also been shown to inhibit the reuptake of serotonin.[44] It has been shown to be a potentiator of analgesia induced by morphine, but not by endogenous opioids, in rats.[45]

Pharmacokinetics[edit]

Oral bioavailability of diphenhydramine is in the range of 40–60% and peak plasma concentration occurs about 2–3 hours after administration.[1] The primary route of metabolism is two successive demethylations of the tertiary amine. The resulting primary amine is further oxidized to the carboxylic acid.[1] The half-life is as short as 8 hours in children to 17 hours in the elderly.[2]

History[edit]

Diphenhydramine was discovered in 1943 by George Rieveschl, a former professor at the University of Cincinnati.[46][47] In 1946, it became the first prescription antihistamine approved by the U.S. FDA.[48]

In the 1960s, diphenhydramine was found to inhibit reuptake of the neurotransmitter serotonin.[44] This discovery led to a search for viable antidepressants with similar structures and fewer side effects, culminating in the invention of fluoxetine (Prozac), a selective serotonin reuptake inhibitor (SSRI).[44][49] A similar search had previously led to the synthesis of the first SSRI, zimelidine, from brompheniramine, also an antihistamine.[50]

Society and culture[edit]

Diphenhydramine is sometimes used recreationally as a deliriant, or as a potentiator of alcohol,[51][52] opiates,[53] DXM and other depressants. Diphenhydramine is deemed to have limited abuse potential in the United States due to its potentially serious side-effect profile and limited euphoric effects, and is not a controlled substance. Since 2002, the U.S. FDA has required special labeling warning against use of multiple products that contain diphenhydramine.[54] In some jurisdictions, diphenhydramine is often present in postmortem specimens collected during investigation of sudden infant deaths; the drug may play a role in these events.[55][56]

Diphenhydramine is among prohibited and controlled substances in the Republic of Zambia,[57] and travelers are advised not to bring the drug into the country. Several Americans have been detained by the Zambian Drug Enforcement Commission for possession of Benadryl and other over-the-counter medications containing diphenhydramine.[58]

Procter & Gamble markets an over-the-counter formulation of diphenhydramine as a sleep-aid under the brand "ZzzQuil". In 2014, this product had annual sales of over $120 million, and had a 29.3% share of the $411 million sleep-aid market category.[59]

Recreational use[edit]

Diphenhydramine is sometimes used as a recreational drug, often by those without access to illegal drugs.[60] Recreational use of diphenhydramine may cause:[61]

- Dysphoria

- Hallucinations (auditory, visual, etc.)
- Heart palpitations
- Extreme drowsiness
- Severe dizziness
- Abnormal speech (inaudibility, forced speech, etc.)
- Flushed skin
- Severe mouth and throat dryness
- Tremors
- Seizures
- Inability to urinate
- Vomiting
- Motor disturbances
- Anxiety/nervousness
- Disorientation
- Abdominal pain
- Delirium
- Coma
- Death

Names[edit]

Diphenhydramine is marketed under the trade name Benadryl by McNeil Consumer Healthcare in the U.S., Canada, and South Africa (trade names in other countries include Dimedrol, Daedalon, and Nytol). It is also available as a generic medication.

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