



WIKIPEDIA  
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Main page  
Contents  
Featured content  
Current events  
Random article  
Donate to Wikipedia  
Wikipedia store

Interaction

Help  
About Wikipedia  
Community portal  
Recent changes  
Contact page

Tools

What links here  
Related changes  
Upload file  
Special pages  
Permanent link  
Page information  
Wikidata item  
Cite this page

Print/export

Create a book  
Download as PDF  
Printable version

In other projects

Wikimedia Commons

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العربية  
تۆرکجه  
Cymraeg  
Deutsch  
Español  
فارسی  
Français

Not logged in [Talk](#) [Contributions](#) [Create account](#) [Log in](#)

Article

[Talk](#)

Read

[Edit](#)

[View history](#)

# Diphenhydramine

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**Diphenhydramine** is an [antihistamine](#) mainly used to treat [allergies](#).<sup>[6]</sup> It is also used for [insomnia](#), symptoms of the [common cold](#), tremor in [parkinsonism](#), and [nausea](#).<sup>[6]</sup> It is used by mouth, [injection into a vein](#), and [injection into a muscle](#).<sup>[6]</sup> Maximal effect is typically around two hours after a dose, and effects can last for up to seven hours.<sup>[6]</sup>

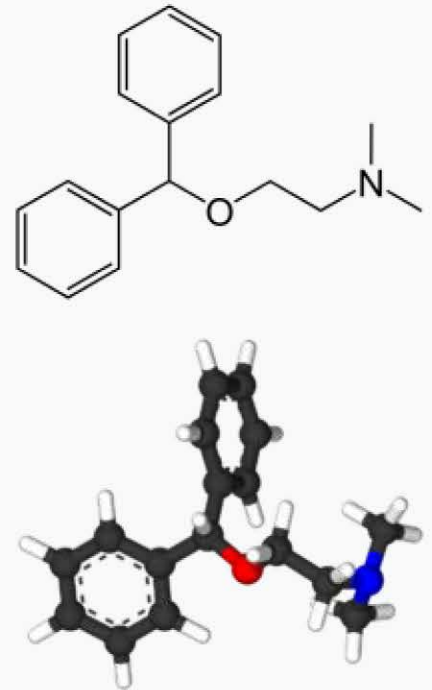
Common side effects include sleepiness, poor coordination, and an upset stomach.<sup>[6]</sup> Its use is not recommended in babies.<sup>[6]</sup> There is no clear risk of harm when used during [pregnancy](#); however, use during [breastfeeding](#) is not recommended.<sup>[7]</sup> It is a [first generation H1-antihistamine](#) and works by blocking certain effects of [histamine](#).<sup>[6]</sup> Diphenhydramine is also an [anticholinergic](#).<sup>[8]</sup>

Diphenhydramine was first made by [George Rieveschl](#) and came into commercial use in 1946.<sup>[9][10]</sup> It is available as a [generic medication](#).<sup>[6]</sup> The wholesale price in the developing world as of 2014 is about [US\\$0.01](#) per dose.<sup>[11]</sup> In the United States, it costs less than [US\\$25](#) for a typical month's supply.<sup>[12]</sup> It is sold under the trade name **Benadryl**, among others.<sup>[6]</sup>

## Contents [hide]

- Medical uses
  - Allergies
  - Movement disorders
  - Sleep
  - Nausea
  - Special populations
- Adverse effects
- Overdose

## Diphenhydramine



### Clinical data

<b>Pronunciation</b>	<span><span>/<span><span>ˈ</span><span>d</span><span>ɑːr</span><span>f</span><span>ən</span><span>ˈ</span><span>h</span><span>ɑːr</span><span>d</span><span>r</span><span>ə</span><span>m</span><span>iː</span><span>n</span></span>/</span></span>
<b>Trade names</b>	Benadryl , Unisom, Sominex , others
<b>AHFS/Drugs.com</b>	Monograph
<b>MedlinePlus</b>	a682539
<b>Pregnancy category</b>	<div><div><b>AU:</b> <span><span>A</span></span></div><div><b>US:</b> <span><span>B</span></span> (No risk in non-human studies)</div></div>
<b>Dependence liability</b>	Very low
<b>Routes of administration</b>	By mouth , intramuscular injection, intravenous , topical , rectal
<b>ATC code</b>	<div><div>D04AA32 <span>(WHO </span>)</div><div>D04AA33 <span>(WHO </span>),</div><div>R06AA02 <span>(WHO </span>)</div></div>
<b>Legal status</b>	
<b>Legal status</b>	<div><div><b>AU:</b> <span><span>S2</span></span> (Pharmacy only)</div></div>

한국어  
Հայերեն  
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Português  
Русский  
Српски / srpski  
Srpskohrvatski /  
српскохрватски

★ Suomi  
ไทย  
Українська  
中文

 [Edit links](#)

- 4 Interactions
- 5 Pharmacology
  - 5.1 Pharmacodynamics
  - 5.2 Pharmacokinetics
- 6 Chemistry
  - 6.1 Detection in body fluids
- 7 History
- 8 Society and culture
  - 8.1 Recreational use
  - 8.2 Names
- 9 References
- 10 Further reading
- 11 External links

## 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](#).<sup>[13][14]</sup>

Diphenhydramine also has [local anesthetic](#) properties, and has been used as such in people allergic to common [local anesthetics](#) such as [lidocaine](#).<sup>[15]</sup>

## Allergies [[edit](#)]

Diphenhydramine is effective in treatment of allergies.<sup>[16]</sup> As of 2007 it was the most commonly used antihistamine for acute allergic reactions in the emergency department.<sup>[17]</sup>

By injection it is often used in addition to [epinephrine](#) for [anaphylaxis](#).<sup>[18]</sup> Its use for this purpose had not been properly studied as of 2007.<sup>[19]</sup> Its use is only recommended once acute symptoms have improved.<sup>[16]</sup>

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.<sup>[20]</sup>

## Movement disorders [[edit](#)]

Diphenhydramine is used to treat [Parkinson's disease](#)–like [extrapyramidal symptoms](#) caused by [antipsychotics](#).<sup>[21]</sup>












## Sleep [[edit](#)]

US: OTC




### Pharmacokinetic data

<b>Bioavailability</b>	40–60% <sup>[2]</sup>
<b>Protein binding</b>	98–99%
<b>Metabolism</b>	Liver (CYP2D6 (80%), CYP3A4 (10%)) <sup>[1]</sup>
<b>Elimination half-life</b>	Range: 2.4–13.5 hrs <sup>[3][2][4]</sup>
<b>Excretion</b>	Urine: 94% <sup>[5]</sup> Feces : 6% <sup>[5]</sup>

### Identifiers

<b>IUPAC name</b>	<span></span> <span>[<a href="#">show</a>]</span>
<b>CAS Number</b>	58-73-1  
<b>PubChem CID</b>	3100 
<b>IUPHAR/BPS</b>	1224 
<b>DrugBank</b>	DB01075  
<b>ChemSpider</b>	2989  
<b>UNII</b>	8GTS82S83M 
<b>KEGG</b>	D00669  
<b>ChEBI</b>	CHEBI:4636  
<b>ChEMBL</b>	CHEMBL657  
<b>ECHA InfoCard</b>	100.000.360  

### Chemical and physical data

<b>Formula</b>	C <sub>17</sub> H <sub>21</sub> NO
<b>Molar mass</b>	255.355 g/mol
<b>3D model (JSmol)</b>	<a href="#">Interactive image</a> 
<b>SMILES</b>	<span></span> <span>[<a href="#">show</a>]</span>
<b>InChI</b>	<span></span> <span>[<a href="#">show</a>]</span>
  (what is this?) <span>[<a href="#">verify</a>]</span>	



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.<sup>[22]</sup> Diphenhydramine can cause [sedation](#) and has also been used as an [anxiolytic](#).<sup>[23]</sup>

## Nausea [\[edit\]](#)

Diphenhydramine also has [antiemetic](#) properties, which make it useful in treating the nausea that occurs in [vertigo](#) and motion sickness.<sup>[24]</sup>

## Special populations [\[edit\]](#)

Diphenhydramine is not recommended for people older than 60 or children under the age of six, unless a physician is consulted.<sup>[25][26]</sup> These populations should be treated with second-generation antihistamines such as [loratadine](#), [desloratadine](#), [fexofenadine](#), [cetirizine](#), [levocetirizine](#), and [azelastine](#).<sup>[27]</sup> Due to its strong anticholinergic effects, diphenhydramine is on the "[Beers list](#)" of drugs to avoid in the elderly.<sup>[28][29]</sup>

Diphenhydramine is category B in the [FDA Classification of Drug Safety During Pregnancy](#).<sup>[30]</sup> It is also excreted in breast milk.<sup>[31]</sup> [Paradoxical reactions](#) to diphenhydramine have been documented, in particular among children, and it may cause excitation instead of sedation.<sup>[32]</sup>

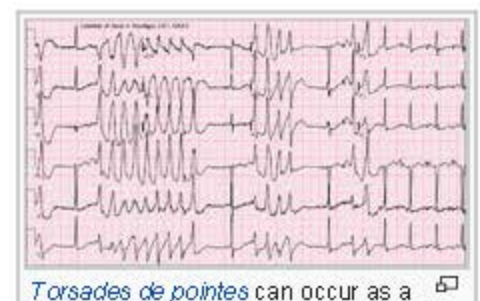
Topical diphenhydramine is sometimes used especially for people in hospice. This use is without indication and topical diphenhydramine should not be used as treatment for nausea because research does not indicate this therapy is more effective than alternatives.<sup>[33]</sup>

## Adverse effects [\[edit\]](#)

The most prominent side effect is sedation. A typical dose creates driving impairment equivalent to a blood-alcohol level of 0.10 which is higher than the 0.08 limit of most drunk driving laws.<sup>[17]</sup>

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.<sup>[34]</sup>

Some people have an allergic reaction to diphenhydramine in the form of [hives](#).<sup>[35][36]</sup> However, [restlessness](#) or [akathisia](#) can also be a side effect made worse by increased levels of diphenhydramine, especially with recreational dosages.<sup>[32]</sup> As diphenhydramine is extensively metabolized by the [liver](#), caution should be exercised when giving the drug



to individuals with hepatic impairment.

side effect of diphenhydramine

Long-term anticholinergic use is associated with an increased risk for cognitive decline and dementia among older people.<sup>[37]</sup>

## Overdose [\[ edit \]](#)

Diphenhydramine overdose symptoms may include<sup>[38]</sup>

- **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

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.<sup>[27]</sup> Diagnosis of toxicity is based on history and clinical presentation, and in general specific levels are not useful.<sup>[39]</sup> 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*.<sup>[40]</sup> No specific **antidote** for diphenhydramine toxicity is known, but the anticholinergic syndrome has been treated with **physostigmine** for severe delirium or tachycardia.<sup>[39]</sup> **Benzodiazepines** may be administered to decrease the likelihood of **psychosis**, **agitation**, and **seizures** in people who are prone to these symptoms.<sup>[41]</sup>

## Interactions [\[ edit \]](#)

**Alcohol** may increase the drowsiness caused by diphenhydramine.<sup>[42][43]</sup>

## Pharmacology [\[ edit \]](#)

### Pharmacodynamics [\[ edit \]](#)

Diphenhydramine, while traditionally known as an **antagonist**, acts primarily as an **inverse agonist** of the **histamine H<sub>1</sub> receptor**.<sup>[55]</sup> It is a member of the **ethanolamine** class of antihistaminergic agents.<sup>[27]</sup> 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<sub>1</sub> receptors

Diphenhydramine<sup>[44]</sup>

Site	K <sub>i</sub> (nM)	Species	Ref
<a href="#">SERT</a>	≥3,800	Human	<sup>[45][46]</sup>
<a href="#">NET</a>	960–2,400	Human	<sup>[45][46]</sup>
<a href="#">DAT</a>	1,100–2,200	Human	<sup>[45][46]</sup>
<b>5-HT<sub>2A</sub></b>	<b>260</b>	<b>Human</b>	<sup>[46]</sup>
<b>5-HT<sub>2C</sub></b>	780	Human	<sup>[46]</sup>



centrally.<sup>[55]</sup> Its effects on central H<sub>1</sub> 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](#).<sup>[56]</sup> 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](#).<sup>[53]</sup>

Diphenhydramine has also been shown to inhibit the reuptake of [serotonin](#).<sup>[57]</sup> It has been shown to be a [potentiator](#) of [analgesia](#) induced by [morphine](#), but not by [endogenous opioids](#), in rats.<sup>[58]</sup> The drug has also been found to act as an [inhibitor](#) of [histamine N-methyltransferase](#) (HNMT).<sup>[59][60][60]</sup>

Overview of diphenhydramine targets and effects

Biological target	Mode of action	Effect
H <sub>1</sub> receptor	inverse agonist	Allergy reduction; Sedation
<a href="#">mACh receptors</a>	Antagonist	Anticholinergic; Antiparkinson
Sodium channels	Blocker	Local anesthetic

Pharmacokinetics [\[ edit \]](#)

Oral [bioavailability](#) of diphenhydramine is in the range of 40% to 60%, and peak plasma concentration occurs about 2 to 3 hours after administration.<sup>[2]</sup> The primary route of metabolism is two successive [demethylations](#) of the [tertiary amine](#). The resulting primary amine is further [oxidized](#) to the [carboxylic acid](#).<sup>[2]</sup> The [elimination half-life](#) of diphenhydramine has not been fully elucidated, but appears to range between 2.4 and 9.3 hours in healthy adults.<sup>[3]</sup> A 1985 review of antihistamine pharmacokinetics found that the elimination half-life of diphenhydramine ranged between 3.4 and 9.3 hours across five studies, with a median elimination half-life of 4.3 hours.<sup>[2]</sup> A subsequent 1990 study found that the elimination half-life of diphenhydramine was 5.4 hours in children, 9.2 hours in young adults, and 13.5 hours in the elderly.<sup>[4]</sup>

<a href="#">α<sub>1B</sub></a>	1,300	Human	<a href="#">[46]</a>
<a href="#">α<sub>2A</sub></a>	2,900	Human	<a href="#">[46]</a>
<a href="#">α<sub>2B</sub></a>	1,600	Human	<a href="#">[46]</a>
<a href="#">α<sub>2C</sub></a>	2,100	Human	<a href="#">[46]</a>
<a href="#">D<sub>2</sub></a>	20,000	Rat	<a href="#">[47]</a>
<a href="#">H<sub>1</sub></a>	<b>9.6–16</b>	<b>Human</b>	<a href="#">[48][46][46]</a>
<a href="#">H<sub>2</sub></a>	>100,000	Canine	<a href="#">[49]</a>
<a href="#">H<sub>3</sub></a>	>10,000	Human	<a href="#">[46][50][51]</a>
<a href="#">H<sub>4</sub></a>	>10,000	Human	<a href="#">[51]</a>
<a href="#">M<sub>1</sub></a>	<b>80–100</b>	<b>Human</b>	<a href="#">[52][46]</a>
<a href="#">M<sub>2</sub></a>	<b>120–490</b>	<b>Human</b>	<a href="#">[52][46]</a>
<a href="#">M<sub>3</sub></a>	<b>84–229</b>	<b>Human</b>	<a href="#">[52][46]</a>
<a href="#">M<sub>4</sub></a>	<b>53–112</b>	<b>Human</b>	<a href="#">[52][46]</a>
<a href="#">M<sub>5</sub></a>	<b>30–260</b>	<b>Human</b>	<a href="#">[52][46]</a>
<a href="#">VGSC</a>	48,000–86,000	Rat	<a href="#">[53]</a>
<a href="#">hERG</a>	27,100 ( <a href="#">IC<sub>50</sub></a> )	Human	<a href="#">[54]</a>

Values are K<sub>i</sub> (nM), unless otherwise noted.  
The smaller the value, the more strongly the drug binds to the site.

## Chemistry [ edit ]

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Diphenhydramine is a [diphenylmethane derivative](#). Analogues of diphenhydramine include [orphenadrine](#), an [anticholinergic](#), [nefopam](#), an [analgesic](#), and [tofenacin](#), an [antidepressant](#). The [selective serotonin reuptake inhibitor](#) (SSRI) antidepressant [fluoxetine](#) is also a close analogue of diphenhydramine.

## Detection in body fluids [ edit ]

Diphenhydramine can be quantified in blood, plasma, or serum.<sup>[61]</sup> [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.<sup>[61]</sup> Rapid urine drug screens using immunoassays based on the principle of competitive binding may show false-positive [methadone](#) results for people having ingested diphenhydramine.<sup>[62]</sup> Quantification can be used to monitor therapy, confirm a diagnosis of poisoning in people who are hospitalized, provide evidence in an impaired driving arrest, or assist in a death investigation.<sup>[61]</sup>

## History [ edit ]

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Diphenhydramine was discovered in 1943 by [George Rieveschl](#), a former professor at the [University of Cincinnati](#).<sup>[63][64]</sup> In 1946, it became the first prescription antihistamine approved by the U.S. FDA.<sup>[65]</sup>

In the 1960s diphenhydramine was found to inhibit [reuptake](#) of the [neurotransmitter serotonin](#).<sup>[57]</sup> 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).<sup>[57][66]</sup> A similar search had previously led to the synthesis of the first SSRI, [zimeclidine](#), from [brompheniramine](#), also an antihistamine.<sup>[67]</sup>

## Society and culture [ edit ]

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Diphenhydramine is sometimes used recreationally as [potentiator](#) of opiates.<sup>[68]</sup>

Diphenhydramine is deemed to have limited abuse potential in the United States owing 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.<sup>[69]</sup> 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.<sup>[70][71]</sup>

Diphenhydramine is among prohibited and controlled substances in the [Republic of Zambia](#),<sup>[72]</sup> 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.<sup>[73]</sup>

## Recreational use [ edit ]

Although diphenhydramine is widely used and generally considered to be safe, multiple cases of [abuse](#) and [addiction](#) have been documented.<sup>[74]</sup> Because the drug is cheap and sold over the



counter in most countries, adolescents without access to stronger, illicit drugs are particularly at risk.<sup>[75]</sup> People with mental health problems—especially those with [schizophrenia](#)—are also prone to abuse the drug, which is [self-administered](#) in large doses to treat [extrapyramidal symptoms](#) caused by the use of [antipsychotics](#).<sup>[76]</sup>

Recreational users report calming effects, mild euphoria, and hallucinations as the desired effects of the drug.<sup>[76][77]</sup> Research has shown that [antimuscarinic agents](#), such as diphenhydramine, "may have antidepressant and mood-elevating properties."<sup>[78]</sup> A study conducted on adult males with a history of [sedative](#) abuse found that subjects who were administered a high dose (400 mg) of diphenhydramine reported a desire to take the drug again, despite also reporting negative effects, such as difficulty concentrating, confusion, [tremors](#), and blurred vision.<sup>[79]</sup>






















































## 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.



[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.<sup>[80]</sup>

















































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- <sup>2</sup> <sup>^</sup> [a](#) [b](#) [c](#) [d](#) [e](#) Paton DM, Webster DR (1985). "Clinical pharmacokinetics of H1-receptor antagonists (the antihistamines)". *Clinical Pharmacokinetics*. **10** (6): 477–97. doi:10.2165/00003088-198510060-00002<sup>[[c](#)]</sup>. PMID 2866055<sup>[[c](#)]</sup>.
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