[Template:Drugbox](/wiki/Template:Drugbox" \o "Template:Drugbox)

**Diazepam**, first marketed as **Valium**, is a medication of the [benzodiazepine](/wiki/Benzodiazepine) family that typically produces a calming effect. It is commonly used to treat a range of conditions including [anxiety](/wiki/Anxiety_disorder), [alcohol withdrawal syndrome](/wiki/Alcohol_withdrawal_syndrome), [benzodiazepine withdrawal syndrome](/wiki/Benzodiazepine_withdrawal_syndrome), [muscle spasms](/wiki/Muscle_spasms), [seizures](/wiki/Seizure), [trouble sleeping](/wiki/Insomnia), and [restless legs syndrome](/wiki/Restless_legs_syndrome).<ref name=Cal2014/> It may also be used to [cause memory loss](/wiki/Amnesia) during certain medical procedures.[[1]](#cite_note-1)<ref name=AHFS2015/> It can be taken by mouth, inserted into the [rectum](/wiki/Rectum), injected into muscle, or [injected into a vein](/wiki/Intravenously).<ref name=AHFS2015/> When given into a vein, effects begin in one to five minutes and last up to an hour.<ref name=AHFS2015>[Template:Cite web](/wiki/Template:Cite_web)</ref> By mouth, effects may take 40 minutes to begin.[[2]](#cite_note-2) Common side effects include sleepiness and trouble with coordination.<ref name=AHFS2015/> Serious side effects are rare.<ref name=Cal2014/> They include [suicide](/wiki/Suicide), decreased breathing, and an increased risk of seizures if used too frequently in those with [epilepsy](/wiki/Epilepsy).<ref name=Cal2014/><ref name=AHFS2015/> Occasionally excitement or [agitation](/wiki/Psychomotor_agitation) may occur.[[3]](#cite_note-3)[[4]](#cite_note-4) [Long term use](/wiki/Long-term_effects_of_benzodiazepines) can result in [tolerance](/wiki/Drug_tolerance), [dependence](/wiki/Benzodiazepine_dependence), and withdrawal symptoms on dose reduction. Abrupt stopping after long term use can be potentially dangerous.<ref name=Cal2014/> After stopping, [cognitive](/wiki/Cognitive) problems may persist for six months or longer.[[3]](#cite_note-3) It is not recommended during pregnancy or breastfeeding.<ref name=AHFS2015/> Its mechanism of action is by increasing the effect of the neurotransmitter [*gamma*-Aminobutyric acid](/wiki/Gamma-Aminobutyric_acid) (GABA).[[3]](#cite_note-3) Diazepam was first synthesized by [Leo Sternbach](/wiki/Leo_Sternbach), and was first manufactured by [Hoffmann-La Roche](/wiki/Hoffmann-La_Roche). It has been one of the most frequently prescribed medications in the world since its launch in 1963. In the United States it was the highest selling medication between 1968 and 1982, selling more than two billion tablets in 1978 alone. In 1985 the patent ended, and there are now more than 500 brands available on the market.<ref name=Cal2014>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Diazepam is on the [World Health Organization's List of Essential Medicines](/wiki/World_Health_Organization's_List_of_Essential_Medicines), the most important medications needed in a basic [health system](/wiki/Health_system).[[5]](#cite_note-5) The wholesale cost in the [developing world](/wiki/Developing_world) is about 0.01 USD per dose as of 2014.[[6]](#cite_note-6) In the United States it is about 0.40 USD per dose.<ref name=AHFS2015/>

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## Medical uses[[edit](/index.php?title=(none)&action=edit&section=1)]

[thumb|Diazepam tablets (2, 5, and 10 mg)](/wiki/File:Diazepam(Valium)_DOJ.jpg) Diazepam is mainly used to treat anxiety, insomnia, panic attacks and symptoms of acute alcohol withdrawal. It is also used as a [premedication](/wiki/Premedication) for inducing sedation, anxiolysis, or amnesia before certain medical procedures (e.g., [endoscopy](/wiki/Endoscopy)).[[7]](#cite_note-7)[[8]](#cite_note-8) Diazepam is the drug of choice for treating benzodiazepine dependence with its long duration of action allowing easier dose reduction. Benzodiazepines have a relatively low toxicity in overdose.[[3]](#cite_note-3) Diazepam has a number of uses including:

* Treatment of anxiety, [panic attacks](/wiki/Panic_attacks), and states of [agitation](/wiki/Psychomotor_agitation)[[7]](#cite_note-7)\* Treatment of neurovegetative symptoms associated with [vertigo](/wiki/Vertigo_(medical))[[9]](#cite_note-9)\* Treatment of the symptoms of alcohol, opiate, and [benzodiazepine withdrawal](/wiki/Benzodiazepine_withdrawal)[[7]](#cite_note-7)[[10]](#cite_note-10)\* Short-term treatment of insomnia[[7]](#cite_note-7)\* Treatment of [tetanus](/wiki/Tetanus), together with other measures of intensive treatment<ref name=tetanus>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>
* Adjunctive treatment of spastic muscular [paresis](/wiki/Paresis) (paraplegia/tetraplegia) caused by cerebral or [spinal cord](/wiki/Spinal_cord) conditions such as [stroke](/wiki/Stroke), [multiple sclerosis](/wiki/Multiple_sclerosis), or spinal cord injury (long-term treatment is coupled with other rehabilitative measures)[[11]](#cite_note-11)\* Palliative treatment of [stiff person syndrome](/wiki/Stiff_person_syndrome)[[12]](#cite_note-12)\* Pre- or postoperative sedation, anxiolysis and/or amnesia (e.g., before endoscopic or surgical procedures)[[11]](#cite_note-11)\* Treatment of complications with a [hallucinogen](/wiki/Hallucinogen) crisis and [stimulant](/wiki/Stimulant) overdoses and psychosis, such as [LSD](/wiki/LSD), [cocaine](/wiki/Cocaine), or [methamphetamine](/wiki/Methamphetamine)[[13]](#cite_note-13)\* Preventative treatment of [oxygen toxicity](/wiki/Oxygen_toxicity) during [hyperbaric oxygen therapy](/wiki/Hyperbaric_oxygen_therapy)[[14]](#cite_note-14)

Dosages should be determined on an individual basis, depending on the condition being treated, severity of symptoms, patient body weight, and any other conditions the person may have.[[13]](#cite_note-13)

### Seizures[[edit](/index.php?title=(none)&action=edit&section=2)]

Intravenous diazepam or [lorazepam](/wiki/Lorazepam) are first-line treatments for status epilepticus.[[3]](#cite_note-3)[[15]](#cite_note-15) However, lorazepam has advantages over diazepam, including a higher rate of terminating seizures and a more prolonged anticonvulsant effect.[[16]](#cite_note-16)[Template:Update inline](/wiki/Template:Update_inline) Diazepam is rarely used for the long-term treatment of [epilepsy](/wiki/Epilepsy) because tolerance to its anticonvulsant effects usually develops within six to 12 months of treatment, effectively rendering it useless for that purpose.[[13]](#cite_note-13)[[17]](#cite_note-17) The anticonvulsant effects of diazepam can help in the treatment of seizures due to a drug overdose or chemical toxicity as a result of exposure to [sarin](/wiki/Sarin), [VX](/wiki/VX_(nerve_agent)), or [soman](/wiki/Soman) (or other [organophosphate](/wiki/Organophosphate) poisons), [lindane](/wiki/Lindane), [chloroquine](/wiki/Chloroquine), [physostigmine](/wiki/Physostigmine), or [pyrethroids](/wiki/Pyrethroid).[[13]](#cite_note-13)[[18]](#cite_note-18) It is sometimes used intermittently for the prevention of [febrile seizures](/wiki/Febrile_seizures) that may occur in children under five years of age.[[3]](#cite_note-3) This use; however, is not typically recommended as the benefits are small and side effects are common.[[19]](#cite_note-19) Long-term use of diazepam for the management of epilepsy is not recommended; however, a subgroup of individuals with treatment-resistant epilepsy benefit from long-term benzodiazepines, and for such individuals, [clorazepate](/wiki/Clorazepate) has been recommended due to its slower onset of tolerance to the anticonvulsant effects.[[3]](#cite_note-3)

### Other[[edit](/index.php?title=(none)&action=edit&section=3)]

Diazepam is used for the emergency treatment of [eclampsia](/wiki/Eclampsia), when [IV](/wiki/Intravenous_therapy) [magnesium sulfate](/wiki/Magnesium_sulfate) and blood-pressure control measures have failed.[[20]](#cite_note-20)[[21]](#cite_note-21) Benzodiazepines do not have any pain-relieving properties themselves, and are generally recommended to avoid in individuals with pain.[[22]](#cite_note-22) However, benzodiazepines such as diazepam can be used for their muscle-relaxant properties to alleviate pain caused by muscle spasms and various [dystonias](/wiki/Dystonia), including [blepharospasm](/wiki/Blepharospasm).[[23]](#cite_note-23)[[24]](#cite_note-24) Tolerance often develops to the muscle relaxant effects of benzodiazepines such as diazepam.<ref name=tdamobd2004>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> [Baclofen](/wiki/Baclofen)[[25]](#cite_note-25) or [tizanidine](/wiki/Tizanidine) is sometimes used as an alternative to diazepam.

### Availability[[edit](/index.php?title=(none)&action=edit&section=4)]

Diazepam is marketed in over 500 brands throughout the world.[[26]](#cite_note-26) It is supplied in oral, injectable, inhalation, and rectal forms.[[13]](#cite_note-13)[[27]](#cite_note-27)[[28]](#cite_note-28) The [United States military](/wiki/United_States_military) employs a specialized diazepam preparation known as [Template:Anchor](/wiki/Template:Anchor) Convulsive Antidote, Nerve Agent (CANA), which contains diazepam. One CANA kit is typically issued to service members, along with three [Mark I NAAK](/wiki/Mark_I_NAAK) kits, when operating in circumstances where chemical weapons in the form of [nerve agents](/wiki/Nerve_agents) are considered a potential hazard. Both of these kits deliver drugs using [autoinjectors](/wiki/Autoinjector). They are intended for use in "buddy aid" or "self aid" administration of the drugs in the field prior to [decontamination](/wiki/Decontamination) and delivery of the patient to definitive medical care.[[29]](#cite_note-29)

## Contraindications[[edit](/index.php?title=(none)&action=edit&section=5)]

Use of diazepam should be avoided, when possible, in individuals with:[[30]](#cite_note-30)\* [Ataxia](/wiki/Ataxia)

* Severe [hypoventilation](/wiki/Hypoventilation)
* Acute narrow-angle [glaucoma](/wiki/Glaucoma)
* Severe [hepatic](/wiki/Hepatic) deficiencies ([hepatitis](/wiki/Hepatitis) and liver [cirrhosis](/wiki/Cirrhosis) decrease elimination by a factor of two)
* Severe [renal](/wiki/Renal) deficiencies (for example, patients on [dialysis](/wiki/Dialysis))
* Liver disorders
* Severe [sleep apnea](/wiki/Sleep_apnea)
* Severe [depression](/wiki/Clinical_depression), particularly when accompanied by suicidal tendencies
* [Psychosis](/wiki/Psychosis)
* [Pregnancy](/wiki/Pregnancy) or [breast feeding](/wiki/Breast_feeding)
* Caution required in elderly or debilitated patients
* [Coma](/wiki/Coma) or shock
* Abrupt discontinuation of therapy
* Acute intoxication with [alcohol](/wiki/Ethanol), [narcotics](/wiki/Narcotics), or other psychoactive substances (with the exception of some hallucinogens and/or stimulants, where it is occasionally used as a treatment for overdose)
* History of alcohol or [drug dependence](/wiki/Drug_dependence)
* [Myasthenia gravis](/wiki/Myasthenia_gravis), an [autoimmune disorder](/wiki/Autoimmune_disorder) causing marked fatiguability
* [Hypersensitivity](/wiki/Hypersensitivity) or [allergy](/wiki/Allergy) to any drug in the benzodiazepine class

### Caution[[edit](/index.php?title=(none)&action=edit&section=6)]

* Benzodiazepine abuse and misuse should be checked if used in the alcohol- or drug-dependent people or those with comorbid [psychiatric disorders](/wiki/Psychiatric_disorders) .[[31]](#cite_note-31)\* Pediatric patients
  + Less than 18 years of age, this treatment is usually not indicated, except for treatment of epilepsy, and pre- or postoperative treatment. The smallest possible effective dose should be used for this group of patients.[[32]](#cite_note-32)\*\* Under 6 months of age, safety and effectiveness have not been established; diazepam should not be given to those in this age group.[[12]](#cite_note-12)[[32]](#cite_note-32)\* Elderly and very ill patients may possibly suffer apnea and/or cardiac arrest. Concomitant use of other central nervous system depressants increases this risk. The smallest possible effective dose should be used for this group of patients.[[12]](#cite_note-12)[[32]](#cite_note-32)[[33]](#cite_note-33) The elderly metabolise benzodiazepines much more slowly than younger adults, and are also more sensitive to the effects of benzodiazepines, even at similar blood plasma levels. Doses of diazepam are recommended to be about half of those given to younger people, and treatment limited to a maximum of two weeks. Long-acting benzodiazepines such as diazepam are not recommended for the elderly.[[3]](#cite_note-3) Diazepam may also be dangerous in geriatric patients owing to a significant increased risk of falls.[[34]](#cite_note-34)\* Intravenous or intramuscular injections in hypotensive people or those in shock should be administered carefully and vital signs should be monitored.[[33]](#cite_note-33)\* Benzodiazepines such as diazepam are lipophilic and rapidly penetrate membranes, so rapidly cross over into the placenta with significant uptake of the drug. Use of benzodiazepines including diazepam in late pregnancy, especially high doses, may result in [floppy infant syndrome](/wiki/Floppy_infant_syndrome).[[35]](#cite_note-35) Diazepam when taken late in pregnancy, during the [third trimester](/wiki/Third_trimester), causes a definite risk of a severe [benzodiazepine withdrawal syndrome](/wiki/Benzodiazepine_withdrawal_syndrome) in the neonate with symptoms including [hypotonia](/wiki/Hypotonia), and reluctance to suck, to [apnoeic](/wiki/Apnoeic) spells, [cyanosis](/wiki/Cyanosis), and impaired [metabolic](/wiki/Metabolic) responses to cold stress. Floppy infant syndrome and sedation in the newborn may also occur. Symptoms of floppy infant syndrome and the neonatal benzodiazepine withdrawal syndrome have been reported to persist from hours to months after birth.[[36]](#cite_note-36)

## Adverse effects[[edit](/index.php?title=(none)&action=edit&section=7)]

Adverse effects of benzodiazepines such as diazepam include anterograde amnesia and confusion (especially pronounced in higher doses) and [sedation](/wiki/Sedation). The elderly are more prone to adverse effects of diazepam, such as confusion, amnesia, ataxia, and hangover effects, as well as falls. Long-term use of benzodiazepines such as diazepam is associated with drug tolerance, benzodiazepine dependence, and benzodiazepine withdrawal syndrome.[[3]](#cite_note-3) Like other benzodiazepines, diazepam can impair short-term memory and learning of new information. While benzodiazepine drugs such as diazepam can cause anterograde amnesia, they do not cause [retrograde amnesia](/wiki/Retrograde_amnesia); information learned before using benzodiazepines is not impaired. Tolerance to the cognitive-impairing effects of benzodiazepines does not tend to develop with long-term use, and the elderly are more sensitive to them.[[37]](#cite_note-37) Additionally, after cessation of benzodiazepines, cognitive deficits may persist for at least six months; it is unclear whether these impairments take longer than six months to abate or if they are permanent. Benzodiazepines may also cause or worsen depression.[[3]](#cite_note-3) Infusions or repeated intravenous injections of diazepam when managing seizures, for example, may lead to drug toxicity, including respiratory depression, sedation and [hypotension](/wiki/Hypotension). Drug tolerance may also develop to infusions of diazepam if it is given for longer than 24 hours.[[3]](#cite_note-3) Adverse effects such as sedation, benzodiazepine dependence, and abuse potential limit the use of benzodiazepines.[[38]](#cite_note-38) Diazepam has a range of side effects common to most benzodiazepines, including:

* Suppression of [REM sleep](/wiki/REM_sleep)
* Impaired motor function
  + Impaired coordination
  + Impaired balance
  + [Dizziness](/wiki/Dizziness)
* Depression[[39]](#cite_note-39)\* [Reflex tachycardia](/wiki/Tachycardia)[[40]](#cite_note-40)

Less commonly, paradoxical side effects can occur, including nervousness, irritability, excitement, worsening of seizures, insomnia, muscle cramps, changes in [libido](/wiki/Libido), and in some cases, rage and violence. These adverse reactions are more likely to occur in children, the elderly, and individuals with a history of drug or alcohol abuse and or aggression.[[3]](#cite_note-3)<ref name=rage>[Template:Cite journal](/wiki/Template:Cite_journal)</ref><ref name=next\_three>[Template:Cite web](/wiki/Template:Cite_web)</ref><ref name=violence>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Diazepam may increase, in some people, the propensity toward self-harming behaviours and, in extreme cases, may provoke suicidal tendencies or acts.[[41]](#cite_note-41) Very rarely [dystonia](/wiki/Dystonia) can occur.[[42]](#cite_note-42) Diazepam may impair the ability to drive vehicles or operate machinery. The impairment is worsened by consumption of alcohol, because both act as central nervous system depressants.[[12]](#cite_note-12) During the course of therapy, tolerance to the sedative effects usually develops, but not to the anxiolytic and myorelaxant effects.<ref name=sedative\_effect\_tolerance>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

Patients with severe attacks of [apnea](/wiki/Apnea) during sleep may suffer [respiratory depression](/wiki/Respiratory_depression) (hypoventilation), leading to respiratory arrest and death.

Diazepam in doses of 5 mg or more causes significant deterioration in [alertness](/wiki/Alertness) performance combined with increased feelings of sleepiness.[[43]](#cite_note-43)

### Tolerance and dependence[[edit](/index.php?title=(none)&action=edit&section=8)]

Diazepam, as with other [benzodiazepine](/wiki/Benzodiazepine) drugs, can cause tolerance, physical dependence, [substance use disorder](/wiki/Substance_use_disorder), and benzodiazepine withdrawal syndrome. Withdrawal from diazepam or other benzodiazepines often leads to withdrawal symptoms similar to those seen during barbiturate or alcohol withdrawal. The higher the dose and the longer the drug is taken, the greater the risk of experiencing unpleasant withdrawal symptoms.

Withdrawal symptoms can occur from standard dosages and also after short-term use, and can range from insomnia and anxiety to more serious symptoms, including seizures and psychosis. Withdrawal symptoms can sometimes resemble pre-existing conditions and be misdiagnosed. Diazepam may produce less intense withdrawal symptoms due to its long [elimination half-life](/wiki/Elimination_half-life).

Benzodiazepine treatment should be discontinued as soon as possible by a slow and gradual dose reduction regimen.[[3]](#cite_note-3)[[44]](#cite_note-44) Tolerance develops to the therapeutic effects of benzodiazepines; for example tolerance occurs to the anticonvulsant effects and as a result benzodiazepines are not generally recommended for the long-term management of epilepsy. Dose increases may overcome the effects of tolerance, but tolerance may then develop to the higher dose and adverse effects may increase. The mechanism of tolerance to benzodiazepines includes uncoupling of receptor sites, alterations in [gene expression](/wiki/Gene_expression), down-regulation of receptor sites, and desensitisation of receptor sites to the effect of GABA. About one-third of individuals who take benzodiazepines for longer than four weeks become dependent and experience withdrawal syndrome on cessation.[[3]](#cite_note-3) Differences in rates of withdrawal (50–100%) vary depending on the patient sample. For example, a random sample of long-term benzodiazepine users typically finds around 50% experience few or no withdrawal symptoms, with the other 50% experiencing notable withdrawal symptoms. Certain select patient groups show a higher rate of notable withdrawal symptoms, up to 100%.[[45]](#cite_note-45) Rebound anxiety, more severe than baseline anxiety, is also a common withdrawal symptom when discontinuing diazepam or other benzodiazepines.[[46]](#cite_note-46) Diazepam is therefore only recommended for short-term therapy at the lowest possible dose owing to risks of severe withdrawal problems from low doses even after gradual reduction.[[47]](#cite_note-47) The risk of pharmacological dependence on diazepam is significant, and patients experience symptoms of benzodiazepine withdrawal syndrome if it is taken for six weeks or longer.[[48]](#cite_note-48) In humans, tolerance to the anticonvulsant effects of diazepam occurs frequently.[[49]](#cite_note-49)

### Dependence[[edit](/index.php?title=(none)&action=edit&section=9)]

Improper or excessive use of diazepam can lead to [dependence](/wiki/Substance_dependence).[[50]](#cite_note-50) At a particularly high risk for diazepam misuse, [abuse](/wiki/Drug_abuse) or dependence are:

* People with a history of alcohol or drug abuse or dependence[[12]](#cite_note-12)[[51]](#cite_note-51) Diazepam increases craving for alcohol in problem alcohol consumers. Diazepam also increases the volume of alcohol consumed by problem drinkers.[[52]](#cite_note-52)\* People with severe personality disorders, such as [borderline personality disorder](/wiki/Borderline_personality_disorder)<ref name=not\_in\_BPD>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

Patients from the aforementioned groups should be monitored very closely during therapy for signs of abuse and development of dependence. Therapy should be discontinued if any of these signs are noted, although if dependence has developed, therapy must still be discontinued gradually to avoid severe withdrawal symptoms. Long-term therapy in these people is not recommended.[[12]](#cite_note-12)[[51]](#cite_note-51) People suspected of being dependent on benzodiazepine drugs should be very gradually tapered off the drug. Withdrawals can be life-threatening, particularly when excessive doses have been taken for extended periods of time. Equal prudence should be used whether dependence has occurred in therapeutic or recreational contexts.

## Overdose[[edit](/index.php?title=(none)&action=edit&section=10)]

[Template:Main article](/wiki/Template:Main_article) An individual who has consumed too much diazepam typically displays one or more of these symptoms in a period of approximately four hours immediately following a suspected overdose:[[12]](#cite_note-12)[[53]](#cite_note-53)\* Drowsiness

* Mental confusion
* [Hypotension](/wiki/Hypotension)
* Impaired motor functions
  + Impaired reflexes
  + Impaired coordination
  + Impaired balance
  + Dizziness
* [Coma](/wiki/Coma)

Although not usually fatal when taken alone, a diazepam overdose is considered a medical emergency and generally requires the immediate attention of medical personnel. The [antidote](/wiki/Antidote) for an overdose of diazepam (or any other benzodiazepine) is [flumazenil](/wiki/Flumazenil) (Anexate). This drug is only used in cases with severe respiratory depression or cardiovascular complications. Because flumazenil is a short-acting drug, and the effects of diazepam can last for days, several doses of flumazenil may be necessary. [Artificial respiration](/wiki/Artificial_respiration) and stabilization of cardiovascular functions may also be necessary. Though not routinely indicated, [activated charcoal](/wiki/Activated_charcoal) can be used for decontamination of the stomach following a diazepam overdose. [Emesis](/wiki/Emesis) is contraindicated. [Dialysis](/wiki/Dialysis) is minimally effective. Hypotension may be treated with [levarterenol](/wiki/Levarterenol) or [metaraminol](/wiki/Metaraminol).[[12]](#cite_note-12)[[13]](#cite_note-13)[[53]](#cite_note-53)[[54]](#cite_note-54) The oral [Template:LD50](/wiki/Template:LD50) (lethal dose in 50% of the population) of diazepam is 720 mg/kg in mice and 1240 mg/kg in rats.[[12]](#cite_note-12) D. J. Greenblatt and colleagues reported in 1978 on two patients who had taken 500 and 2000 mg of diazepam, respectively, went into moderately deep comas, and were discharged within 48 hours without having experienced any important complications, in spite of having high concentrations of diazepam and its metabolites desmethyldiazepam, oxazepam, and temazepam, according to samples taken in the hospital and as follow-up.<ref name=Greenblatt\_et\_al\_1978>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

Overdoses of diazepam with alcohol, opiates and/or other depressants may be fatal.[[54]](#cite_note-54)[[55]](#cite_note-55)

## Interactions[[edit](/index.php?title=(none)&action=edit&section=11)]

If diazepam is administered concomitantly with other drugs, attention should be paid to the possible pharmacological interactions. Particular care should be taken with drugs that potentiate the effects of diazepam, such as barbiturates, [phenothiazines](/wiki/Phenothiazines), [opioids](/wiki/Opioid), and [antidepressants](/wiki/Antidepressants).[[12]](#cite_note-12) Diazepam does not increase or decrease hepatic enzyme activity, and does not alter the metabolism of other compounds. No evidence would suggest diazepam alters its own metabolism with chronic administration.[[13]](#cite_note-13) Agents with an effect on hepatic cytochrome P450 pathways or conjugation can alter the rate of diazepam metabolism. These interactions would be expected to be most significant with long-term diazepam therapy, and their clinical significance is variable.[[13]](#cite_note-13)\* Diazepam increases the central depressive effects of alcohol, other [hypnotics](/wiki/Hypnotic)/sedatives (e.g., barbiturates), other [muscle relaxants](/wiki/Muscle_relaxant), certain antidepressants, sedative [antihistamines](/wiki/Antihistamines), [opioids](/wiki/Opioid), and [antipsychotics](/wiki/Antipsychotics), as well as [anticonvulsants](/wiki/Anticonvulsants) such as [phenobarbital](/wiki/Phenobarbital), [phenytoin](/wiki/Phenytoin), and [carbamazepine](/wiki/Carbamazepine). The euphoriant effects of opioids may be increased, leading to increased risk of psychological dependence.[[3]](#cite_note-3)[[32]](#cite_note-32)[[56]](#cite_note-56)\* [Cimetidine](/wiki/Cimetidine), [omeprazole](/wiki/Omeprazole), [oxcarbazepine](/wiki/Oxcarbazepine), [ticlopidine](/wiki/Ticlopidine), [topiramate](/wiki/Topiramate), [ketoconazole](/wiki/Ketoconazole), [itraconazole](/wiki/Itraconazole), [disulfiram](/wiki/Disulfiram), [fluvoxamine](/wiki/Fluvoxamine), [isoniazid](/wiki/Isoniazid), [erythromycin](/wiki/Erythromycin), [probenecid](/wiki/Probenecid), [propranolol](/wiki/Propranolol), [imipramine](/wiki/Imipramine), [ciprofloxacin](/wiki/Ciprofloxacin), [fluoxetine](/wiki/Fluoxetine), and [valproic acid](/wiki/Valproic_acid) prolong the action of diazepam by inhibiting its elimination.[[3]](#cite_note-3)[[13]](#cite_note-13)[[27]](#cite_note-27)\* [Alcohol](/wiki/Ethanol) in combination with diazepam may cause a synergistic enhancement of the hypotensive properties of benzodiazepines and alcohol.[[57]](#cite_note-57)\* Oral contraceptives significantly decrease the elimination of desmethyldiazepam, a major metabolite of diazepam.[[32]](#cite_note-32)[[58]](#cite_note-58)\* Rifampin, phenytoin, carbamazepine, and phenobarbital increase the metabolism of diazepam, thus decreasing drug levels and effects.[[13]](#cite_note-13) [Dexamethasone](/wiki/Dexamethasone) and [St John's wort](/wiki/Hypericum_perforatum) also increase the metabolism of diazepam.[[3]](#cite_note-3)\* Diazepam increases the serum levels of phenobarbital.[[59]](#cite_note-59)\* [Nefazodone](/wiki/Nefazodone) can cause increased blood levels of benzodiazepines.[[32]](#cite_note-32)\* [Cisapride](/wiki/Cisapride) may enhance the absorption, and therefore the sedative activity, of diazepam.[[60]](#cite_note-60)\* Small doses of [theophylline](/wiki/Theophylline) may inhibit the action of diazepam.<ref name=theophylline>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

* Diazepam may block the action of [levodopa](/wiki/Levodopa) (used in the treatment of [Parkinson's disease](/wiki/Parkinson's_disease)).[[56]](#cite_note-56)\* Diazepam may alter [digoxin](/wiki/Digoxin) serum concentrations.[[13]](#cite_note-13)\* Other drugs that may have interactions with diazepam include [antipsychotics](/wiki/Antipsychotic) (e.g. [chlorpromazine](/wiki/Chlorpromazine)), [MAO inhibitors](/wiki/MAO_inhibitors), and [ranitidine](/wiki/Ranitidine).[[32]](#cite_note-32)\* Because it acts on the GABA receptor, the herb [valerian](/wiki/Valerian_(herb)) may produce an adverse effect.[[61]](#cite_note-61)\* Foods that acidify the urine can lead to faster absorption and elimination of diazepam, reducing drug levels and activity.[[56]](#cite_note-56)\* Foods that alkalinize the urine can lead to slower absorption and elimination of diazepam, increasing drug levels and activity.[[13]](#cite_note-13)\* Reports conflict as to whether food in general has any effects on the absorption and activity of orally administered diazepam.[[56]](#cite_note-56)

## Pharmacology[[edit](/index.php?title=(none)&action=edit&section=12)]

[thumb|10 mg Valium.](/wiki/File:10mg_Valium_pill.jpg) Diazepam is a long-acting "classical" benzodiazepine. Other classical benzodiazepines include [chlordiazepoxide](/wiki/Chlordiazepoxide), [clonazepam](/wiki/Clonazepam), lorazepam, oxazepam, [nitrazepam](/wiki/Nitrazepam), [temazepam](/wiki/Temazepam), [flurazepam](/wiki/Flurazepam), [bromazepam](/wiki/Bromazepam), and [clorazepate](/wiki/Clorazepate).[[62]](#cite_note-62) Diazepam has [anticonvulsant](/wiki/Anticonvulsant) properties.[[63]](#cite_note-63) Diazepam has no effect on GABA levels and no effect on glutamate decarboxylase activity, but has a slight effect on gamma-aminobutyric acid transaminase activity. It differs from some other anticonvulsive drugs with which it was compared.[[64]](#cite_note-64) Benzodiazepines act via [micromolar](/wiki/Micromolar) benzodiazepine binding sites as [Ca2+](/wiki/Ca2+) channel blockers and significantly inhibit depolarization-sensitive Calcium uptake in rat nerve cell preparations.[[65]](#cite_note-65) Diazepam inhibits acetylcholine release in mouse hippocampal synaptosomes. This has been found by measuring sodium-dependent high-affinity choline uptake in mouse brain cells *in vitro*, after pretreatment of the mice with diazepam *in vivo*. This may play a role in explaining diazepam's anticonvulsant properties.[[66]](#cite_note-66) Diazepam binds with high affinity to [glial cells](/wiki/Glial_cells) in animal cell cultures.[[67]](#cite_note-67) Diazepam at high doses has been found to decrease histamine turnover in mouse brain via diazepam's action at the benzodiazepine-GABA receptor complex.[[68]](#cite_note-68) Diazepam also decreases [prolactin](/wiki/Prolactin) release in rats.[[69]](#cite_note-69)

### Mechanism of action[[edit](/index.php?title=(none)&action=edit&section=13)]

[Template:See also](/wiki/Template:See_also)

Benzodiazepines are positive allosteric modulators of the GABA type A receptors ([GABAA](/wiki/GABAA)). The GABAA receptors are ligand-gated chloride-selective ion channels that are activated by GABA, the major inhibitory neurotransmitter in the brain. Binding of benzodiazepines to this receptor complex promotes binding of GABA, which in turn increases the total conduction of chloride ions across the neuronal cell membrane. This increased chloride ion influx hyperpolarizes the neuron's membrane potential. As a result, the difference between resting potential and threshold potential is increased and firing is less likely.

The GABAA receptor is a heteromer composed of five subunits, the most common ones being two αs, two βs, and one γ (α2β2γ). For each subunit, many subtypes exist (α1–6, β1–3, and γ1–3). GABAA receptors containing the α1 subunit mediate the sedative, the anterograde amnesic, and partly the anticonvulsive effects of diazepam. GABAA receptors containing α2 mediate the anxiolytic actions and to a large degree the myorelaxant effects. GABAA receptors containing α3 and α5 also contribute to benzodiazepines myorelaxant actions, whereas GABAA receptors comprising the α5 subunit were shown to modulate the temporal and spatial memory effects of benzodiazepines.[[70]](#cite_note-70) Diazepam appears to act on areas of the [limbic system](/wiki/Limbic_system), [thalamus](/wiki/Thalamus), and [hypothalamus](/wiki/Hypothalamus), inducing anxiolytic effects. Benzodiazepine drugs including diazepam increase the inhibitory processes in the cerebral cortex.[[71]](#cite_note-71) The anticonvulsant properties of diazepam and other benzodiazepines may be in part or entirely due to binding to voltage-dependent sodium channels rather than benzodiazepine receptors. Sustained repetitive firing seems limited by benzodiazepines' effect of slowing recovery of sodium channels from inactivation.[[72]](#cite_note-72) The muscle relaxant properties of diazepam are produced via inhibition of [polysynaptic](/wiki/Polysynaptic) pathways in the spinal cord.[[73]](#cite_note-73)

### Pharmacokinetics[[edit](/index.php?title=(none)&action=edit&section=14)]

Diazepam can be administered orally, intravenously (must be diluted, as it is painful and damaging to veins), [intramuscularly](/wiki/Intramuscular_injection) (IM), or as a [suppository](/wiki/Suppository).[[13]](#cite_note-13) When administered orally, it is rapidly absorbed and has a fast onset of action. The onset of action is one to five minutes for IV administration and 15–30 minutes for IM administration. The duration of diazepam's peak pharmacological effects is 15 minutes to one hour for both routes of administration.[[40]](#cite_note-40) The bioavailability after oral administration is 100%, and 90% after rectal administration. Peak plasma levels occur between 30 and 90 minutes after oral administration and between 30 and 60 minutes after intramuscular administration; after rectal administration, peak plasma levels occur after 10 to 45 minutes. Diazepam is highly protein-bound, with 96 to 99% of the absorbed drug being protein-bound. The distribution half-life of diazepam is two to 13 minutes.[[3]](#cite_note-3) When diazepam is administered IM, absorption is slow, erratic, and incomplete.[[7]](#cite_note-7) Diazepam is highly lipid-soluble, and is widely distributed throughout the body after administration. It easily crosses both the [blood–brain barrier](/wiki/Blood–brain_barrier) and the [placenta](/wiki/Placenta), and is excreted into breast milk. After absorption, diazepam is redistributed into [muscle](/wiki/Muscle) and [adipose](/wiki/Adipose) tissue. Continual daily doses of diazepam quickly build to a high concentration in the body (mainly in [adipose tissue](/wiki/Adipose_tissue)), far in excess of the actual dose for any given day.[[3]](#cite_note-3)[[13]](#cite_note-13) Diazepam is stored preferentially in some organs, including the heart. Absorption by any administered route and the risk of accumulation is significantly increased in the [neonate](/wiki/Neonate), and withdrawal of diazepam during pregnancy and breast feeding is clinically justified.[[74]](#cite_note-74) Diazepam undergoes oxidative metabolism by demethylation (CYP 2C9, 2C19, 2B6, 3A4, and 3A5), hydroxylation (CYP 3A4 and 2C19) and [glucuronidation](/wiki/Glucuronidation) in the liver as part of the [cytochrome P450](/wiki/Cytochrome_P450) enzyme system. It has several pharmacologically [active metabolites](/wiki/Active_metabolites). The main active metabolite of diazepam is [desmethyldiazepam](/wiki/Nordiazepam) (also known as nordazepam or nordiazepam). Its other active metabolites include the minor active metabolites temazepam and oxazepam. These metabolites are conjugated with glucuronide, and are excreted primarily in the urine. Because of these active metabolites, the serum values of diazepam alone are not useful in predicting the effects of the drug. Diazepam has a biphasic half-life of about one to three days, and two to seven days for the active metabolite desmethyldiazepam.[[3]](#cite_note-3) Most of the drug is metabolised; very little diazepam is excreted unchanged.[[13]](#cite_note-13) The elimination half-life of diazepam and also the active metabolite [desmethyldiazepam](/wiki/Desmethyldiazepam) increases significantly in the elderly, which may result in prolonged action, as well as accumulation of the drug during repeated administration.[[75]](#cite_note-75)

## Physical and chemical properties[[edit](/index.php?title=(none)&action=edit&section=15)]

Diazepam occurs as solid white or yellow crystals with a melting point of 131.5 to 134.5 °C. It is odorless, and has a slightly bitter taste. The [British Pharmacopoeia](/wiki/British_Pharmacopoeia) lists it as being very slightly soluble in water, soluble in alcohol, and freely soluble in chloroform. The [United States Pharmacopoeia](/wiki/United_States_Pharmacopoeia) lists diazepam as soluble 1 in 16 ethyl alcohol, 1 in 2 of chloroform, 1 in 39 [ether](/wiki/Ether), and practically insoluble in water. The [pH](/wiki/PH) of diazepam is neutral (i.e., pH = 7). Diazepam has a shelf life of five years for oral tablets and three years for IV/IM solutions.[[13]](#cite_note-13)Diazepam should be stored at room temperature (15–30 °C). The solution for parenteral injection should be protected from light and kept from freezing. The oral forms should be stored in air-tight containers and protected from light.[[27]](#cite_note-27) Diazepam can absorb into plastics, so liquid preparations should not be kept in plastic bottles or syringes, etc. As such, it can leach into the plastic bags and tubing used for intravenous infusions. Absorption appears to depend on several factors, such as temperature, concentration, flow rates, and tube length. Diazepam should not be administered if a precipitate has formed and does not dissolve.[[27]](#cite_note-27)

### Detection in body fluids[[edit](/index.php?title=(none)&action=edit&section=16)]

Diazepam may be quantified in blood or plasma to confirm a diagnosis of poisoning in hospitalized patients, provide evidence in an impaired driving arrest, or to assist in a medicolegal death investigation. Blood or plasma diazepam concentrations are usually in a range of 0.1–1.0 mg/l in persons receiving the drug therapeutically, 1–5 mg/l in those arrested for impaired driving, and 2–20 mg/l in victims of acute overdose. Most commercial immunoassays for the benzodiazepine class of drugs cross-react with diazepam, but confirmation and quantitation are usually performed using chromatographic techniques.[[76]](#cite_note-76)[[77]](#cite_note-77)[[78]](#cite_note-78)

## History[[edit](/index.php?title=(none)&action=edit&section=17)]

Diazepam was the second benzodiazepine invented by Dr. [Leo Sternbach](/wiki/Leo_Sternbach) of [Hoffmann-La Roche](/wiki/Hoffmann-La_Roche) at the company's [Nutley, New Jersey](/wiki/Nutley,_New_Jersey), facility[[79]](#cite_note-79) following [chlordiazepoxide](/wiki/Chlordiazepoxide) (Librium), which was approved for use in 1960. Released in 1963 as an improved version of Librium, diazepam became incredibly popular, helping Roche to become a pharmaceutical industry giant. It is 2.5 times more potent than its predecessor, which it quickly surpassed in terms of sales. After this initial success, other pharmaceutical companies began to introduce other benzodiazepine derivatives.[[80]](#cite_note-80) The benzodiazepines gained popularity among medical professionals as an improvement over [barbiturates](/wiki/Barbiturate), which have a comparatively narrow [therapeutic index](/wiki/Therapeutic_index), and are far more sedative at therapeutic doses. The benzodiazepines are also far less dangerous; death rarely results from diazepam overdose, except in cases where it is consumed with large amounts of other [depressants](/wiki/Depressants) (such as alcohol or opioids).[[54]](#cite_note-54) Benzodiazepine drugs such as diazepam initially had widespread public support, but with time the view changed to one of growing criticism and calls for restrictions on their prescription.[[81]](#cite_note-81) Diazepam was the top-selling pharmaceutical in the United States from 1969 to 1982, with peak sales in 1978 of 2.3 billion tablets.[[80]](#cite_note-80) Diazepam, along with [oxazepam](/wiki/Oxazepam), [nitrazepam](/wiki/Nitrazepam) and [temazepam](/wiki/Temazepam), represents 82% of the benzodiazepine market in Australia.[[82]](#cite_note-82) While psychiatrists continue to prescribe diazepam for the short-term relief of anxiety, neurology has taken the lead in prescribing diazepam for the [palliative](/wiki/Palliative) treatment of certain types of epilepsy and spastic activity, for example, forms of [paresis](/wiki/Paresis). It is also the first line of defense for a rare disorder called [stiff-person syndrome](/wiki/Stiff-person_syndrome).[[11]](#cite_note-11)

## Society and culture[[edit](/index.php?title=(none)&action=edit&section=18)]

### Recreational use[[edit](/index.php?title=(none)&action=edit&section=19)]

[Template:See also](/wiki/Template:See_also) Diazepam is a drug of potential abuse and can cause [drug dependence](/wiki/Drug_dependence). Urgent action by national governments has been recommended to improve prescribing patterns of benzodiazepines such as diazepam.[[83]](#cite_note-83)[[84]](#cite_note-84) A single dose of diazepam modulates the [dopamine](/wiki/Dopamine) system in similar ways to how morphine and [alcohol](/wiki/Ethanol) modulate the dopaminergic pathways.[[85]](#cite_note-85)Between 50 and 64% of rats will self-administer diazepam.[[86]](#cite_note-86)Diazepam has been shown to be able to substitute for the behavioural effects of [barbiturates](/wiki/Barbiturates) in a [primate](/wiki/Primate) study.[[87]](#cite_note-87)Diazepam has been found as an [adulterant](/wiki/Adulterant) in [heroin](/wiki/Heroin).<ref name=heroin\_adulterant>[Template:Cite web](/wiki/Template:Cite_web)</ref>

Diazepam drug misuse can occur either through [recreational misuse](/wiki/Recreational_drug_use) where the drug is taken to achieve a high or when the drug is continued long term against medical advice.[[88]](#cite_note-88) Sometimes, it is used by [stimulant](/wiki/Stimulant) users to "come down" and sleep and to help control the urge to binge.<ref name=with\_meth>[Template:Cite web](/wiki/Template:Cite_web)</ref>

A large-scale study in the US, conducted by [SAMHSA](/wiki/SAMHSA), using data from 2011, determined benzodiazepines were present in 28.7% of emergency department visits involving nonmedical use of pharmaceuticals. In this regard, benzodiazepines are second only to [opiates](/wiki/Opiate), the study found in 39.2% of visits. About 29.3% of drug-related suicide attempts involve benzodiazepines, making them the most frequently represented class in drug-related [suicide](/wiki/Suicide_in_the_United_States) attempts. Males abuse benzodiazepines as commonly as females.[[89]](#cite_note-89) Benzodiazepines, including diazepam, nitrazepam, and flunitrazepam, account for the largest volume of forged drug prescriptions in [Sweden](/wiki/Sweden), a total of 52% of drug forgeries being for benzodiazepines.[[90]](#cite_note-90) Diazepam was detected in 26% of cases of people suspected of [driving under the influence](/wiki/Driving_under_the_influence) of drugs in Sweden, and its active metabolite nordazepam was detected in 28% of cases. Other benzodiazepines and zolpidem and zopiclone also were found in high numbers. Many drivers had blood levels far exceeding the therapeutic dose range, suggesting a high degree of abuse potential for benzodiazepines and [zolpidem](/wiki/Zolpidem) and [zopiclone](/wiki/Zopiclone).[[76]](#cite_note-76) In [Northern Ireland](/wiki/Northern_Ireland) in cases where drugs were detected in samples from impaired drivers who were not impaired by alcohol, benzodiazepines were found in 87% of cases. Diazepam was the most commonly detected benzodiazepine.[[91]](#cite_note-91)

### Legal status[[edit](/index.php?title=(none)&action=edit&section=20)]

Diazepam is regulated in most countries as a [prescription drug](/wiki/Prescription_drug):

* International: diazepam is a Schedule IV controlled drug under the [Convention on Psychotropic Substances](/wiki/Convention_on_Psychotropic_Substances).[[92]](#cite_note-92)\* UK: classified as a controlled drug, listed under Schedule IV, Part I (CD Benz POM) of the Misuse of Drugs Regulations 2001, allowing possession with a valid prescription. The [Misuse of Drugs Act 1971](/wiki/Misuse_of_Drugs_Act_1971) makes it illegal to possess the drug without a prescription, and for such purposes it is classified as a Class C drug.[[93]](#cite_note-93)\* Germany: classified as a prescription drug, or in high dosage as a restricted drug (*Betäubungsmittelgesetz, Anhang III*).[[94]](#cite_note-94)\*Australia: Diazepam is Schedule 4 substance under the [Poisons Standard](/wiki/Standard_for_the_Uniform_Scheduling_of_Medicines_and_Poisons) (October 2015).[[95]](#cite_note-95)

## Veterinary uses[[edit](/index.php?title=(none)&action=edit&section=22)]

Diazepam is used as a short-term sedative and [anxiolytic](/wiki/Anxiolytic) for cats and dogs,[[97]](#cite_note-97) sometimes used as an appetite stimulant.[[97]](#cite_note-97)[[98]](#cite_note-98) It can also be used to stop seizures in dogs and cats.[[99]](#cite_note-99)[[100]](#cite_note-100)

## References[[edit](/index.php?title=(none)&action=edit&section=23)]

[Template:Research help](/wiki/Template:Research_help) [Template:Reflist](/wiki/Template:Reflist)

## External links[[edit](/index.php?title=(none)&action=edit&section=24)]

[Template:Commons category](/wiki/Template:Commons_category)

* [Roche Pharmaceuticals (AUS) – Valium Product Information](http://www.roche-australia.com/fmfiles/re7229005/downloads/central-nervous-agents/valium-pi.pdf)
* [US National Library of Medicine: Drug Information Portal – Diazepam](http://druginfo.nlm.nih.gov/drugportal/dpdirect.jsp?name=Diazepam)
* [Flash animation about how bromazepam works (mechanism of action)](http://pharmacologycorner.com/animation-benzodiazepines-diazepam-lorazepam-alprazolam/)
* [Template:Wayback](/wiki/Template:Wayback)

[Template:Anticonvulsants](/wiki/Template:Anticonvulsants) [Template:Antidotes](/wiki/Template:Antidotes) [Template:Anxiolytics](/wiki/Template:Anxiolytics) [Template:Benzodiazepines](/wiki/Template:Benzodiazepines) [Template:GABAAR PAMs](/wiki/Template:GABAAR_PAMs) [Template:Glycinergics](/wiki/Template:Glycinergics) [Template:Authority control](/wiki/Template:Authority_control)

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