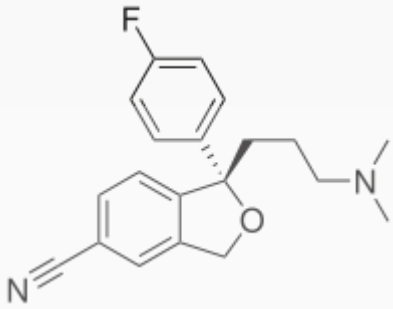
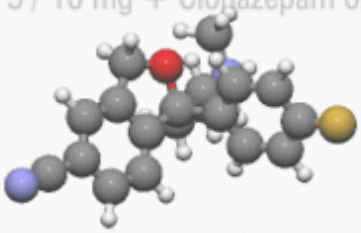
# Escitalopram

**Escitalopram**





| **Systematic (IUPAC) name** | |
|---|---|
| (*S*)-1-[3-(Dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile | |
| **Clinical data** | |
| **Trade names** | Lexapro |
| **AHFS/Drugs.com** | monograph |
| **MedlinePlus** | a603005 |
| **Licence data** | US FDA:link |
| **Pregnancy cat.** | C (AU) C (US) |

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|---|---|
| **Legal status** | Prescription Only (S4) (AU) POM (UK) ℞-only (US) |
| **Routes** | Oral |
| **Pharmacokinetic data** | |
| **Bioavailability** | 80% |
| **Protein binding** | ~56% |
| **Metabolism** | Liver, specifically the enzymes CYP3A4 and CYP2C19 |
| **Half-life** | 27–32 hours |
| **Identifiers** | |
| **CAS number** | 128196-01-0 |
| **ATC code** | N06AB10 |
| **PubChem** | CID 146570 |
| **DrugBank** | DB01175 |
| **ChemSpider** | 129277 |
| **UNII** | 4O4S742ANY |
| **ChEBI** | CHEBI:36791 |
| **ChEMBL** | CHEMBL1508 |
| **Chemical data** | |

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|---|---|
| **Formula** | $C_{20}H_{21}FN_2O$ |
| **Mol. mass** | 324.392 g/mol<br>(414.43 as oxalate) |
| **SMILES** | • Fc1ccc(cc1)[C@@]3(OCc2cc(C#N)ccc23)CCCN(C)C |
| **InChI** | InChI=1S/C20H21FN2O/c1-23(2)11-3-10-20(17-5-7-18(21)8-6-17)19-9-4-15(13-22)12-16(19)14-24-20/h4-9,12H,3,10-11,14H2,1-2H3/t20-/m0/s1<br>Key:WSEQXVZVJXJVFP-FQEVSTJZSA-N |



**Escitalopram** is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class. It is approved by the U.S. Food and Drug Administration (FDA) for the treatment of adults and children over 12 years of age with major depressive disorder (MDD) and generalized anxiety disorder (GAD). Escitalopram is the (*S*)-stereoisomer (enantiomer) of the earlier Lundbeck drug citalopram, hence the name *es*citalopram. Whether escitalopram exhibits superior therapeutic properties to citalopram or merely represents an example of "evergreening" is controversial.[1]

# Medical uses

Escitalopram has FDA approval for the treatment of major depressive disorder and generalized anxiety disorder in adults.[2] In European countries, it is approved for depression (MDD) and certain anxiety disorders: general anxiety disorder (GAD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), and panic disorder with or without agoraphobia.

## Depression

Escitalopram was approved by regulatory authorities for the treatment of major depressive disorder on the basis of four placebo controlled, multi-center, double-blind clinical trials, three of which demonstrated a statistical superiority to placebo.[3] Nonetheless, considerable controversy exists regarding the superiority of escitalopram to its predecessor citalopram. The importance of

this issue follows from the greater cost of escitalopram relative to the generic mixture of isomers citalopram prior to the expiration of the escitalopram patent in 2012, which led to charges of "evergreening". Accordingly, this issue has been examined in at least 10 different systematic reviews and meta analyses. The most recent of these have concluded (with caveats in some cases) that escitalopram is modestly superior to citalopram in efficacy and/or tolerability.[4][5][6][7]

In contrast to these findings, a 2011 review concluded that all second generation antidepressants are equally effective,[8] and treatment guidelines issued by the National Institute of Health and Clinical Excellence and by the American Pyschiatric Association generally reflect this viewpoint.[9][10]

The utility of antidepressant drugs in the treatment of mild-to-moderate depression is itself controversial. This issue is discussed in detail in the SSRI article.

### Anxiety disorder

There may be a significant improvement in GAD symptoms as early as the first week and the majority of patients respond by week eight with a significant improvement in functioning.[11] It also seems effective in the long-term with relapse on escitalopram (20%) less than placebo (50%).[12]

Escitalopram and citalopram appear equally effective in panic disorder.[13]

### Other

Escitalopram as well as other SSRIs are effective in reducing the symptoms of premenstrual syndrome, whether taken in the luteal phase only or continuously.[14] There is no good data available for escitalopram for seasonal affective disorder as of 2011.[15]

## Adverse effects

Escitalopram, like other SSRIs, has been shown to affect sexual functions causing side effects such as decreased libido, delayed ejaculation, genital anesthesia,[16] andanorgasmia.[17][18]

An analysis conducted by the FDA found a statistically insignificant 1.5 to 2.4-fold (depending on the statistical technique used) increase of suicidality among the adults treated with escitalopram for psychiatric indications.[19][20][21] Similarly, the UK MHRA data indicate an 80% increase of suicide-related events, not reaching statistical significance, in the escitalopram vs. placebo patients.[22] The authors of a related study note the general problem with statistical approaches: due to the rarity of suicidal events in clinical trials, it is hard to draw firm conclusions with a sample smaller than two million patients.[23]

Escitalopram is not associated with significant weight gain. For example, 0.6 kg mean weight change after 6 months of treatment with escitalopram for depression was insignificant and similar to that with placebo (0.2 kg).[24] 1.4–1.8 kg mean weight gain was reported in 8-month trials of escitalopram for depression,[25] and generalized anxiety disorder.[26] A 52-week trial of escitalopram for the long-term treatment of depression in elderly also found insignificant 0.6 kg mean weight gain.[27] Escitalopram may help reduce weight in those treated forbinge eating associated obesity.[28]

Citalopram and escitalopram are associated with dose-dependent QT interval prolongation[29] and should not be used in those with congenital long QT syndrome or known pre-existing QT interval prolongation, or in combination with other medicines that prolong the QT interval. ECG measurements should be considered for patients with cardiac disease, and electrolyte disturbances should be corrected before starting treatment. In December 2011, the UK implemented new restrictions on the maximum daily doses:

- for citalopram, 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment.
- for escitalopram, 10 mg for patients older than 65 years; other doses remain unchanged.[30][31]

Escitalopram should be taken with caution when using Saint John's wort.[32] Exposure to escitalopram is increased moderately, by about 50%, when it is taken with omeprazole. The

authors of this study suggested that this increase is unlikely to be of clinical concern.[33] Caution should be used when taking cough medicine containing dextromethorphan (DXM) as serotonin syndrome, liver damage, and other negative side effects have been reported.

## List of adverse effects

[34][35][36][37]

**Very common (>10% incidence) adverse effects include:**

- Headache
- Nausea

**Common (1-10% incidence) adverse effects include:**

- Insomnia
- Somnolence
- Dizziness
- Paraesthesia
- Tremor
- Decreased appetite
- Increased appetite
- Anxiety
- Restlessness
- Abnormal dreams
- Libido decreased
- Anorgasmia
- Sinusitis
- Yawning
- Diarrhea
- Constipation
- Vomiting
- Dry mouth
- Excessive sweating
- Arthralgia (joint pain)
- Myalgia (muscular aches and pains)
- Fatigue
- Pyrexia (fever)
- Ejaculation disorder,
- Impotence (erectile dysfunction)



## Discontinuation symptoms

*Main article: SSRI discontinuation syndrome*

Escitalopram discontinuation, particularly abruptly, may cause certain withdrawal symptoms such as "electric shock" sensations[38] (also known as "brain shivers" or "brain zaps"), dizziness, acute depressions and irritability, bladder control issues, as well as heightened senses of akathisia.[39]

Human data suggests there's a risk when taking Lexapro in the third trimester of pregnancy.[40]

## Overdose

Excessive doses of escitalopram usually cause relatively minor untoward effects such as agitation and tachycardia. However, dyskinesia, hypertonia, and clonus may occur in some cases. Plasma escitalopram concentrations are usually in a range of 20-80 µg/L in therapeutic situations and may reach 80-200 µg/L in the elderly, patients with hepatic dysfunction, those who are poor CYP2C19 metabolizers or following acute overdose. Monitoring of the drug in plasma or serum is generally accomplished using chromatographic methods. Chiral techniques are available to distinguish escitalopram from its racemate, citalopram.[41][42][43] Escitalopram seems to be less dangerous than citalopram in overdose and comparable to other SSRIs.[44]

# Drug/Food Interactions

Escitalopram, similarly to other SSRIs (with the exception of fluvoxamine), inhibits CYP2D6 and hence may increase plasma levels of a number of CYP2D6 substrates such as aripiprazole, risperidone, codeine, etc. Escitalopram can also prolong the QT interval and hence it is not recommended in patients that are concurrently on other medications that have the ability to prolong the QT interval. Being a SSRI escitalopram should not be given concurrently with MAOIs or other serotonergic medications.[45]

# Pharmacology

Escitalopram increases intrasynaptic levels of the neurotransmitter serotonin by blocking the reuptake of the neurotransmitter into the presynaptic neuron. Of the SSRIs currently on the market, escitalopram has the highest affinity for the human serotonin transporter (SERT). The enantiomer of escitalopram ((*R*)-citalopram) counteracts to a certain degree the serotonin-enhancing action of escitalopram. As a result, escitalopram has been claimed to be a more potent antidepressant than citalopram, which is a racemic mixture of the two enantiomers. In order to explain this phenomenon, researchers from Lundbeck proposed that escitalopram enhances its own binding via an additional interaction with another allosteric site on the transporter.[46] Further research by the same group showed that (*R*)-citalopram also enhances binding of escitalopram,[47] and therefore the allosteric interaction cannot explain the observed counteracting effect. In the most recent paper, however, the same authors again reversed their findings and reported that (*R*)-citalopram decreases binding of escitalopram to the transporter.[48] Although allosteric binding of escitalopram to the serotonin transporter is of unquestionable research interest, its clinical relevance is unclear since the binding of escitalopram to the allosteric site is at least 1000 times weaker than to the primary binding site.

Escitalopram is a substrate of P-glycoprotein and hence P-glycoprotein inhibitors such as verapamil and quinidine may improve its blood-brain penetrability.[49] In a preclinical study in rats combining escitalopram with a P-glycoprotein inhibitor enhanced its antidepressant-like effects.[49]

# History

Escitalopram was developed in close cooperation between Lundbeck and Forest Laboratories. Its development was initiated in the summer of 1997, and the resulting new drug application was submitted to the U.S. FDA in March 2001. The short time (3.5 years) it took to develop escitalopram can be attributed to the previous extensive experience of Lundbeck and Forest with citalopram, which has similar pharmacology.[50] The FDA issued the approval of escitalopram for major depression in August 2002 and for generalized anxiety disorder in December 2003. On May 23, 2006, the FDA approved a generic version of escitalopram by Teva.[51] On July 14 of that year, however, the U.S. District Court of Delaware decided in favor of Lundbeck regarding the patent infringement dispute and ruled the patent on escitalopram valid.[52]

In 2006 Forest Laboratories was granted an 828 day (2 years and 3 months) extension on its US patent for escitalopram.[53] This pushed the patent expiration date from December 7, 2009 to September 14, 2011. Together with the 6-month pediatric exclusivity, the final expiration date was March 14, 2012.

# Society and culture

## Allegations of illegal marketing

In 2004, two separate civil suits alleging illegal marketing of citalopram and escitalopram for use by children and teenagers by Forest were initiated by two whistleblowers, one by a non-practicing physician named Joseph Piacentile, and the other by a Forest salesman named Christopher Gobble.[54] In February 2009, these two suits received support from the US Attorney for Massachusetts and were combined into one. Eleven states and the District of Columbia have

also filed notices of intention to intervene as plaintiffs in the action. The suits allege that Forest illegally engaged in off-label promoting of Lexapro for use in children, that the company hid the results of a study showing lack of effectiveness in children, and that the company paid kickbacks to doctors to induce them to prescribe Lexapro to children. It was also alleged that the company conducted so-called "seeding studies" that were, in reality, marketing efforts to promote the drug's use by doctors.[55][56] Forest responded to these allegations that it "is committed to adhering to the highest ethical and legal standards, and off-label promotion and improper payments to medical providers have consistently been against Forest policy.[57]"

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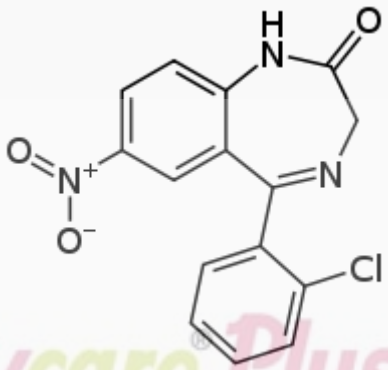
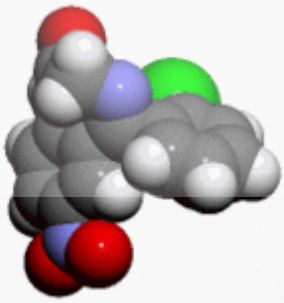
# Clonazepam

**Clonazepam**





| **Systematic (IUPAC) name** | |
|---|---|
| 5-(2-chlorophenyl)-7-nitro-2,3-dihydro-1,4-benzodiazepin-2-one | |
| **Clinical data** | |
| **Trade names** | Klonopin |
| **AHFS/Drugs.com** | monograph |
| **MedlinePlus** | a682279 |
| **Licence data** | US FDA:link |

| | |
|---|---|
| **Pregnancy cat.** | C (AU) D (US) |
| **Legal status** | Prescription Only (S4) (AU) Schedule IV (CA) schedule Q (UK) Schedule IV(US) |
| **Dependence liability** | Moderate[1] |
| **Routes** | Oral, I.M., I.V, sublingual |
| **Pharmacokinetic data** | |
| **Bioavailability** | 90% |
| **Protein binding** | ~85% |
| **Metabolism** | Hepatic CYP3A4 |
| **Half-life** | 18-50 hours |
| **Excretion** | Renal |
| **Identifiers** | |
| **CAS number** | 1622-61-3 |
| **ATC code** | N03AE01 |
| **PubChem** | CID 2802 |
| **DrugBank** | DB01068 |
| **ChemSpider** | 2700 |
| **UNII** | 5PE9FDE8GB |
| **KEGG** | D00280 |
| **ChEBI** | CHEBI:3756 |

| | |
|---|---|
| **ChEMBL** | CHEMBL452 |

**Chemical data**

| | |
|---|---|
| **Formula** | $C_{15}H_{10}ClN_3O_3$ |
| **Mol. mass** | 315.715 |



**SMILES**

- [O-][N+](C1=CC2=C(C=C1)NC(CN=C2C3=CC=CC=C3Cl)=O)=O

**InChI**

InChI=1S/C15H10ClN3O3/c16-12-4-2-1-3-10(12)15-11-7-9(19(21)22)5-6-13(11)18-14(20)8-17-15/h1-7H,8H2,(H,18,20)

Key:DGBIGWXXNGSACT-UHFFFAOYSA-N

**Clonazepam**[2] is a benzodiazepine drug having anxiolytic, anticonvulsant,[3] muscle relaxant, sedative, and hypnotic properties.[4] It is marketed under the trade name **Rivotril** by Rochein Argentina, Australia, Brazil, Bulgaria, Canada, Colombia, Costa Rica, Denmark, Germany, Ireland, Italy, Mexico, Portugal, South Africa and Spain; **Linotril** and **Clonotril** in India, South Korea, and other parts of Europe; and under the trade name **Klonopin** by Roche in the United States. Other names, such as Ravotril, Rivatril, Iktorivil, Clonex, Paxam, Petril, Naze and Kriadex, are known throughout the world.[*citation needed*] Clonazepam has an unusually long elimination half-life of 18–50 hours, making it generally considered to be among the longest-acting benzodiazepines.[5] Clonazepam is a chlorinated derivative of nitrazepam[6] and therefore a chloro-nitrobenzodiazepine.[7]

Clonazepam has an intermediate onset of action, with a peak blood level occurring one to four hours after oral administration. Long-term effects of benzodiazepines include tolerance,benzodiazepine dependence, and benzodiazepine withdrawal syndrome, which occurs in one third of patients treated with clonazepam for longer than four weeks.[8]

Benzodiazepines such as clonazepam have a fast onset of action, high effectivity rate, and low toxicity in overdose; however, as with most medications, it may have drawbacks due to adverse or paradoxical effects. The benzodiazepine clorazepate may be an alternative to clonazepam due to a slow onset of tolerance and its availability in a slow-release formula to counter fluctuations in blood levels. The pharmacological property of clonazepam, as with other benzodiazepines, is the enhancement of the neurotransmitter GABA via modulation of the$GABA_A$ receptor.[8]

# Medical uses

Clonazepam may be prescribed for epilepsy.[9][10] Clonazepam is approved by the Food and Drug Administration for treatment of epilepsy, panic disorder. It is also approved for treatment of typical and atypical absences, infantile myoclonic, myoclonic and akinetic seizures[11] and also as a second line agent. Clonazepam, like other benzodiazepines, while being a first-line treatment for acute seizures, is not suitable for the long-term treatment of seizures due to the development of tolerance to the anticonvulsant effects. The benzodiazepine clorazepatemay be preferred over clonazepam due to a slower onset of tolerance and availability in slow-release formulation to counter fluctuations in blood levels, although there is not a manufacturer of this slow-release formulation in the United States as of January 2014. Clonazepam is also used for the treatment of panic disorder. The pharmacological property of clonazepam as with other benzodiazepines is the enhancement of the neurotransmitter GABA via modulation of the $GABA_A$ receptor.[8] A subgroup of people with treatment resistant epilepsy may benefit from long-term use of clonazepam; the benzodiazepine clorazepate may be an alternative due to its slow onset of tolerance.[8]
Clonazepam has been found effective in treating epilepsy in children, and the inhibition of seizure activity seemed to be achieved at low plasma levels of clonazepam.[12] As a result, clonazepam is sometimes used for certain rare childhood epilepsies; however, it has been found to be ineffective in the control of infantile spasms.[13] Clonazepam is less effective and less potent as an anticonvulsant in controlling infantile seizure compared to nitrazepam in the treatment of West syndrome, an age-dependent epilepsy affecting the very young.

Clonazepam is mainly prescribed for the acute management of epilepsies. Clonazepam has been found to be effective in the acute control of non-convulsive status epilepticus; however, the benefits tended to be transient in many of the patients, and the addition of phenytoin for lasting control was required in these patients.[14]

Clonazepam has also been found effective in treating:

- Anxiety disorders, such as social phobia[15] and panic disorders.
- Certain types of migraines[16]
- Panic disorder[17]
- Initial treatment of mania or acute psychosis together with first-line drugs such as lithium, haloperidol or risperidone[18][19]
- For the management of the visual effects of HPPD[20]
- Hyperekplexia[21]
- Many forms of parasomnia are sometimes treated with clonazepam.[22] Restless legs syndrome can be treated using clonazepam as a third-line treatment option as the use of clonazepam is still investigational.[23][24] Bruxism also responds to clonazepam in the short-term[25] Rapid eye movement behavior disorder responds well to low doses of clonazepam.[26]
- The treatment of acute and chronic akathisia induced by neuroleptics, also called antipsychotics.[27][28]
- Spasticity related to amyotrophic lateral sclerosis.[29]
- Alcohol withdrawal syndrome

The effectiveness of clonazepam in the short-term treatment of panic disorder has been demonstrated in controlled clinical trials. Some long-term trials have suggested a benefit of clonazepam for up to three years without the development of tolerance but these trials were not placebo-controlled. Clonazepam is also effective in the management of acute mania.[30]

Clonazepam may aggravate or cause major depressive disorder and/or increase anxiety in the long-run, similar to other benzodiazepines in general. Clonazepam may help reduce the severity of tinnitus symptoms.[31]

### Formulations

Clonazepam was approved in the United States as a generic drug in 1997 and is now manufactured and marketed by several companies.

Clonazepam is available as tablets (0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg) and orally disintegrating tablets (wafers) (0.25 mg, 0.5 mg), an oral solution (drops), and as a solution for injection or intravenous infusion.

## Adverse effects

### Common

- Drowsiness[32]
- Motor impairment

### Less common

- Confusion[8]
- Irritability and aggression[33]
- Psychomotor agitation[34]
- Lack of motivation[35]
- Loss of libido
- Impaired motor function[*vague*]
  - Impaired coordination
  - Impaired balance
  - Dizziness
- Cognitive impairments[*vague*][36]
  - Hallucinations[37]
  - Short-term memory loss[38]
  - Anterograde amnesia (common with higher doses)[39]
- Some users report hangover-like symptoms of drowsiness, headaches, sluggishness, and irritability upon waking up if the medication was taken before sleep. This is likely the result of the medication's long half-life, which continues to affect the user after waking up.[*citation needed*]
- The "hangover effect" some experience not only results from clonazepam's considerably long half-life, but also, like many other benzodiazepines, when taken as a sleep aid, clonazepam's disruption or interference with the brain's delta waves. Delta waves signify the brain's slowest waves (~4 Hz) and occur during Stage 4 sleep, which designates humans' deepest sleep state (when the muscles are the most relaxed; breathing slows and becomes shallow), and the stage right before R.E.M. sleep and dreaming (Stage 5). Therefore, upon waking, this disruption of Stage 4 delta wave sleep causes a deficit in adequate brain/body rest or "recharge".

[40][41] While benzodiazepines induce sleep, they tend to reduce the quality of sleep by suppressing or disrupting REM sleep.[42] After regular use, rebound insomnia may occur when discontinuing clonazepam.[43]

- Benzodiazepines may cause or worsen depression.[8]

### Occasional

- Dysphoria[44]
- Thrombocytopenia[45]
- Induction of seizures[46][47] or increased frequency of seizures[48]
- Personality changes[49]
- Behavioural disturbances[50]
- Ataxia[8]
- Euphoria (possibly attributed to its anxiolytic properties)

### Rare

- Psychosis[51]
- Incontinence[52][53][54]
- Liver damage[55]
- Paradoxical behavioural disinhibition[8][56] (most frequently in children, the elderly, and in persons with developmental disabilities)
  - Rage
  - Excitement
  - Impulsivity

## Long term effects

The long term effects of clonazepam can include depression,[8] disinhibition, and sexual dysfunction.[57]

### Withdrawal-related

- Anxiety, irritability, insomnia, tremors
- Potential to exacerbate existing panic disorder upon discontinuation
- Seizures[58] similar to delirium tremens (with long-term use of excessive doses)

Benzodiazepines such as clonazepam can be very effective in controlling status epilepticus, but, when used for longer periods of time, some potentially serious side-effects may develop, such as interference with cognitive functions and behavior.[59] Many individuals treated on a long-term basis develop a form of dependence known as "low-dose dependence,"[*according to whom?*] as was shown in one double-blind, placebo-controlled study of 34 therapeutic low-dose benzodiazepine users. Physiological dependence was demonstrated by flumazenil-precipitated withdrawal.[60] Use of alcohol or other CNS depressants while taking clonazepam greatly intensifies the effects (and side-effects) of the drug.

### Tolerance and withdrawal

*Main article: Benzodiazepine withdrawal syndrome*

Like all benzodiazepines, clonazepam is a benzodiazepine receptor agonist.[61][62] One third of individuals treated with benzodiazepines for longer than four weeks develop a dependence on the drug and experience a withdrawal syndrome upon dose reduction. High dosage and long-term use increases the risk and severity of dependence and withdrawal symptoms. Withdrawal seizures and psychosis can occur in severe cases of withdrawal, and anxiety and insomnia can occur in less severe cases of withdrawal. Gradual reduction in dosage reduces the severity of the benzodiazepine withdrawal syndrome. Due to the risks of tolerance and withdrawal seizures, clonazepam is generally not recommended for the long-term management of epilepsies. Increasing the dose can overcome the effects of tolerance, but tolerance to the higher dose may occur and adverse effects may intensify. The mechanism of tolerance includes receptor desensitisation, down regulation, receptor decoupling, and alterations in subunit composition and in gene transcription coding.[8]

### Tolerance

Tolerance to the anticonvulsant effects of clonazepam occurs in both animals and humans. In humans, tolerance to the anticonvulsant effects of clonazepam occurs frequently.[63][64] Chronic use of benzodiazepines can lead to the development of tolerance with a decrease of benzodiazepine binding sites. The degree of tolerance is more pronounced with clonazepam than with chlordiazepoxide.[65] In general, short-term therapy is more effective than long-term therapy with clonazepam for the treatment of epilepsy.[66] Many studies have found that tolerance develops to the anticonvulsant properties of clonazepam with chronic use, which limits its long-term effectiveness as an anticonvulsant.[67]

### Withdrawal

Abrupt or over-rapid withdrawal from clonazepam may result in the development of the benzodiazepine withdrawal syndrome, causing psychosis characterised by dysphoric manifestations, irritability, aggressiveness, anxiety, and

hallucinations.[68][69][70] Sudden withdrawal may also induce the potentially life-threatening condition, status epilepticus. Anti-epileptic drugs, benzodiazepines such as clonazepam in particular, should be reduced in dose slowly and gradually when discontinuing the drug to mitigate withdrawal effects.[49] Carbamazepine has been tested in the treatment of clonazepam withdrawal and was found to be ineffective in preventing clonazepam withdrawal-induced status epilepticus from occurring.[71]

### Overdose

*Main article: Benzodiazepine overdose*

An individual who has exceeded their recommended dosage of clonazepam may display one or more of the following symptoms:

- Somnolence (difficulty staying awake)
- Mental confusion
- Nausea
- Impaired motor functions
  - Impaired reflexes
  - Impaired coordination
  - Impaired balance
  - Dizziness
- Respiratory depression
- Hypotension
- Coma



Coma can be cyclic, with the individual alternating from a comatose state to a hyper-alert state of consciousness, which occurred in a 4-year-old boy who suffered an overdose of clonazepam.[72] The combination of clonazepam and certain barbiturates, e.g. amobarbital, at prescribed doses has resulted in a synergistic potentiation of the effects of each drug, leading to serious respiratory depression.[73]

Overdose symptoms may include extreme drowsiness, confusion, muscle weakness, and fainting.[74]

Although an overdose of clonazepam is a serious medical concern, there have been no known instances of death from such an overdose. The LD50 for both mice and rats is greater than 2,000 mg per kilogram of body weight.[75]

### Detection in biological fluids

Clonazepam and 7-aminoclonazepam may be quantified in plasma, serum or whole blood in order to monitor compliance in those receiving the drug therapeutically. Results from such tests can be used to confirm the diagnosis in potential poisoning victims or to assist in the forensic investigation in a case of fatal overdosage. Both the parent drug and 7-aminoclonazepam are unstable in biofluids, and therefore specimens should be preserved with sodium fluoride, stored at the lowest possible temperature and analyzed quickly to minimize losses.[76]

## Special precautions

The elderly metabolise benzodiazepines more slowly than younger individuals and are also more sensitive to the effects of benzodiazepines, even at similar blood plasma levels. Doses for the elderly are recommended to be about half of that given to younger adults and are to be administered for no longer than 2 weeks. Long-acting benzodiazepines such as clonazepam are not generally recommended for the elderly due the risk of drug accumulation.[8]

The elderly are especially susceptible to increased risk of harm from motor impairments and drug accumulation side effects. Benzodiazepines also require special precaution if used by individuals that may be pregnant, alcohol- or drug-dependent, or may have comorbid psychiatric disorders.[77] Clonazepam is generally not recommended for use in elderly people for insomnia due to its high potency relative to other benzodiazepines.[78]

Clonazepam is not recommended for use in those under 18. Use in very young children may be especially hazardous. Of anticonvulsant drugs, behavioural disturbances occur most frequently with clonazepam and phenobarbital.[77][79]

Doses higher than 0.5–1 mg per day are associated with significant sedation.[80]

Clonazepam may aggravate hepatic porphyria.[81][82]

Clonazepam is not recommended for patients with chronic schizophrenia. A 1982 double-blinded, placebo-controlled study found clonazepam increases violent behavior in individuals with chronic schizophrenia.[83]

# Interactions

Clonazepam decreases the levels of carbamazepine,[84][85] and, likewise, clonazepam's level is reduced by carbamazepine. Azole antifungals, such as ketoconazole, may inhibit the metabolism of clonazepam.[8] Clonazepam may affect levels of phenytoin (diphenylhydantoin).[84][86][87][88] In turn, Phenytoin may lower clonazepam plasma levels by increasing the speed of clonazepam clearance by approximately 50% and decreasing its half-life by 31%.[89] Clonazepam increases the levels of primidone[87] and phenobarbital.[90]

Combined use of clonazepam with certain antidepressants, antiepileptics, such as phenobarbital, phenytoin and carbamazepine, sedative antihistamines, opiates, antipsychotics, nonbenzodiazepine hypnotics like zolpidem and alcohol may result in enhanced sedative effects.[8]

## Warnings

Clonazepam, like other benzodiazepines, will impair one's ability to drive or operate machinery. The central nervous system-depressing effects of the drug can be intensified by alcohol consumption, and therefore alcohol should be avoided while taking this medication. Benzodiazepines have been shown to cause both psychological and physical dependence. Patients physically dependent on clonazepam should be slowly titrated off under the supervision of a qualified healthcare professional to reduce the intensity of withdrawal or rebound symptoms.

# Pregnancy

*See also: Long-term effects of benzodiazepines § Neonatal effects*

There is some medical evidence of various malformations, e.g., cardiac or facial deformations, when used in early pregnancy; however, the data is not conclusive. The data are also inconclusive on whether benzodiazepines such as clonazepam cause developmental deficits or decreases in IQ in the developing fetus when taken by the mother during pregnancy. Clonazepam, when used late in pregnancy, may result in the development of a severe benzodiazepine withdrawal syndrome in the neonate. Withdrawal symptoms from benzodiazepines in the neonate may include hypotonia, apnoeic spells, cyanosis and impaired metabolic responses to cold stress.[91]

The safety profile of clonazepam during pregnancy is less clear than that of other benzodiazepines, and if benzodiazepines are indicated during pregnancy, chlordiazepoxide and diazepam may be a safer choice. The use of clonazepam during pregnancy should only occur if the clinical benefits are believed to outweigh the clinical risks to the fetus. Caution is also required if clonazepam is used during breast feeding. Possible adverse effects of use of benzodiazepines such as clonazepam during pregnancy include: miscarriage, malformation, intrauterine growth retardation, functional deficits, floppy infant syndrome, carcinogenesis and mutagenesis. Neonatal withdrawal syndrome associated with benzodiazepines include hypertonia, hyperreflexia, restlessness, irritability, abnormal sleep patterns, inconsolable crying, tremors or jerking of the extremities, bradycardia, cyanosis, suckling difficulties, apnea, risk of aspiration of feeds,diarrhea and vomiting, and growth retardation. This syndrome can develop between 3 days to 3 weeks after birth and can have a duration of up to several months. The pathway by which clonazepam is metabolised is usually impaired in newborns. If clonazepam is used during

pregnancy or breast feeding, it is recommended that serum levels of clonazepam are monitored and that signs of central nervous system depression and apnea are also checked for. In many cases, non-pharmacological treatments, such as relaxation therapy, psychotherapy and avoidance of caffeine, can be an effective and safer alternative to the use of benzodiazepines for anxiety in pregnant women.[92]

# Pharmacology

Clonazepam's primary mechanism of action is the modulation of GABA function in the brain, by the benzodiazepine receptor, located on $GABA_A$ receptors, which, in turn, leads to enhanced GABAergic inhibition of neuronal firing. Benzodiazepines do not replace GABA, but instead enhance the effect of GABA at the $GABA_A$ receptor by increasing the opening frequency of chloride ion channels, which leads to increased inhibitory effects with resultant central nervous system depression.[8] In addition, clonazepam decreases the utilization of 5-HT (serotonin) by neurons[93][94] and has been shown to bind tightly to central-type benzodiazepine receptors.[95] Because clonazepam is effective in low milligram doses (0.5 mg clonazepam = 10 mg diazepzm),[96] it is said to be among the class of "highly potent" benzodiazepines.[97] The anticonvulsant properties of benzodiazepines are due to the enhancement of synaptic GABA responses, and the inhibition of sustained, high-frequency repetitive firing.[98]

Benzodiazepines, including clonazepam, bind to mouse glial cell membranes with high affinity.[99][100] Clonazepam decreases release of acetylcholine in the feline brain[101] and decreases prolactin release in rats.[102] Benzodiazepines inhibit cold-induced thyroid stimulating hormone (also known as TSH or thyrotropin) release.[103] Benzodiazepines acted via micromolar benzodiazepine binding sites as $Ca^{2+}$ channel blockers and significantly inhibit depolarization-sensitive calcium uptake in experimentation on rat brain cell components. This has been conjectured as a mechanism for high-dose effects on seizures in the study.[104]

# Mechanism of action

Clonazepam acts by binding to the benzodiazepine site of the GABA receptors, which enhances the electric effect of GABA binding on neurons, resulting in an increased influx of chloride ions into the neurons. This further results in an inhibition of synaptic transmission across the central nervous system.[105][106]

Benzodiazepines do not have any effect on the levels of GABA in the brain.[107] Clonazepam has no effect on GABA levels and has no effect on gamma-aminobutyric acid transaminase. Clonazepam does, however, affect glutamate decarboxylase activity. It differs from other anticonvulsant drugs it was compared to in a study.[108]

# Pharmacokinetics

Clonazepam is lipid soluble, rapidly crosses the blood–brain barrier, and penetrates the placenta. It is extensively metabolised into pharmacologically inactive metabolites. Clonazepam is metabolized extensively via nitroreduction by cytochrome P450 enzymes, particularly CYP2C19 and to a lesser extent CYP3A4. Erythromycin, clarithromycin, ritonavir, itraconazole, ketoconazole, nefazodone, and grapefruit juice are inhibitors of CYP3A4 and can affect the metabolism of benzodiazepines.[109] It has an elimination half-life of 19–60 hours.[8] Peak blood concentrations of 6.5–13.5 ng/mL were usually reached within 1–2 hours following a single 2 mg oral dose of micronized clonazepam in healthy adults. In some individuals, however, peak blood concentrations were reached at 4–8 hours.[110]

Clonazepam passes rapidly into the central nervous system, with levels in the brain corresponding with levels of unbound clonazepam in the blood serum.[111] Clonazepam plasma levels are very unreliable amongst patients. Plasma levels of clonazepam can vary as much as tenfold between different patients.[112]

Clonazepam is largely bound to plasma proteins.[113] Clonazepam passes through the blood–brain barrier easily, with blood and brain levels corresponding equally with each other.[114] The metabolites of clonazepam include 7-aminoclonazepam, 7-acetaminoclonazepam and 3-hydroxy clonazepam.[115][116]

# Recreational use

*See also: Benzodiazepine drug misuse*

A 2006 US government study of nationwide emergency department (ED) visits conducted by SAMHSA found that sedative-hypnotics in the US were the most frequently implicated pharmaceutical drug in ED visits, with benzodiazepines accounting for the majority of these. Clonazepam was the second most frequently implicated benzodiazepine in ED visits in the study. The study examined the number of times non-medical use of certain drugs were implicated in ED visit. The criteria for non-medical use in this study were purposefully broad, and include, for example, drug abuse, accidental or intentional overdose, or adverse reactions resulting from legitimate use of the medication.[117]



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