Klonopin

Pharmacology Prescription Drug Presentation

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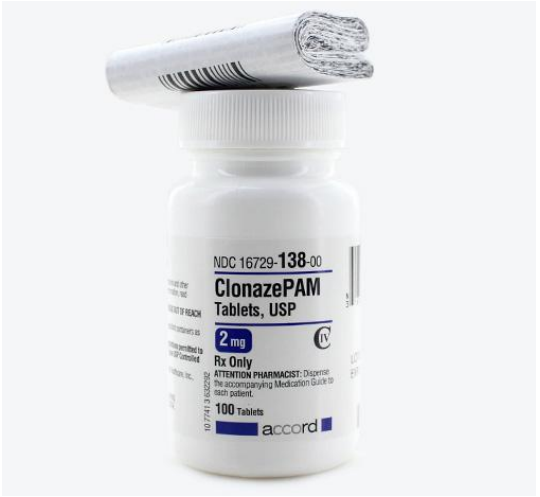
Klonopin

- **Generic Name**
  Clonazepam
- **Trade Name**
  Klonopin (United States), although it is also sold under the names Clonex, Clonapam, Iktorivil, Paxam, Rivatril, Rivotril, and Solfidin elsewhere.

(a)

(b)

Common Forms of Klonopin (Clonazepam):
(a) tablet form, 0.5 mg;
(b) tablet form, 1.0 mg;
(c) pharmaceutical supply of 2 mg tablets



(c)

Overview

Clonazepam is an anti-anxiety medication in the benzodiazepine family, the same family that includes *diazepam* (Valium), *alprazolam* (Xanax), *lorazepam* (Ativan), *flurazepam* (Dalmane), and others. Clonazepam and other benzodiazepines are sedative-hypnotic drugs that act by enhancing the effects of **gamma-aminobutyric acid** (GABA) in the brain. **GABA** is a neurotransmitter that inhibits brain activity.

It is believed that excessive activity in the brain may lead to anxiety or other psychiatric disorders. Clonazepam is primarily used for treating panic disorder and preventing certain types of seizures. It is a **Schedule IV controlled substance**.

When clonazepam is used to treat panic disorder, it is more sedating than *alprazolam* (Xanax). However, unlike *alprazolam*, clonazepam may trigger depressive episodes in patients with a previous history of depression. In people who experience social phobia, treatment with clonazepam reduces the rate of depression. The use of clonazepam for social phobia is considered off-label use.

KLONOPIN®
(clonazepam)

Corporate trademark & commercial logo for Klonopin (clonazepam)

History of the Drug

Until the 1950's, **barbiturates** were the main prescription option for treating anxiety and other conditions requiring sedation. These drugs, however, had a very high potential for addiction and for accidental overdose. Thus, there was a market need for a safer class of drugs.

In 1955, the **Hoffman-La Roche** company commissioned chemist Leo Sternbach to design this new drug compound, which ended up being the drug class **benzodiazepines**.

Clonazepam (Klonopin) was developed and patented in 1964 by the Hoffman-La Roche company following the extreme success of other benzodiazepines in the market. By 1975, Roche was marketing the drug for treating epileptic seizures. The FDA approved clonazepam in June of 1975. Clonazepam was approved in the United States as a generic drug in 1997 and is now manufactured and marketed by several companies.

F. Hoffmann-La Roche AG
is a Swiss multinational healthcare & pharmaceutical company

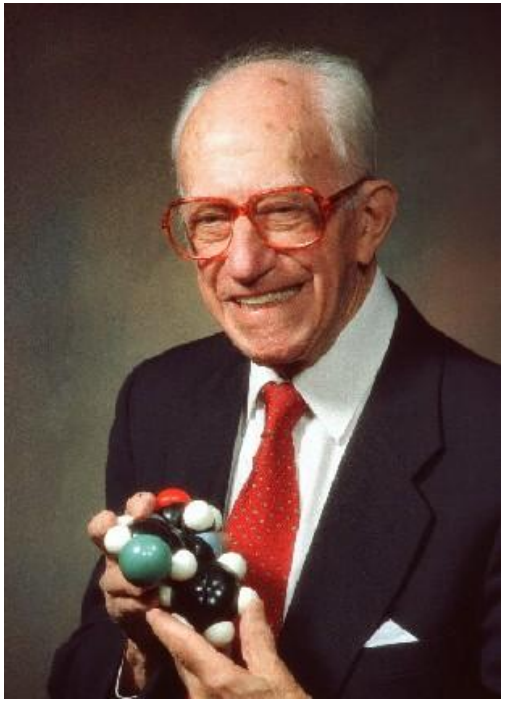
History of the Drug

Leo Henryk Sternbach was a Polish-Jewish chemist who is credited with discovering benzodiazepines, the main class of tranquilizers. Beginning work for **Hoffmann-La Roche** in 1941 in Nutley, New Jersey, Sternbach did significant work on new drugs.

He is credited with the discovery of *chlordiazepoxide* (**Librium**), *diazepam* (**Valium**), *flurazepam* (**Dalmane**), *nitrazepam* (**Mogadon**), *flunitrazepam* (**Rohypnol**), *clonazepam* (**Klonopin**), and *trimethaphan* (**Arfonad**). Librium, based on the *R0 6-690* compound discovered by Sternbach in 1956, was approved for use in 1960.

In 1963, its improved version, **Valium**, was released and became astonishingly popular: between 1969 and 1982, it was the most prescribed drug in America, with over 2.3 billion doses sold in its peak year of 1978. With Moses Wolf Goldberg, Sternbach also developed "the first commercially applicable" method for synthesizing **Biotin**.

Sternbach held **241** patents, and his discoveries helped to turn Roche into a pharmaceutical industry giant. He did not become wealthy from his discoveries, but he was happy; he treated chemistry as a passion and said, "I always did just what I wanted to do". He went into the office until he was 95, passing away in 2005.



Leo Sternbach:
The renowned chemist credited with discovering benzodiazepines, while working for Hoffmann-La Roche.

Therapeutic Uses: *Psychiatric Disorders*

PANIC DISORDER: Recurrent unexpected panic attacks, which are sudden periods of intense fear that may include palpitations, sweating, shaking, shortness of breath, numbness, or a feeling that something terrible is going to happen; the maximum degree of symptoms occurs within minutes.

AGORAPHOBIA: Disorder characterized by symptoms of anxiety in situations where the person perceives the environment to be unsafe with no easy way to get away.

SOCIAL ANXIETY DISORDER: Also known as social phobia, is an anxiety disorder characterized by a significant amount of fear in one or more social situations, causing considerable distress and impaired ability to function in at least some parts of daily life. These fears can be triggered by perceived or actual scrutiny from others.

ACUTE MANIA: state of abnormally elevated arousal, affect, and energy level, or "a state of heightened overall activation with enhanced affective expression together with lability of affect." Although the vast majority of cases occur in the context of bipolar disorder, it is a key component of other psychiatric disorders (as schizoaffective disorder, bipolar type) and may also occur secondary to various general medical conditions, as multiple sclerosis; certain medications, as prednisone; or certain substances of abuse, as cocaine or anabolic steroids; indeed, as the mania intensifies, irritability can be more pronounced and result in violence.

ACUTE PSYCHOSIS: an abnormal condition of the mind that involves a loss of contact with reality. People experiencing psychosis may exhibit personality changes and thought disorder. Depending on its severity, this may be accompanied by unusual or bizarre behavior, as well as difficulty with social interaction and impairment in carrying out daily life activities.

Therapeutic Uses: *Seizures*

Clonazepam is mainly prescribed for the acute management of **epilepsies**. It 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 people, and the addition of **phenytoin** (trade name: *Dilantin*, an anti-seizure medication) for lasting control was required in these patients.

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. 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.

It is also approved for treatment of **typical and atypical absences, infantile myoclonic, myoclonic and akinetic seizures**. A subgroup of people with **treatment resistant epilepsy** may benefit from long-term use of clonazepam. The benzodiazepine **clorazepate** (trade name: *Tranxene*) may be an alternative due to its slow onset of tolerance. Certain types of seizures, specifically **petit mal seizures** as well as **Lennox-Gastaut syndrome** (childhood epileptic encephalopathy) may also benefit from clonazepam treatment.

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 its anticonvulsant effects.

Therapeutic Uses: *Muscle Disorders*

RESTLESS LEGS SYNDROME (RLS): a disorder that causes a strong urge to move one's legs. There is often an unpleasant feeling in the legs that improves somewhat with moving them. Occasionally the arms may also be affected. The feelings generally happen when at rest and therefore can make it hard to sleep. Due to the disturbance in sleep, people with RLS may have daytime sleepiness, low energy, irritability, and a depressed mood. Additionally, many have limb twitching during sleep. RLS can be treated using clonazepam as a third-line treatment option, as the use of clonazepam is still investigational.

BRUXISM: excessive teeth grinding or jaw clenching. It is an oral parafunctional activity; i.e., it is unrelated to normal function such as eating or talking. Bruxism is a common behavior; reports of prevalence range from 8–31% in the general population. Several symptoms are commonly associated with bruxism, including hypersensitive teeth, aching jaw muscles, headaches, tooth wear, and damage to dental restorations (e.g. crowns and fillings) to teeth. Symptoms may be minimal though, without patient awareness of the condition. Treatment of bruxism responds to clonazepam in the short-term.

VIDEO: Bruxism explained

RAPID EYE MOVEMENT BEHAVIOR DISORDER (RBD): a parasomnia (dissociated sleep states which are partial arousals during the transitions between wakefulness and NREM sleep, or wakefulness and REM sleep) that involves abnormal behavior during the sleep phase with rapid eye movement (REM) sleep. The major and arguably only abnormal feature of RBD is loss of paralysis during otherwise intact REM sleep, during which paralysis is not only normal but necessary. The loss of motor inhibition leads to a wide spectrum of behavioral release during sleep, from simple limb twitches to more complex integrated movement, in which people appear to be unconsciously acting out their dreams. These behaviors can be violent in nature and in some cases will result in injury to either the patient or their bed partner. Treatment of RBD responds well to low doses of clonazepam.

VIDEO: Sleep talking in a patient with RBD

Therapeutic Uses: *Muscle Disorders (cont'd)*

AKATHISIA: movement disorder characterized by a feeling of inner restlessness and a compelling need to be in constant motion, as well as by actions such as rocking while standing or sitting, lifting the feet as if marching on the spot, and crossing and uncrossing the legs while sitting. People with akathisia are unable to sit or keep still, are prone to feelings of restlessness, and they may also fidget, rock from foot to foot, and pace. Antipsychotics (neuroleptics), particularly the first generation antipsychotics, are the leading cause of akathisia. When antipsychotic-induced, akathisia is an extrapyramidal side effect. Akathisia is also a symptom of psychosis, bipolar disorder, and agitated depression. Akathisia is a component of the repetitive movements in some cases of autism and intellectual disability. Other known causes include side effects of other medications, and nearly any physical dependence-inducing drug during drug withdrawal. It is also associated with Parkinson's disease and related syndromes. The treatment of acute and chronic akathisia induced by neuroleptics responds well to short-term clonazepam use.

VIDEO: Common symptom-expression of akathisia

SPASTICITY RELATED TO AMYOTROPHIC LATERAL SCLEROSIS (ALS): Spasticity is a feature of altered skeletal muscle performance with a combination of paralysis, increased tendon reflex activity and hypertonia. It is also colloquially referred to as an unusual "tightness", stiffness, or "pull" of muscles. Clinically, spasticity results from the loss of inhibition of motor neurons, causing excessive velocity-dependent muscle contraction. This ultimately leads to hyperreflexia, an exaggerated deep tendon reflex. Medical interventions may include such medications as baclofen, diazepam, dantrolene, or clonazepam.

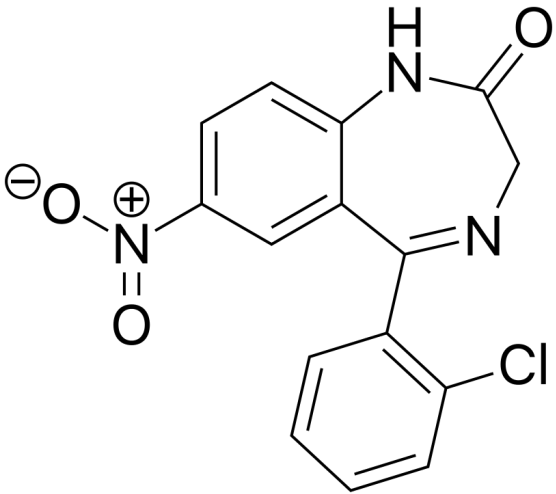
Pharmacodynamics

The way in which **GABA** sends its inhibitory message is by a clever electronic device. It's reaction with special sites (GABA-receptors) on the outside of the receiving neuron opens a channel, allowing negatively charged particles (chloride ions) to pass to the inside of the neuron. These negative ions "supercharge" the neuron, making it less responsive to other neurotransmitters which would normally excite it.

Benzodiazepines also react at their own special sites (benzodiazepine receptors), situated on the GABA-receptor. Introduction of a benzodiazepine at this site acts as a booster to the actions of GABA, allowing more chloride ions to enter the neuron, making it even more resistant to excitation. Various subtypes of benzodiazepine receptors have slightly different actions. One subtype *(alpha 1)* is responsible for sedative effects, another *(alpha 2)* for anti-anxiety effects, and both *alpha 1* and *alpha 2*, as well as *alpha 5*, for anticonvulsant effects. All benzodiazepines combine, to a greater or lesser extent, with all these subtypes and all enhance GABA activity in the brain.

As a consequence of the enhancement of GABA's inhibitory activity caused by benzodiazepines, the brain's output of **excitatory neurotransmitters**, including norepinephrine (noradrenaline), serotonin, acetylcholine, and dopamine, is reduced. Such excitatory neurotransmitters are necessary for normal alertness, memory, muscle tone and coordination, emotional responses, endocrine gland secretions, heart rate and blood pressure control and a host of other functions, all of which may be impaired by benzodiazepines.

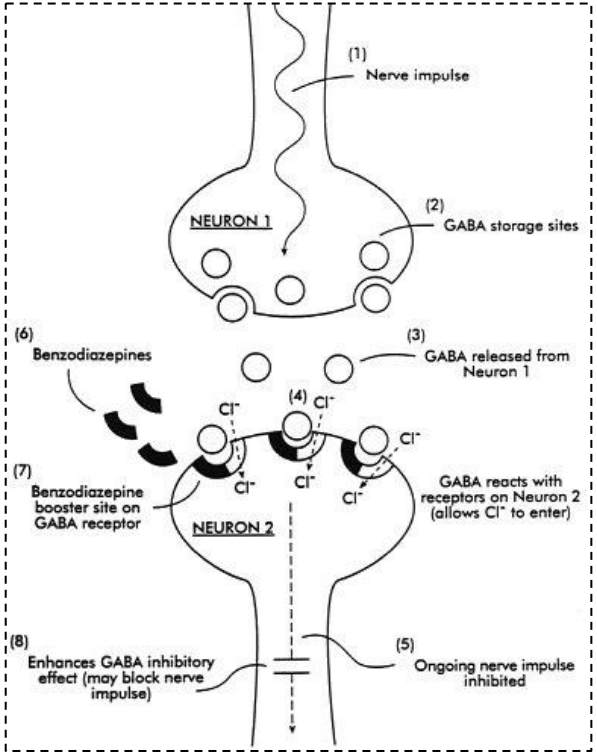
Other benzodiazepine receptors, not linked to GABA, are present in the kidney, colon, blood cells and adrenal cortex and these may also be affected by some benzodiazepines. These direct and indirect actions are responsible for the well-known **adverse effects** of dosage with benzodiazepines.



Molecular Structure of Clonazepam:
5-(2-chlorophenyl)-7-nitro-1H
-benzo[e][1,4]diazepin-2(3H)-one.

Mechanism of Action

- Action potential *(nerve impulse)* causes release of **GABA** from storage sites on **neuron 1**
- **GABA** released into space between neurons
- **GABA** reacts with receptors on **neuron 2**; this reaction allows **chloride ions (Cl-)** to enter the neuron
- This effect inhibits further progress of the action potential *(nerve impulse)*
- **BENZODIAZEPINES** react with booster site on **GABA** receptors
- This reaction enhances the inhibitory effects of **GABA**; the ongoing action potential *(nerve impulse)* may be completely blocked



Mechanism of action of the natural neurotransmitter GABA and benzodiazepines on neurons in the brain.

Pharmacokinetics

Allosteric interactions between central benzodiazepine receptors and gamma-aminobutyric acid (GABA) receptors potentiate the effects of GABA. As GABA is an inhibitory neurotransmitter, this results in increased inhibition of the ascending reticular activating system. Benzodiazepines, in this way, block the cortical and limbic arousal that occurs following stimulation of the reticular pathways.

Clonazepam, being 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, cimetidine, and grapefruit juice are inhibitors of CYP3A4 and can affect the metabolism of benzodiazepines. It has an elimination half-life of 19–60 hours. 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.

Clonazepam passes rapidly into the central nervous system, with levels in the brain corresponding with levels of unbound clonazepam in the blood serum. Clonazepam plasma levels are very unreliable amongst patients. Plasma levels of clonazepam can vary as much as tenfold between different patients. Clonazepam is largely bound to plasma proteins.

Clonazepam passes through the blood–brain barrier easily, with blood and brain levels corresponding equally with each other. The metabolites of clonazepam include 7-aminoclonazepam, 7-acetaminoclonazepam and 3-hydroxy clonazepam. It is effective for 6–8 hours in children, and 6–12 in adults.

ABSORPTION: Well absorbed from the GI tract

DISTRIBUTION: Probably crosses the blood-brain barrier (BBB) and the placenta

BIOAVAILABILITY: 90%

PROTEIN BINDING: 85%

METABOLISM: Mostly metabolised by the liver (hepatically)

HALF-LIFE: 18-50 hours

EXCRETION: Kidney

Route	Onset	Peak	Duration
PO	20-60 min.	1-2 hr.	6-12 hr.

Typical Dosage

Panic Disorder

For panic disorder, the initial recommended dose is 0.25 mg twice daily.

This dose can be increased every three days in increments of 0.125–0.25 mg twice daily.

The target dose for panic disorder is 1.0 mg per day, although some people benefit from doses up to a maximum of 4 mg per day.

When a person stops taking clonazepam, the drug should be gradually discontinued by decreasing the dose by 0.125 mg twice daily every three days.

Seizures

For seizures in adults, the initial dose is 1.5 mg daily in 3 divided doses.

Dosage may be increased by 0.5 to 1 mg daily every 3 days until seizures are controlled or side effects preclude further increases in dose.

The maximum dose is 20 mg daily. The initial dose for panic disorders is 0.25 mg twice daily.

The dose may be increased to the target dose of 1 mg daily after 3 days.

Other

Although clonazepam is not FDA-approved for the treatment of post-traumatic stress disorder, doses in the range of 0.25–3 mg daily appears to help treat symptoms of this disorder.

Daily dosages for the treatment of social phobia range from 1.0–2.5 mg, while the dosage to control mania may be as high as 10 mg daily.

Indications

PROPHYLAXIS OF:	UNLABELED USES:
Petit mal	Social Anxiety Disorder
Lennox-Gastaut Syndrome	Restless Legs Syndrome
Akinetic & Myoclonic seizures	Neuralgias
Panic disorder with or without agoraphobia.	Sedation
	Adjunct management of acute mania, acute psychosis, or insomnia.
	Spasticity related to ALS
	Akathisia

Contraindications

CONTRAINDICATED IN:	USE CAUTIOUSLY IN:
Hypersensitivity to clonazepam or other benzodiazepines	All patients (may increase risk of suicidal thoughts/behaviors)
Severe hepatic impairment	Angle-closure glaucoma
Acute narrow angle glaucoma (it may be used in patients with open angle glaucoma who are receiving appropriate therapy)	Obstructive sleep apnea
	Chronic respiratory disease
	History of porphyria
	Do not discontinue abruptly

Side Effects

The main side effects of clonazepam are sedation, dizziness, impaired coordination, depression, and fatigue. Some people experience decreased sex drive while taking clonazepam.

A small number of people develop sinus problems and upper respiratory tract infections while taking clonazepam. One of the side effects of clonazepam may be increased salivation. This may cause some people to start coughing while taking clonazepam. Clonazepam may also cause anorexia and dry mouth. It may cause either constipation or diarrhea. There are a few reports of clonazepam causing menstrual irregularities or blurred vision.

Other Adverse Reactions

- **CENTRAL NERVOUS SYSTEM**
  - Suicidal thoughts
  - Behavioral changes
  - Drowsiness
  - Fatigue
  - Slurred speech
  - Ataxia
  - Sedation
  - Diplopia (double vision)
  - Nystagmus
  - Hypotonia
- **RESPIRATORY**
  - Increased secretions
- **CARDIOVASCULAR**
  - Palpitations
- **DERMATOLOGICAL**
  - Rash
- **GASTROINTESTINAL**
  - Constipation
  - Diarrhea
  - Hepatitis
  - Weight gain
- **GENITOURINARY**
  - Dysuria
  - Nocturia
  - Urinary retention
- **HEMATOLOGICAL**
  - Anemia
  - Eosinophilia
  - Leukopenia
  - Thrombocytopenia
- **MISCELLANEOUS**
  - Fever
  - Physical/psychological dependence
  - Tolerance

Expected Outcomes

- Decrease or cessation of **seizure activity** without undue sedation. Dose adjustments may be required after several months of therapy.
- Decrease in frequency and severity of **panic attacks**.
- Relief of **leg movements** during sleep.
- Decrease in pain from **neuralgia**.

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