

= Alprazolam =

Alprazolam , available under the trade name Xanax among others , is a short @-@ acting anxiolytic of the benzodiazepine class . It is commonly used for the treatment of panic disorder , and anxiety disorders , such as generalized anxiety disorder (GAD) or social anxiety disorder (SAD) . It was the 12th most prescribed medicine in the USA in 2010 . Alprazolam , like other benzodiazepines , binds to specific sites on the GABAA receptor . It possesses anxiolytic , sedative , hypnotic , skeletal muscle relaxant , anticonvulsant , and amnesic properties . Alprazolam is available for oral administration in compressed tablet (CT) and extended @-@ release capsule (XR) formulations .

Peak benefits achieved for generalized anxiety disorder (GAD) may take up to a week . Tolerance to the anxiolytic / antipanic effects is controversial with some authoritative sources reporting the development of tolerance , and others reporting no development of tolerance ; tolerance will , however , develop to the sedative @-@ hypnotic effects within a couple of days . Withdrawal symptoms or rebound symptoms may occur after ceasing treatment abruptly following a few weeks or longer of steady dosing , and may necessitate a gradual dose reduction .

Alprazolam was first released by Upjohn (now a part of Pfizer) in 1981 . The first approved use was panic disorder and within two years of its original marketing Xanax became a blockbuster drug in the US . Presently , alprazolam is the most prescribed and the most misused benzodiazepine in the US . The potential for misuse among those taking it for medical reasons is controversial with some expert reviews stating that the risk is low and similar to that of other benzodiazepine drugs and others stating that there is a substantial risk of misuse and dependence in both patients and non @-@ medical users of alprazolam and that the pharmacological properties of alprazolam , high affinity binding , high potency , having a short elimination half @-@ life as well as a rapid onset of action may increase the misuse potential of alprazolam . Compared to the large number of prescriptions , relatively few individuals increase their dose on their own initiative or engage in drug @-@ seeking behavior . Alprazolam is classified as a schedule IV controlled substance by the U.S. Drug Enforcement Administration (DEA) .

= = Medical uses = =

Alprazolam is mostly used to treat anxiety disorders , panic disorders , and nausea due to chemotherapy . The FDA label advises that the physician should periodically reassess the usefulness of the drug . Alprazolam may also be indicated for the treatment of generalized anxiety disorder , as well as for the treatment of anxiety conditions with co @-@ morbid depression . Alprazolam is also often prescribed with instances of hypersomnia and co @-@ morbid sleep deficits .

= = = Panic disorder = = =

Alprazolam is effective in the relief of moderate to severe anxiety and panic attacks . However , it is not a first line treatment since the development of selective serotonin reuptake inhibitors , and alprazolam is no longer recommended in Australia for the treatment of panic disorder due to concerns regarding tolerance , dependence and abuse . Evidence supporting the effectiveness of alprazolam in treating panic disorder has been limited to 4 to 10 weeks . However , people with panic disorder have been treated on an open basis for up to 8 months without apparent loss of benefit .

In the United States , alprazolam is FDA @-@ approved for the treatment of panic disorder with or without agoraphobia . Alprazolam is recommended by the World Federation of Societies of Biological Psychiatry (WFSBP) for treatment @-@ resistant cases of panic disorder where there is no history of tolerance or dependence .

= = = Anxiety disorders = = =

Anxiety associated with depression is responsive to alprazolam . Demonstrations of the effectiveness by systematic clinical study are limited to 4 months duration for anxiety disorder . However , the research into antidepressant properties of alprazolam is of poor quality and only assessed the short @-@ term effects of alprazolam against depression . In one study , some long term , high @-@ dosage users of alprazolam developed reversible depression . In the US , alprazolam is FDA @-@ approved for the management of anxiety disorders (a condition corresponding most closely to the APA Diagnostic and Statistical Manual DSM @-@ IV @-@ TR diagnosis of generalized anxiety disorder) or the short @-@ term relief of symptoms of anxiety . In the UK , alprazolam is recommended for the short @-@ term treatment (2 ? 4 weeks) of severe acute anxiety .

= = Nausea due to chemotherapy = =

Alprazolam may be used in combination with other medications for chemotherapy @-@ induced nausea and vomiting .

= = Pregnancy and lactation = =

Benzodiazepines cross the placenta , enter the fetus and are also excreted with breast milk . The use of benzodiazepines during pregnancy or lactation has potential risks . The use of alprazolam in pregnancy is believed to be associated with congenital abnormalities .

Women who are pregnant or are planning on becoming pregnant should avoid starting alprazolam . Use in the last trimester may cause fetal drug dependence and withdrawal symptoms in the post @-@ natal period as well as neonatal flaccidity and respiratory problems . However , in long @-@ term users of benzodiazepines abrupt discontinuation due to concerns of teratogenesis has a high risk of causing extreme withdrawal symptoms and a severe rebound effect of the underlying mental health disorder . Spontaneous abortions may also result from abrupt withdrawal of psychotropic medications including benzodiazepines .

Benzodiazepines , including alprazolam , are known to be excreted in human milk . Chronic administration of diazepam , another benzodiazepine , to nursing mothers has been reported to cause their infants to become lethargic and to lose weight .

= = Contraindications = =

Benzodiazepines require special precaution if used in children and in alcohol- or drug @-@ dependent individuals . Particular care should be taken in pregnant or elderly patients , patients with substance abuse history , particularly alcohol dependence and patients with comorbid psychiatric disorders . Use of alprazolam should be avoided or carefully monitored by medical professionals in individuals with the following conditions : myasthenia gravis , acute narrow @-@ angle glaucoma , severe liver deficiencies (e.g. , cirrhosis) , severe sleep apnea , pre @-@ existing respiratory depression , marked neuromuscular respiratory weakness including unstable myasthenia gravis , acute pulmonary insufficiency , chronic psychosis , hypersensitivity or allergy to alprazolam or other drugs in the benzodiazepine class , borderline personality disorder (may induce suicidality and dyscontrol) .

Like all central nervous system depressants , including alcohol , alprazolam in larger @-@ than @-@ normal doses can cause significant deterioration in alertness , combined with increased feelings of drowsiness , especially in those unaccustomed to the drug 's effects . People driving or conducting activities that require vigilance should exercise caution in using alprazolam or any other depressant until they know how it affects them .

Elderly individuals should be cautious in the use of alprazolam due to the possibility of increased susceptibility to side @-@ effects , especially loss of coordination and drowsiness .

= = Adverse effects = =

Allergic reactions are unlikely to occur . The only common side effect is sleepiness when treatment is initiated .

Possible side effects include :

Disinhibition

Jaundice (very rare)

Hallucinations (rare)

Dry mouth (infrequent)

Ataxia , slurred speech

Suicidal ideation (rare)

Urinary retention (infrequent)

Skin rash , respiratory depression , constipation

Anterograde amnesia and concentration problems

Drowsiness , dizziness , lightheadedness , fatigue , unsteadiness and impaired coordination , vertigo

== Paradoxical reactions ==

Although unusual , the following paradoxical reactions have been shown to occur :

Aggression

Rage , hostility

Twitches and tremor

Mania , agitation , hyperactivity and restlessness

== Food and drug interactions ==

Alprazolam is primarily metabolised via CYP3A4 . Combining CYP3A4 inhibitors such as cimetidine , erythromycin , norfluoxetine , fluvoxamine , itraconazole , ketoconazole , nefazodone , propoxyphene , and ritonavir delay the hepatic clearance of alprazolam , which may result in excessive accumulation of alprazolam . This may result in exacerbation of its adverse effect profile .

Imipramine and desipramine have been reported to be increased an average of 31 % and 20 % , respectively , by the concomitant administration of alprazolam tablets in doses up to 4 mg / day . Combined oral contraceptive pills reduce the clearance of alprazolam , which may lead to increased plasma levels of alprazolam and accumulation .

Alcohol is one of the most important and common interactions . Alcohol and benzodiazepines such as alprazolam taken in combination have a synergistic effect on one another , which can cause severe sedation , behavioral changes , and intoxication . The more alcohol and alprazolam taken the worse the interaction . Combination of alprazolam with the herb kava can result in the development of a semi @-@ comatose state . Hypericum conversely can lower the plasma levels of alprazolam and reduce its therapeutic effect .

== Overdose ==

Overdoses of alprazolam can be mild to severe depending on how much of the drug is taken and any other drugs that have been taken .

Alprazolam overdoses cause excess central nervous system (CNS) depression and may include one or more of the following symptoms :

Somnolence (drowsiness)

Hypotension (low blood pressure)

Orthostatic hypotension (fainting while standing up too quickly)

Hypoventilation (shallow breathing)

Impaired motor functions

Dizziness

Impaired balance

Muscle weakness

Impaired or absent reflexes

Fainting

Coma and death are possible if alprazolam is combined with other substances .

= = = Dependence and withdrawal = = =

Alprazolam , like other benzodiazepines , binds to specific sites on the GABAA gamma @-@ amino @-@ butyric acid receptor . When bound to these sites , which are referred to as benzodiazepine receptors , it modulates the effect of GABA A receptors and , thus , GABAergic neurons . Long @-@ term use causes adaptive changes in the benzodiazepine receptors , making them less sensitive to stimulation and less powerful in their effects .

Withdrawal and rebound symptoms commonly occur and necessitate a gradual reduction in dosage to minimize withdrawal effects when discontinuing .

Not all withdrawal effects are evidence of true dependence or withdrawal . Recurrence of symptoms such as anxiety may simply indicate that the drug was having its expected anti @-@ anxiety effect and that , in the absence of the drug , the symptom has returned to pretreatment levels . If the symptoms are more severe or frequent , the patient may be experiencing a rebound effect due to the removal of the drug . Either of these can occur without the patient 's actually being drug @-@ dependent .

Alprazolam and other benzodiazepines may also cause the development of physical dependence , tolerance , and benzodiazepine withdrawal symptoms during rapid dose reduction or cessation of therapy after long @-@ term treatment . There is a higher chance of withdrawal reactions if the drug is administered in a higher dosage than recommended , or if a patient stops taking the medication altogether without slowly allowing the body to adjust to a lower @-@ dosage regimen .

In 1992 , Romach and colleagues reported that dose escalation is not a characteristic of long @-@ term alprazolam users , and that the majority of long @-@ term alprazolam users change their initial pattern of regular use to one of symptom control only when required .

Some common symptoms of alprazolam discontinuation include malaise , weakness , insomnia , tachycardia , lightheadedness , and dizziness .

Patients taking a dosing regimen larger than 4 mg per day have an increased potential for dependence . This medication may cause withdrawal symptoms upon abrupt withdrawal or rapid tapering , which in some cases have been known to cause seizures . The discontinuation of this medication may also cause a reaction called rebound anxiety .

Delirium similar to that produced by the tropane alkaloids (gaba antagonists) of Datura (scopolamine and atropine) and seizures have been reported in the medical literature from abrupt alprazolam discontinuation .

In a 1983 study of patients who had taken long @-@ acting benzodiazepines , e.g. , clorazepate , for extended periods , the medications were stopped abruptly . Only 5 % of patients who had been taking the drug for less than 8 months demonstrated withdrawal symptoms , but 43 % of those who had been taking them for more than 8 months did . With alprazolam ? a short @-@ acting benzodiazepine ? taken for 8 weeks , 65 % of patients experienced significant rebound anxiety . To some degree , these older benzodiazepines are self @-@ tapering .

The benzodiazepines diazepam (Valium) and oxazepam (Serepax) have been found to produce fewer withdrawal reactions than alprazolam (Xanax) , temazepam (Restoril / Normison) , or lorazepam (Temesta / Ativan) . Factors that determine the risk of psychological dependence or physical dependence and the severity of the benzodiazepine withdrawal symptoms experienced during dose reduction of alprazolam include : dosage used , length of use , frequency of dosing , personality characteristics of the individual , previous use of cross @-@ dependent / cross @-@ tolerant drugs (alcohol or other sedative @-@ hypnotic drugs) , current use of cross @-@ dependent / -tolerant drugs , use of other short @-@ acting , high @-@ potency benzodiazepines , and method of discontinuation .

= = Detection in body fluids = =

Alprazolam may be quantitated 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 alprazolam concentrations are usually in a range of 10 ? 100 ?g / L in persons receiving the drug therapeutically , 100 ? 300 ?g / L in those arrested for impaired driving and 300 ? 2000 ?g / L in victims of acute overdosage . Most commercial immunoassays for the benzodiazepine class of drugs will cross @-@ react with alprazolam , but confirmation and quantitation is usually performed using chromatographic techniques .

= = Pharmacology = =

Alprazolam is classed as a high @-@ potency benzodiazepine and is a triazolobenzodiazepine , namely a benzodiazepine with a triazole ring attached to its structure . Benzodiazepines produce a variety of therapeutic and adverse effects by binding to the benzodiazepine receptor site on the GABAA receptor and modulating the function of the GABA receptor , the most prolific inhibitory receptor within the brain . The GABA chemical and receptor system mediates inhibitory or calming effects of alprazolam on the nervous system . The GABAA receptor is made up of 5 subunits out of a possible 19 , and GABAA receptors made up of different combinations of subunits , have different properties , different locations within the brain , and , importantly , different activities with regard to benzodiazepines . Benzodiazepines and in particular alprazolam causes a marked suppression of the hypothalamicpituitary @-@ adrenal axis . The therapeutic properties of alprazolam are similar to other benzodiazepines and include anxiolytic , anticonvulsant , muscle relaxant , hypnotic and amnesic .

Administration of alprazolam , but not lorazepam , has been demonstrated to elicit a statistically significant increase in extracellular dopamine D1 and D2 concentrations in the striatum .

= = Pharmacokinetics = =

Absorption

Following oral administration , alprazolam is readily absorbed . Peak concentrations in the plasma occur in one to two hours following administration . Plasma levels are proportionate to the dose given ; over the dose range of 0 @.@ 5 to 3 @.@ 0 mg , peak levels of 8 @.@ 0 to 37 ng / mL were observed . Using a specific assay methodology , the mean plasma elimination half @-@ life of alprazolam has been found to be about 11 @.@ 2 hours (range : 6 @.@ 3 to 26 @.@ 9 hours) in healthy adults .

Distribution

In vitro , alprazolam is bound (80 percent) to human serum protein . Serum albumin accounts for the majority of the binding .

Metabolism / Elimination

Alprazolam is extensively metabolized in humans , primarily by cytochrome P450 3A4 (Cyp3A4) , to two major metabolites in plasma : 4 @-@ hydroxyalprazolam and ?- hydroxyalprazolam . A benzophenone derived from alprazolam is also found in humans . Half @-@ lives are similar to that of alprazolam . The plasma concentrations of 4 @-@ hydroxyalprazolam and ? @-@ hydroxyalprazolam relative to unchanged alprazolam concentration were always less than 4 % . The reported relative potencies in benzodiazepines receptor binding experiments and in animals models of induced seizure inhibition are 0 @.@ 2 and 0 @.@ 66 , respectively , for 4 @-@ hydroxyalprazolam and ? @-@ hydroxyalprazolam . Such low concentrations and lesser potencies of 4 @-@ hydroxyalprazolam and ? @-@ hydroxyalprazolam suggest that they are unlikely to contribute much to the pharmacological effects of alprazolam . The benzophenone metabolite is essentially inactive .

Alprazolam and its metabolites are excreted primarily in the urine .

= = Forms of alprazolam = =

Alprazolam regular release and orally disintegrating tablets are available as 0.25 mg , 0.5 mg , 1 mg , 2 mg strength tablets .

Alprazolam extended release tablets are available as 0.5 mg , 1 mg , 2 mg , and 3 mg strength tablets .

Alprazolam oral solutions are available as 0.5 mg / 5 mL and as 1 mg / 1 mL oral solutions .

Active ingredient : alprazolam

Inactive ingredients : microcrystalline cellulose , corn starch , docusate sodium , povidone , sodium starch glycolate , lactose monohydrate , magnesium stearate , colloidal silicon dioxide and sodium benzoate . In addition , the 0.25 mg tablet contains D & C Yellow No. 10 and the 0.5 mg tablet contains FD & C Yellow No. 6 and D & C Yellow No. 10

= = Society and culture = =

= = = Patent = = =

It is covered under U.S. Patent 3,987,052 , which was filed on 29 October 1969 , granted on 19 October 1976 , and expired in September 1993 .

= = = Recreational use = = =

There is a risk of misuse and dependence in both patients and non-medical users of alprazolam ; the pharmacological properties of alprazolam such as high affinity binding , high potency , being short-acting and having a rapid onset of action increase the abuse potential of alprazolam . The physical dependence and withdrawal syndrome of alprazolam also adds to the addictive nature of alprazolam . In the small subgroup of individuals who escalate their doses there is usually a history of alcohol or other substance use disorders . Despite this , most prescribed alprazolam users do not use their medication recreationally , and the long-term use of benzodiazepines does not generally correlate with the need for dose escalation . However , based on US findings from the Treatment Episode Data Set (TEDS) , an annual compilation of patient characteristics in substance abuse treatment facilities in the United States , admissions due to " primary tranquilizer " (including , but not limited to , benzodiazepine type) drug use increased 79 % from 1992 to 2002 , suggesting that misuse of benzodiazepines may be on the rise . The New York Times also reported in 2011 that " The Centers for Disease Control and Prevention last year reported an 89 percent increase in emergency room visits nationwide related to nonmedical benzodiazepine use between 2004 and 2008 . "

Alprazolam is one of the most commonly prescribed and misused benzodiazepines in the United States . A large-scale nationwide U.S. government study conducted by SAMHSA found that , in the U.S. , benzodiazepines are recreationally the most frequently used pharmaceuticals due to their widespread availability , accounting for 35 % of all drug-related visits to hospital emergency and urgent care facilities . Men and women are equally likely to use benzodiazepines recreationally . The report found that alprazolam is the most common benzodiazepine for recreational use followed by clonazepam , lorazepam , and diazepam . The number of emergency room visits due to benzodiazepines increased by 36 % between 2004 and 2006 .

Regarding the significant increases detected , it is worthwhile to consider that the number of pharmaceuticals dispensed for legitimate therapeutic uses may be increasing over time , and DAWN estimates are not adjusted to take such increases into account . Nor do DAWN estimates take into account the increases in the population or in ED use between 2004 and 2006 .

At a particularly high risk for misuse and dependence are people with a history of alcoholism or drug abuse and / or dependence and people with borderline personality disorder .

Alprazolam , along with other benzodiazepines , is often used with other recreational drugs . These uses include aids to relieve the panic or distress of dysphoric (" bad trip ") reactions to psychedelic drugs , such as LSD , and the drug @-@ induced agitation and insomnia in the " comedown " stages of stimulant use , such as amphetamine , cocaine , and phencyclidine allowing sleep . Alprazolam may also be used in conjunction with other depressant drugs , such as ethanol , heroin and other opioids , in an attempt to enhance the psychological effect of these drugs . Alprazolam may be used in conjunction with cannabis , with users citing a synergistic effect achieved after consuming the combination .

The poly @-@ drug use of powerful depressant drugs poses the highest level of health concerns due to a significant increase in the likelihood of experiencing an overdose which may result in fatal respiratory depression .

A 1990 study claimed that diazepam has a higher misuse potential relative to other benzodiazepines , and that some data suggests that alprazolam and lorazepam resemble diazepam in this respect .

Anecdotally injection of alprazolam has been reported , causing dangerous damage to blood vessels , closure of blood vessels (embolization) and decay of muscle tissue (rhabdomyolysis) . Alprazolam is practically not soluble in water , when crushed in water it will not fully dissolve (40 µg / ml of H₂O at pH 7) . There have also been anecdotal reports of alprazolam being snorted . Due to the low weight of a dose , alprazolam in one case was found to be distributed on blotter paper in a manner similar to LSD .

== = Popular culture == =

Slang terms for alprazolam vary from place to place . Some of the more common terms are shortened versions of the trade name " Xanax " , such as Bars or Xannies (or Xanies) ; references to their drug classes , such as benzos or downers ; or remark upon their shape or color (most commonly a straight , perforated tablet or an oval @-@ shaped pill) : bars , Z @-@ bars , footballs , planks , poles , blues , or blue footballs .

== = Availability == =

Alprazolam is available in English @-@ speaking countries under the following brand names :

Alprax , Alprocontin , Alzam , Alzolam , Anzilum , Apo @-@ Alpraz , Kalma , Mylan @-@ Alprazolam , Niravam , Novo @-@ Alprazol , Nu @-@ Alpraz , Pacyl , Restyl , Tranax , Trika , Xycalm , Xanax , Xanor , Zolam , Zopax , Helex .

As of December 2013 , in anticipation of the rescheduling of alprazolam to Schedule 8 in Australia ? Pfizer Australia announced they would be discontinuing the Xanax brand in Australia as it is no longer commercially viable .

== = Legal status == =

Alprazolam has varied legal status depending on jurisdiction :

In the United States , alprazolam is a prescription drug and is assigned to Schedule IV of the Controlled Substances Act by the Drug Enforcement Administration .

Under the UK drug misuse classification system benzodiazepines are class C drugs (Schedule 4) . Note that in the UK , alprazolam is not available on the NHS and can only be obtained on a private prescription .

In Ireland , alprazolam is a Schedule 4 medicine .

In Sweden , alprazolam is a prescription drug in List IV (Schedule 4) under the Narcotics Drugs Act (1968) .

In the Netherlands , alprazolam is a List 2 substance of the Opium Law and is available for prescription .

In Australia , alprazolam was originally a Schedule 4 (Prescription Only) medication ; however , as

of February 2014 , it has become a Schedule 8 medication , subjecting it to more rigorous prescribing requirements .

Internationally , alprazolam is included under the United Nations Convention on Psychotropic Substances as Schedule IV .