

FDA Drug Safety Communication

FDA requiring Boxed Warning updated to improve safe use of benzodiazepine drug class
Includes potential for abuse, addiction, and other serious risks

09-23-2020 FDA Drug Safety Communication

What safety concern is FDA announcing?

To address the serious risks of abuse, addiction, physical dependence, and withdrawal reactions, the U.S. Food and Drug Administration (FDA) is requiring the *Boxed Warning* be updated for all benzodiazepine medicines. Benzodiazepines are widely used to treat many conditions, including anxiety, insomnia, and seizures. The current prescribing information for benzodiazepines does not provide adequate warnings about these serious risks and harms associated with these medicines so they may be prescribed and used inappropriately. This increases these serious risks, especially when benzodiazepines are used with some other medicines and substances.

Benzodiazepines can be an important treatment option for treating disorders for which these drugs are indicated. However, even when taken at recommended dosages, their use can lead to misuse, abuse, and addiction. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioid pain relievers, alcohol, or illicit drugs. Physical dependence can occur when benzodiazepines are taken steadily for several days to weeks, even as prescribed. Stopping them abruptly or reducing the dosage too quickly can result in withdrawal reactions, including seizures, which can be life-threatening.

What is FDA doing?

We are requiring the *Boxed Warning*, FDA's most prominent warning, be updated and adding other information to the [prescribing information](#) for all benzodiazepine medicines. This information will describe the risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions consistently across all the medicines in the class. We are also requiring updates to the existing patient [Medication Guides](#) to help educate patients and caregivers about these risks.

Other changes are also being required to several sections of the prescribing information, including to the *Warnings and Precautions*, *Drug Abuse and Dependence*, and *Patient Counseling Information* sections.

What are benzodiazepines and how can they help me?

Benzodiazepines are a class of medicines approved to treat generalized anxiety disorder, insomnia, seizures, social phobia, and panic disorder. Most benzodiazepines are recommended for periods of weeks or months to treat these disorders. However, the amount, frequency, and duration of treatment vary depending on the patient and the medical condition being treated. Benzodiazepines are also used as premedication before some medical procedures.

Chlordiazepoxide was the first benzodiazepine approved in 1960, and FDA approved many subsequent medicines in this class in the 1960s and 1970s (see List of Benzodiazepines). These

medicines differ in how long they take to start working and how long their effects last, but they all work to slow brain activity by binding to gamma-aminobutyric acid (GABA) receptors in the brain, which causes drowsiness or calming effects.

What should health care professionals do?

When deciding whether the benefits of prescribing a benzodiazepine outweigh the risks, health care professionals should consider the patient's condition and the other medicines being taken, and [assess the risk of abuse, misuse, and addiction](#). Particular caution should be taken when [prescribing benzodiazepines with opioids](#) and other medicines that depress the central nervous system (CNS), which has resulted in serious side effects, including severe respiratory depression and death. Advise patients to seek immediate medical attention if they experience symptoms, such as difficulty breathing.

Limit the dosage and duration of each medicine to the minimum needed to achieve the desired clinical effect when prescribing benzodiazepines, alone or in combination with other medicines. Throughout therapy, monitor the patient for signs and symptoms of abuse, misuse, or addiction. If a substance use disorder is suspected, evaluate the patient and institute, or refer them for, early substance abuse treatment, as appropriate.

To reduce the risk of acute withdrawal reactions, use a gradual taper to reduce the dosage or to discontinue benzodiazepines. No standard benzodiazepine tapering schedule is suitable for all patients; therefore, create a patient-specific plan to gradually reduce the dosage, and ensure ongoing monitoring and support as needed to avoid serious withdrawal symptoms or worsening of the patient's medical condition.

Take precautions when [benzodiazepines are used in combination with opioid addiction medications](#). Careful medication management by health care professionals can reduce the increased risk of serious side effects.

What should patients, parents, and caregivers do?

Always tell your health care professionals about all the prescription and over-the-counter (OTC) medicines you are taking or any other substances you are using, including alcohol. Take benzodiazepines and all medicines exactly as prescribed by your health care professional. To avoid serious problems, including withdrawal reactions, patients taking benzodiazepines should not suddenly stop taking them without first discussing with your health care professional a plan for slowly decreasing the dose and frequency. Contact your health care professional if you experience withdrawal symptoms or your medical condition worsens. Go to an emergency room or call 911 if you have trouble breathing or other serious side effects such as seizures.

What did FDA find?

We reviewed postmarketing databases, adverse event cases reported to FDA,* and the published literature on abuse, misuse, addiction, dependence, and withdrawal associated with benzodiazepine use (see Data Summary). Our review found that benzodiazepines are widely prescribed in the U.S., often for long periods of time. They are also widely abused and misused, often together with alcohol, prescription opioids, and illicit drugs, which worsen the risks of

serious problems. We also found that some patients have had serious withdrawal reactions after benzodiazepines were stopped suddenly or the dose was reduced too quickly. Some patients experienced withdrawal symptoms lasting many months.

We previously communicated about the serious risks of combining benzodiazepines with opioid pain or cough medicines in [August 2016](#), and cautioned about withholding medication for opioid use disorder from patients taking benzodiazepines or CNS depressants in [September 2017](#).

*The cases were reported to the [FDA Adverse Event Reporting System \(FAERS\) database](#).

What is my risk?

All medicines have risks even when used correctly as prescribed. It is important to know that people respond differently to medicines depending on their health, the diseases they have, genetic factors, other medicines they are taking, and many other factors. As a result, we cannot determine how likely it is that someone will experience adverse side effects when taking benzodiazepines. Your health care professionals know you best, so talk to them if you have questions or concerns about risks of taking benzodiazepine medicines.

How do I report side effects from a benzodiazepine?

To help FDA track safety issues with benzodiazepines, we urge patients and health care professionals to report side effects involving benzodiazepines or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

How can I get new safety information on medicines I’m prescribing or taking?

You can sign up for [email alerts](#) about Drug Safety Communications on medicines or medical specialties of interest to you.

List of Benzodiazepines

Generic Name	Brand Name(s)
alprazolam	Xanax, Xanax XR
chlordiazepoxide HCl/clidinium bromide	Librax
chlordiazepoxide HCl	Librium
chlordiazepoxide HCl/amitriptyline HCl	Limbitrol, Limbitrol DS
clobazam	Onfi
clonazepam	Klonopin
clorazepate	Gen-Xene, Tranxene
diazepam	Diastat, Diastat Acudial, Valium, Valtoco
estazolam	No brand name currently marketed
flurazepam	No brand name currently marketed
lorazepam	Ativan
	Nayzilam, Seizalam
oxazepam	No brand name currently marketed

quazepam	Doral
temazepam	Restoril
triazolam	Halcion

Facts about Benzodiazepines

- Benzodiazepines are a class of medicines approved to treat generalized anxiety disorder, insomnia, seizures, social phobia, and panic disorder. They are also used as premedication before some medical procedures (see List of Benzodiazepines).
- Most benzodiazepines are recommended for use for weeks or months. However, the dose, frequency, and duration of treatment vary depending on the patient, the medicine being prescribed, and the medical condition it is being used to treat.
- Benzodiazepines work by binding to GABA receptors in the brain to slow brain activity, causing drowsy or calming effects.
- Common side effects of benzodiazepines include drowsiness, dizziness, weakness, and slowed breathing.
- Benzodiazepines are commonly prescribed medicines. In 2019, an estimated 92 million benzodiazepine prescriptions were dispensed from U.S. outpatient retail and mail-order pharmacies, with alprazolam (38%) being the most common followed by clonazepam (24%) and lorazepam (20%).¹

Additional Information for Patients

- FDA is requiring the *Boxed Warning* be updated for all benzodiazepine medicines to include warnings about the risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions.
- Do not drink alcohol with benzodiazepines. Alcohol can increase the risk of serious and life-threatening side effects.
- Always inform all your health care professionals about all the medicines you are taking, including prescription and OTC medicines and other substances. It is helpful to keep a list of all your current medicines in your wallet or another location where it is easily retrieved. You can fill out and print a copy of [My Medicine Record](#).
- Take benzodiazepines and all medicines exactly as your health care professional prescribes. Seek medical attention immediately by going to an emergency room or calling 911 if you experience serious side effects and have symptoms like trouble breathing.
- Most benzodiazepines are recommended for use for periods of weeks or months. However, the dose, frequency, formulation, and duration of treatment vary depending on the patient, the medical condition treated, and the medicine prescribed.
- Patients who have been taking a benzodiazepine for weeks or months should not suddenly stop taking your benzodiazepine without first discussing a plan for gradually getting off the medicine with your health care professional. Stopping benzodiazepines abruptly or reducing the dosage too quickly can result in serious withdrawal reactions, including seizures, which can be life-threatening.
- Even when the benzodiazepine dosage is decreased gradually, you may experience withdrawal symptoms, such as abnormal involuntary movements, anxiety, blurred vision,

memory problems, irritability, insomnia, muscle pain and stiffness, panic attacks, and tremors.

- Contact your health care professional if you experience more severe withdrawal symptoms, such as:
 - Catatonia (unable to speak, rigid body, repetitive and meaningless movements)
 - Seizures
 - Delirium tremens (shaking, shivering, irregular heartrate, sweating)
 - Depression
 - Hallucinations (seeing or hearing things that others do not see or hear)
 - Thoughts about killing yourself or someone else
 - Mania (euphoria, delusions, overactivity)
 - Psychosis (false beliefs)
- Treatments other than benzodiazepine medicines may be useful to manage some conditions, such as insomnia, stress and anxiety. Visit the National Center for Complementary and Integrative Health for resources, including [Mind and Body Approaches for Stress and Anxiety: What the Science Says](#) and [Insomnia: Relaxation Techniques and Sleeping Habits](#).
- Benzodiazepine abuse occurs when the medicine is not taken as prescribed to treat a medical condition but is instead taken to produce a “high” or euphoric feeling or some other desired effect. Misuse occurs when the medication is not taken as prescribed to manage a medical condition (for example, taking more than the recommended dose or taking medicine prescribed for someone else).
- Physical dependence is the body’s adaptation to repeated use of a drug, resulting in withdrawal reactions when the medicine is abruptly discontinued or the dose is significantly reduced. Dependence may also lead some individuals to continue using the medicine to avoid symptoms of withdrawal.
- It is important to lock up benzodiazepines and [dispose](#) of them properly to keep them from being taken accidentally by children or falling into the wrong hands.
- Read the patient [Medication Guide](#) every time you receive a prescription for a benzodiazepine because there may be new or important additional information about your medicine. The Medication Guide explains the important things you need to know about the medicine, including the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when you are taking the medicine.
- To help FDA track safety issues with medicines, report side effects from benzodiazepines or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.
- You can sign up for [email alerts](#) about Drug Safety Communications on medicines or medical specialties of interest to you.

Additional Information for Health Care Professionals

- FDA is requiring the *Boxed Warning* be updated for all benzodiazepine medicines to include warnings about the risks of abuse, misuse, addiction, physical dependence, and withdrawal reactions.

- Before prescribing a benzodiazepine and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. [Standardized screening tools](#) are available.
- Particular caution should be taken when [prescribing benzodiazepines with opioids](#) and other medicines that depress the CNS, which has resulted in serious side effects, including severe respiratory depression and death. Advise patients to seek immediate medical attention if they experience symptoms such as trouble breathing.
- Take precautions when [benzodiazepines are used in combination with opioid addiction medications](#). Careful medication management by health care professionals can reduce the increased risk of serious side effects.
- Warn patients and caregivers about the risks of abuse, misuse, addiction, dependence, and withdrawal with benzodiazepines and the associated signs and symptoms. Also alert them of the serious risks of taking benzodiazepines with alcohol or other substances, including opioids.
- Use a gradual taper to discontinue benzodiazepines or reduce the dosage. There are no standard benzodiazepine tapering schedules suitable for all patients. A patient-specific plan should be used to taper the dosage of the benzodiazepine gradually.
- Most benzodiazepines are recommended for use for periods of weeks or months. However, the dose, frequency, formulation, and duration of treatment vary depending on the patient, the medical condition treated, and the medicine prescribed.
- If benzodiazepines indicated for very short-term use (i.e., 1 to 2 doses) are used inappropriately for long-term use, their abrupt discontinuation or rapid dosage reduction may precipitate acute withdrawal reactions, which can be life-threatening.
Benzodiazepines approved for very short-term use include:
 - Diazepam injection (Diazepam)
 - Diazepam nasal spray (Valtoco)
 - Diazepam rectal gel (Diastat)
 - Midazolam nasal spray (Nayzilam)
 - Midazolam injection (Seizalam)
 - Lorazepam injection (Ativan)
- If a patient experiences withdrawal symptoms, it may be necessary to pause the taper for a period of time, or raise the benzodiazepine to the previous dosage and then proceed with a more gradual taper once stable.
- Frequent follow-up with patients receiving benzodiazepines is important. Reassess these patients regularly to manage their medical conditions and any withdrawal symptoms.
- Be prepared to address more severe or life-threatening reactions, including:
 - Catatonia
 - Seizures
 - Delirium tremens
 - Depression
 - Hallucinations
 - Homicidal thoughts
 - Mania
 - Psychosis
 - Suicidal ideation and behavior

- Protracted withdrawal syndrome persists beyond 4 to 6 weeks after initial benzodiazepine withdrawal. Symptoms may last weeks to as long as 12 months. These include:
 - Anxiety
 - Cognitive impairment
 - Depression
 - Insomnia
 - Formication
 - Motor symptoms (e.g., weakness, tremor, muscle twitches)
 - Paresthesia
 - Tinnitus
- Consider all therapeutic options for management of the patient’s condition, and provide information about non-drug alternatives to help with stress, anxiety, insomnia, etc.
- Benzodiazepine abuse occurs when the medicine is not taken as prescribed to treat a medical condition, but instead taken to produce a euphoric effect or some other desired effect. Misuse occurs when the medication is not taken as prescribed to manage a medical condition (e.g., taking more than the recommended dose or taking medicine prescribed for someone else).
- Physical dependence is the body’s adaptation to repeated use of a drug, resulting in withdrawal reactions when the medicine is abruptly discontinued or the dose is significantly reduced. Dependence may lead some individuals to continue using the medicine to avoid symptoms of withdrawal.
- Encourage patients to read the [Medication Guide](#) they receive with their benzodiazepine prescriptions because there may be new or important additional information about the medicine.
- To help FDA track safety issues with medicines, report adverse events involving benzodiazepines or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.
- You can sign up for [email alerts](#) about Drug Safety Communications on medicines or medical specialties of interest to you.

Data Summary

We reviewed postmarketing databases and the published literature on the use of benzodiazepines and associated abuse, misuse, addiction, and physical dependence. In 2019, an estimated 92 million benzodiazepine prescriptions were dispensed from U.S outpatient pharmacies, with alprazolam (38%) being the most common followed by clonazepam (24%) and lorazepam (20%). In 2018, an estimated 50% of patients who were dispensed oral benzodiazepines received them for a duration of two months or longer.²

Postmarketing data suggest that benzodiazepine abuse and misuse are common and that associated harms are substantial but occur primarily when people use benzodiazepines in combination with other drugs. In 2018, an estimated 5.4 million U.S. individuals 12 years and older abused or misused benzodiazepines in the previous year.³ In 2016, the nationally estimated number of emergency department (ED) visits due to nonmedical use of benzodiazepines (n=167,845) was higher than the corresponding estimate for prescription opioids (n=129,863). A

relatively smaller proportion involved benzodiazepines alone – 14% (n=23,335) compared to 31% (n=40,499) of visits due to prescription opioid nonmedical use.⁴ Similarly, among the 8,761 U.S. poison control center calls involving benzodiazepine misuse or abuse in 2017, 63% involved multiple substances – most commonly prescription opioids, alcohol or stimulants – and medical outcomes in these cases were more severe than in cases involving benzodiazepines alone.⁵ Benzodiazepine-involved overdose deaths increased from 1,298 in 2010 to 11,537 in 2017.⁶ The proportion of these reported deaths documenting involvement of only benzodiazepines alone was small and decreased over this period, from 3.7% in 2010 to 2.7% in 2017. From 2013-2017, 55% of benzodiazepine-involved overdose deaths also documented involvement of prescription opioids.⁶

The exact risk of addiction associated with benzodiazepine use is uncertain; however, population data clearly indicate that both primary benzodiazepine use disorders and polysubstance addiction involving benzodiazepines do occur. In one published analysis of National Survey on Drug Use and Health data from 2015 to 2016, a half million community-dwelling U.S. adults were estimated to have a benzodiazepine use disorder.⁷ In 2017, approximately 1% (n=10,316) of admissions to publicly-funded substance use disorder treatment programs indicated that benzodiazepines were the primary drug of abuse; however, an additional 7% and 10% of admissions indicated benzodiazepines were the secondary and tertiary drug of abuse, respectively.⁸ For context, the primary drug of abuse was prescription opioids in approximately 3.6% of admissions, and the majority of admissions listed the primary drug of abuse as a non-pharmaceutical substance such as alcohol (33%), heroin (31%), marijuana/hashish (12%), and methamphetamine/speed (6.3%).

Epidemiologic data on benzodiazepine dependence and withdrawal are scarce. A small number of published longitudinal studies identified female sex, older age, mental health conditions and concomitant use of certain medications (e.g., antidepressants) as possible risk factors for long-term or high-dose benzodiazepine use or dependence.⁹⁻¹¹

We evaluated 104 cases from the FDA Adverse Event Reporting System (FAERS) database of abuse, dependence, or withdrawal involving a benzodiazepine as a single drug substance reported by patients or health care professionals directly to FDA from January 1, 1968, through June 30, 2019. While this is a small subset of FAERS cases received for benzodiazepines as a whole, we selected a focused case series to identify the most descriptive reports of dependence or withdrawal. Most patients reported that dependence and subsequent withdrawal symptoms developed even when the benzodiazepine (clonazepam, alprazolam, lorazepam, diazepam, triazolam, or oxazepam) was prescribed for therapeutic use. However, patients or others using these medications are unlikely to report directly to FDA about abuse or illicit uses. Approximately 80% of the FAERS cases described benzodiazepine withdrawal, including CNS effects (e.g., insomnia, increased anxiety or panic attacks, memory impairment, depression), cardiovascular effects (e.g., heart rate or rhythm fluctuations), and gastrointestinal effects (e.g., abdominal pain, nausea, diarrhea). These cases reported a wide range of time to dependence, with some describing the onset as early as days to weeks after the start of a benzodiazepine. Similarly, there were variations in the duration of the withdrawal symptoms that lasted from weeks to years. Most of the FAERS cases reported use of the benzodiazepine for months to

years. In some cases, the patient reported that the prescriber abruptly discontinued the benzodiazepine rather than prescribing a taper to mitigate withdrawal symptoms. An important limitation in the assessment of these cases was the difficulty in differentiating withdrawal symptoms from potential re-emergence or continuation of symptoms for which the benzodiazepine was being used.

References

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11. H. J. Luijendijk, H. Tiemeier, A. Hofman, J. Heeringa and B. H. C. Stricker, "Determinants of chronic benzodiazepine use in the elderly: a longitudinal study," *British Journal of Clinical Pharmacology* 2008;65;593-599.

Related Information

- Information about Benzodiazepines (create landing page)
- [National Institute on Drug Abuse: Screening and Assessment Tools Chart](#)
- [National Center for Complementary and Integrative Health for resources including Mind and Body Approaches for Stress and Anxiety: What the Science Says](#)
- [Insomnia: Relaxation Techniques and Sleeping Habits](#)
- [FDA Drug Safety Communication: FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning](#)

- [FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks](#)
- Press Release (add title)
- [The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)
- [Think It Through: Managing the Benefits and Risks of Medicines](#)