



BENZODIAZEPINES

(Street Names: Benzos, Downers, Nerve Pills, Tranks)

Introduction:

Benzodiazepines are a class of drugs that produce central nervous system (CNS) depression and are most commonly used to treat insomnia and anxiety. There is the potential for dependence on and abuse of benzodiazepines particularly by individuals with a history of multi-substance abuse. Alprazolam (e.g., Xanax), lorazepam (e.g., Ativan), clonazepam (e.g., Klonopin), diazepam (e.g., Valium), and temazepam (e.g., Restoril) are the five most commonly prescribed, as well as the most frequently encountered benzodiazepines on the illicit market. In recent years, there has been a dramatic increase in the trafficking and abuse of the “novel designer benzodiazepines” including clonazolam, diclazepam, flubromazolam, flualprazolam, etizolam, and bromazolam. Serious adverse effects associated with the use of “novel designer benzodiazepines” have been documented and include central nervous system depression, loss of motor coordination, respiratory depression, memory loss, and blackouts.

Licit Uses:

Benzodiazepines are widely prescribed drugs. According to IQVIA™, there were 34.6 million alprazolam, 21.3 million lorazepam, 23.7 million clonazepam, 9.1 million diazepam, and 4.7 million temazepam prescriptions dispensed in the U.S. in 2021. In the U.S., benzodiazepines are prescribed for their sedative-hypnotic (e.g., temazepam, triazolam, flurazepam, and estazolam), anti-anxiety (e.g., alprazolam, chlordiazepoxide, clorazepate, diazepam, lorazepam, and oxazepam), muscle relaxant (e.g., diazepam), and anti-convulsant (e.g., diazepam and clonazepam) effects. They are also used as an adjunct to anesthesia (e.g., midazolam) and for treatment of alcohol withdrawal (e.g., chlordiazepoxide) and panic disorders (e.g., alprazolam and clonazepam). Most benzodiazepines are available as tablet and capsule preparations; several are also available as injectable preparations and as syrup.

Chemistry and Pharmacology:

All benzodiazepines are composed of a benzene ring fused to a seven-member diazepine ring. Most benzodiazepines also possess a phenyl ring attached at the 5-position of the diazepine ring. Small modifications of this basic structure account for the varied pharmacologic effects of these drugs.

Benzodiazepines produce CNS depression by enhancing the effects of the major inhibitory neurotransmitter, gamma-aminobutyric acid, thereby decreasing brain activity. Benzodiazepines are classified by their duration of action that ranges from less than 6 hours to more than 24 hours. Some benzodiazepines have active metabolites that prolong their effects.

Adverse effects include increased reaction time, motor incoordination, anterograde amnesia, slurred speech, restlessness, delirium, aggression, depression, hallucinations, and paranoia. Unlike barbiturates, large doses of benzodiazepines are rarely fatal unless combined with other CNS depressant drugs, such as alcohol or opioids. Flumazenil can be administered by injection to reverse the adverse effects of benzodiazepines. Tolerance often develops after long term use requiring larger doses to achieve the desired effect. Physical and psychological dependence may develop, whether taken under a doctor's orders or used illicitly. Withdrawal symptoms, the severity of which is dependent on the dose, duration of use, and drug used, include anxiety, insomnia,

dysphoria, tremors, and seizures. Withdrawal can be precipitated by the administration of flumazenil to individuals dependent upon benzodiazepines.

Illicit Uses:

Benzodiazepines, particularly those having a rapid onset, are abused to produce a euphoric effect. Abuse of benzodiazepines is often associated with multiple-substance abuse. Diazepam and alprazolam are used in combination with methadone to potentiate methadone's euphoric effect. Those who misuse cocaine or other stimulants, may also use benzodiazepines to relieve the side effects (e.g., irritability and agitation) associated with cocaine or stimulant binges. Benzodiazepines are also used to augment alcohol's effects and modulate withdrawal states. Those who misuse sedative hypnotics often use prescription benzodiazepines in excess of the recommended therapeutic dose. Also, benzodiazepines, have long been associated with drug facilitated sexual assaults by using prescription medication such as diazepam, temazepam and flunitrazepam. More recently, the “novel designer benzodiazepines”, including flualprazolam, etizolam, clonazolam, flubromazolam, diclazepam, and bromazolam, have become increasingly popular, appearing in a significant number of driving under the influence of drug (DUID) cases, toxicology reports, and death investigations. According to the United Nations Office on Drugs and Crime (UNODC Current NPS Threats, 2022), benzodiazepine-type novel psychoactive substances (NPS) continue to constitute the greatest number of NPS reported to the Tox-Portal, accounting for 47% of all NPS cases associated with postmortem investigations, and 67% of all DUID cases.

The American Association of Poison Control Centers reports 53,190 case mentions, 19,431 single exposures, and 16 deaths associated with benzodiazepines in 2020. Among these poison control cases and single exposures, 12,664 cases, involving only a single substance, were due to 'intentional' versus 'unintentional' reasons.

Illicit Distribution:

Individuals abusing benzodiazepines obtain them by getting prescriptions from several doctors, forging prescriptions, or buying diverted pharmaceutical products on the illicit market. Domestic and foreign products are found in the illicit market. Alprazolam is one of the top three prescription drugs diverted from the licit market. In 2021, there were 16,896 alprazolam, 5,290 clonazepam, 2,079 diazepam, 879 lorazepam and 60 temazepam reports from federal, state and local forensic laboratories. With respect to the “novel designer benzodiazepines”, NFLIS reporting for 2022 indicates that there were 2,114 drug reports associated with flualprazolam, 638 flubromazolam reports, 4,260 etizolam reports, 6,844 clonazolam reports and 786 bromazolam reports.

Control Status:

Benzodiazepines are controlled in schedule IV under the Controlled Substances Act, with the exception of flualprazolam, etizolam, clonazolam, flubromazolam, and diclazepam which are placed in schedule I. Flunitrazepam is unique among the benzodiazepines in being placed in schedule IV but having schedule I penalties.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 571-362-4250, Telephone 571-362-3249, or Email DPE@usdoj.gov.