

## BENZODIAZEPINES

### (Street Names: Benzos, Downers, Nerve Pills, Tranxs)

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#### Introduction:

Benzodiazepines are a class of drugs that produce central nervous system (CNS) depression and that 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 prescribed, as well as the most frequently encountered benzodiazepines on the illicit market.

#### Licit Uses:

Benzodiazepines are widely prescribed drugs. According to IMS Health™, there were 49.0 million alprazolam, 27.6 million lorazepam, 26.9 million clonazepam, 15.0 million diazepam, and 8.5 million temazepam prescriptions dispensed in the U.S. in 2011. 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-convulsants (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. Cocaine addicts use benzodiazepines to relieve the side effects (e.g., irritability and agitation) associated with cocaine binges. Benzodiazepines are also used to augment alcohol's effects and modulate withdrawal states. The doses of benzodiazepines taken by abusers are usually in excess of the recommended therapeutic dose. Benzodiazepines have been used to facilitate sexual assault.

The American Association of Poison Control Centers reports 81,427 case mentions, 31,255 single exposures, and 11 deaths associated with benzodiazepines in 2010. There were an estimated 345,691 emergency department visits attributed to benzodiazepines in 2010 (New DAWN ED), a statistically significant increase from 271,698 visits in 2008. Of the 345,691, 124,902 were alprazolam, 62,811 were clonazepam, 36,675 were lorazepam, and 26,860 were diazepam. According to the 2011 National Survey for Drug Use and Health (NSDUH), 20.4 million individuals aged 12 and older have misused benzodiazepines in their lifetime.

#### 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 2011, there were 39,408 alprazolam, 10,686 clonazepam, 6,535 diazepam, 2,346 lorazepam and 341 temazepam reports from Federal, state and local forensic laboratories. From January through June 2012, there were 18,068 alprazolam, 5,150 clonazepam, 2,960 diazepam, 1,214 lorazepam and 198 temazepam reports from Federal, state and local forensic laboratories.

#### Control Status:

Benzodiazepines are classified as schedule IV depressants under the Controlled Substances Act. 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 202-353-1263, telephone 202-307-7183, or Email ODE@usdoj.gov.