ToxTalks:

A Bulletin for Healthcare Professionals Who Manage Poisoned Patients

In Partnership with the UVA Division of Medical Toxicology – Department of Emergency Medicine

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Designer Benzodiazepines

Overview

Designer benzodiazepines, also known as novel benzodiazepines, are analogs of pharmaceutical or prescription benzodiazepines, some are even precursors or metabolites. Examples include etizolam, flualprazolam, and bromazolam. Some are benzodiazepines that are used overseas but not approved in the U.S. While others are made by altering the chemical structure of approved benzodiazepines in illegal factories. These substances can be easily purchased online where they are marketed as "research chemicals" or "not for human consumption" in an attempt to evade regulatory oversight. These substances pose a significant public health threat due to their unpredictable pharmacology and their potential for severe toxicity, drug interactions, and withdrawal.

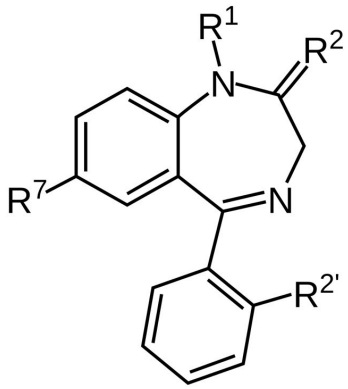

Image: Wikipedia

Pharmacology

The basic chemical structures of designer benzodiazepines resemble those of prescription benzodiazepine. While prescription benzodiazepines are sedative-hypnotic drugs and exert their effects primarily by enhancing inhibitory neurotransmission mediated by gamma-aminobutyric acid (GABA) at GABA-A receptors, designer benzodiazepines pharmacology and toxicology are less clear and remain understudied. Available literature describes their toxicology, and effects similar to those observed in prescription benzodiazepine poisonings. However, subtle structural modifications can significantly alter their potency, receptor subtype selectivity, and pharmacokinetic profiles.

Clinical Effects

The limited available clinical toxicological data shows the clinical effects of designer benzodiazepines are similar to those of prescription benzodiazepines and included sedation, confusion, ataxia, retrograde amnesia and in severe

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cases can progress to coma, respiratory depression, hypotension, bradycardia. Respiratory arrest and death have been reported with benzodiazepines alone but is more common when combined with other central nervous system depressants such as opioids or alcohol.

Benzodiazepine withdrawal is similar to alcohol withdrawal. It is characterized by restlessness, agitation, nausea and vomiting, anxiety, and tachycardia. Those in severe withdrawal can experience hallucinations, confusion, autonomic instability, and seizures.

Available Forms

These drugs are often found in tablet, pill, or powdered form. However, they have also been found recently in association with illicit opioids. This can lead to physiologic dependence and therefore withdrawal in patients who may not be aware they are consuming benzodiazepines.

Diagnostic Evaluation

Diagnosing designer benzodiazepine intoxication can be challenging because standard urine immunoassay drug screens may not detect these substances. Whether a benzodiazepine screen will be positive depends on the specific drug and immunoassay used. Even more precise analysis such as a liquid chromatography tandem mass spectrometry used for urine drug screen confirmation may not be able to detect these novel drugs if it is not in the instrument's library and there is no reference.

Management

Management of benzodiazepines overdose is mainly supportive. In severe toxicity, airway management may be indicated for respiratory depression or lack of protective reflexes, especially when coexisting sedatives such as alcohol or opioids are present. Hypotension can be treated with intravenous fluids and vasopressors if required. Withdrawal is treated by giving benzodiazepines until symptoms are controlled and then tapering the dose over several days.

Flumazenil is a competitive benzodiazepines receptor antagonist that can be used as an antidote for benzodiazepine toxicity. However, in those with physiologic dependence or in polysubstance overdoses, flumazenil administration can induce seizures and withdrawal which can be life-threatening and should be used with caution.

Summary

Designer benzodiazepines pose a significant clinical challenge due to their unpredictable pharmacology and limited detection by standard urine drug screens. Healthcare professionals should be aware of the potential for severe toxicity requiring airway management and mechanical ventilation. Benzodiazepine withdrawal also requires prompt identification and treatment. Advanced analytical techniques may be necessary for identification of novel benzodiazepines which is often not present at most hospitals and requires samples being sent to a larger laboratory with sophisticated detection equipment. Continued monitoring and research are crucial to address the evolving threat of designer benzodiazepines.

If questions, please contact the UVA Health's Blue Ridge Poison Center at 1-800-222-1222, or call the dedicated healthcare provider line at 1-800-451-1428.