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# Benzodiazepines



500 Chipeta Way, Salt Lake City, UT 84108 | (800) 522-2787 | (801) 583-2787 | www.aruplab.com | www.arupconsult.com

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## INTRODUCTION

Misuse and abuse of prescription drugs is a growing social and medical problem nationwide. Prescription drugs are known to be shared inappropriately among friends or family, have motivated many pharmacy robberies, and are at risk for being stolen and/or sold on the black market. Not surprisingly, control of prescription-drug trafficking is a major concern of the Drug Enforcement Administration and the United States Department of Justice.

Although much of the concern regarding misuse of prescription drugs has focused on opioid pain relievers, benzodiazepines are also frequently misused. Benzodiazepines are comparable to opioids relative to frequency of emergency department visits and dependency concerns. The most commonly prescribed benzodiazepines in the United States in 2010 were alprazolam, clonazepam, diazepam, and lorazepam. Monitoring compliance with prescribed benzodiazepines using periodic urine drug testing is a useful tool for management of patients with chronic pain.

## BENZODIAZEPINES AND PAIN MANAGEMENT

Benzodiazepines are psychoactive drugs that are often taken by chronic pain patients to improve sleep, relax musculature, and relieve anxiety that may be attributed to or exacerbate the sensation of pain. Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA), which results in sedative, hypnotic, anti-anxiety, anticonvulsant, muscle relaxant, and amnesic action.

Chronic use of benzodiazepines can produce tolerance and withdrawal. Tolerance is defined as a state of progressively decreased responsiveness to a drug. In benzodiazepines, tolerance develops relatively quickly to the sedative, hypnotic actions of drugs indicated for pain patients. Withdrawal is defined as a constellation of symptoms that occur after a patient stops taking the drug. Most frequent symptoms of withdrawal from benzodiazepines are insomnia, muscle cramps and spasms, agitation, paresthesias, sensitivity to light and sound, and dizziness. Sudden withdrawal from high-dose therapy may precipitate seizures and delirium.

More than a dozen benzodiazepines are available by prescription in trade and generic formulations. Benzodiazepines are categorized based on comparison to diazepam as full agonists or partial agonists. They are also classified based on half-life. Short-acting compounds, such as midazolam and triazolam, have half-lives of 1–12 hours. Intermediate-acting compounds have half-lives of 12–40 hours. Examples are clonazepam and lorazepam. Long-acting compounds have half-lives that may exceed days. There is a risk of accumulation in the elderly and in individuals with severely impaired liver function with these long-acting compounds. Examples are diazepam, chlordiazepoxide, and flurazepam. Both diazepam and chlordiazepoxide have a long-acting active metabolite called nordiazepam, which has a half-life of 85–110 hours. Flurazepam also has a long-acting metabolite desalkylflurazepam, with a half-life of 34–150 hours.

Benzodiazepines, when taken alone, rarely cause severe complications or fatalities, even in overdose. However, when combined with opioids/opiates, alcohol, or other central nervous system depressants, the potential for toxicity increases and may lead to increased sedation, impaired motor coordination, respiratory suppression, and other adverse effects that can be lethal.

Despite limitations and challenges, benzodiazepines remain a component of chronic pain management for many patients.

## URINE DRUG TESTING

Routine urine drug testing has been incorporated into national and state practice guidelines for physicians who prescribe drugs to control chronic pain. Urine drug testing is an important tool for holding the patient accountable to the therapeutic goals through verification of compliance with prescribed therapy and abstinence from non-prescribed drugs. Monitoring benzodiazepine compliance helps clinicians select the best drug and dose for optimal response, evaluate the side effects, and thereby improve patient care. Monitoring compliance also assures that benzodiazepine medications are not being diverted, hoarded, or otherwise misused.

Laboratories that provide testing for benzodiazepines strive to implement very specific and sensitive analytical methodologies. However, urine drug tests for benzodiazepines are currently not standardized. Considering the wide range of drugs a patient may be prescribed and the variable dilution of urine possible with random collection, laboratory tests designed to detect benzodiazepines may have inadequate sensitivity and specificity.

False positive rates for benzodiazepine immunoassays are relatively low (<5 percent). However, most benzodiazepine immunoassays used for screening are susceptible to false negative results. The false-negative rate for benzodiazepines in an immunoassay screen is approximately 25-30 percent, and is particularly problematic for clonazepam. One reason for false-negative clonazepam results is that the drug appears in the urine almost entirely as 7-aminoclonazepam, a metabolite that is not detected by many commercial immunoassay screens. A similar challenge exists for some other extensively metabolized benzodiazepines.

Concerns about false-negative results in confirmation/quantitation tests for benzodiazepines also exist due to variation among laboratories in the cutoff concentrations (sensitivity), the actual analytes detected, and the sample preparation methods. Regarding sample preparation, some laboratory methods includes a sample pretreatment reaction prior to analysis that liberates glucuronide metabolites (e.g., hydrolysis). Hydrolysis pretreatment will improve detection of most benzodiazepines. Inclusion of multiple benzodiazepine metabolites will also improve detection of benzodiazepines in urine confirmation/quantitation tests. The table below depicts the relationship and potential complexity in metabolism of common benzodiazepines:

| BENZODIAZEPINE (GENERIC NAME) | TRADE NAME EXAMPLE | DURATION OF PARENT DRUG ACTIVITY | METABOLITE EXAMPLES FOUND IN URINE |
|---|---|---|---|
| Alprazolam | Xanax | Intermediate | Alpha-hydroxyalprazolam |
| Chlordiazepoxide | Librium | Pro-drug | Nordiazepam |
| Clonazepam | Klonopin | Intermediate | 7-aminoclonazepam |
| Diazepam | Valium | Long acting | Nordiazepam and temazepam, both of which metabolize into oxazepam |
| Flunitrazepam | Rohypnol | Intermediate | 7-aminoflunitrazepam |
| Flurazepam | Dalmane | Short acting | Desalkylflurazepam, 2-hydroxyethylflurazepam |
| Lorazepam | Ativan | Short acting | Lorazepam glucuronide |
| Midazolam | Versed | Short acting | Alpha-hydroxymidazolam |
| Nordiazepam | | Long acting | Oxazepam |
| Oxazepam | Serax | Short acting | Oxazepam glucuronide (liberated by hydrolysis treatment) |
| Prazepam | Centrac | Long acting | Nordiazepam |
| Temazepam | Restoril | Intermediate | Oxazepam |
| Triazolam | Halcion | Short acting | Alpha-hydroxytriazolam |

Concentrations of the various benzodiazepines relative to prescribed doses, individual drug pharmacokinetics, dosing intervals, and metabolic pathways known for the prescribed drug(s) must be considered to accurately assess compliance. Overall activity and detection depend on the metabolites and associated half-lives of those metabolites, and the fact that most benzodiazepines form glucuronide metabolites beyond those shown above. Benzodiazepines included above, except for those in shaded boxes, are detected in ARUP's urine benzodiazepine panel by quantitative LC-MS/MS (ARUP test code 0090358).

## RESULTS INTERPRETATION

Results may be useful to detect:

- Compliance with prescribed benzodiazepines.
- Use of non-prescribed benzodiazepines.

Time periods of drug detection vary with specimen type and drug, but most are detected for two to four days after the last dose. Urine is the most commonly used specimen due to convenience of collection and because drug use can be detected for the longest period with urine. However, blood testing may be indicated when urine is unavailable or to support investigation of individual patient pharmacokinetic parameters (e.g., evaluate absorption and elimination kinetics, or drug-drug interactions).

- Results cannot always identify the formulation of drug used, the dose administered, or the specific time(s) of drug administration.
- Results may be useful for detecting specimen adulteration, such as adding parent drug directly to urine to mimic compliance with prescribed therapy.
- Dilution of urine specimens through overhydration (excessive intake of fluids prior to voiding) may compromise detection limits.

Quantitative confirmation of benzodiazepines is necessary for interpretation because:

- Immunoassays have variable sensitivity to benzodiazepines and related structures. False negatives and false positives are common.
- Many benzodiazepine metabolites are also available as independent drugs.
- Detection of drug metabolites assures that drug was taken.
- Patterns of benzodiazepine concentrations may guide interpretation.

## REFERENCES


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## CONTRIBUTORS


Gwendolyn McMillin, PhD, University of Utah School of Medicine and ARUP Laboratories
Norkio Kusukawa, PhD, University of Utah School of Medicine and ARUP Laboratories
Gordon Nelson, C(ASCP), NRCC-TC, ARUP Laboratories

ARUP Laboratories
Salt Lake City, Utah

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