



New High-Resolution Targeted Benzodiazepine Screen

Superior Sensitivity and Specificity to Evaluate Adherence to Prescribed Benzodiazepine Therapy

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Disclosures

- None

Objectives

- Describe the clinical utility of benzodiazepines and understand the limitations of the following urine drug tests used to support adherence monitoring of these medications:
 - Laboratory or point of care-based benzodiazepine immunoassays
 - Mass spectrometry-based targeted screening assays
- Define the metabolic profiles of benzodiazepines commonly prescribed and discuss how to interpret screening/definitive test results

Benzodiazepines¹

- A large class of central nervous system (CNS) depressant medications with useful sedative, hypnotic, anxiolytic, and anticonvulsant properties
- Types:
 - Short, Intermediate, and Long-acting benzodiazepines
- FDA-approved uses:
 - Generalized anxiety disorders
 - Panic disorders
 - Social phobia
 - Insomnia
 - Status epilepticus/seizures
 - Premedication for anesthetic procedures

Benzodiazepines^{2,3}

- Mechanism of Action:
 - Raise levels of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the brain
- Common examples:
 - Diazepam (Valium)
 - Alprazolam (Xanax)
 - Clonazepam (Klonopin)
 - Lorazepam (Ativan)
- Class IV Controlled Substance
- >30% Opioid Overdoses also involved a Benzodiazepine

Screening Assays

Types:

- Traditional screening assays
 - Point-Of-Collection Tests (POCT)
 - Laboratory-based (commercial immunoassays)
- Targeted screening assays
 - Laboratory-Developed-Tests (LDT) using TOF-MS or other MS/MS analyzers

Test	Advantages	Disadvantages
POCT	Fastest TAT CLIA-waived versions available Instant result to review/discuss with patient Great if patient resides far from care Good for high-risk patient	Limited sensitivity Higher cutoffs Limited specificity Maintain inventory/regulatory compliance Higher cost
Immunoassay-lab based	Automated CLIA environment Most economic Larger test menu	Limited sensitivity Limited specificity
Targeted screen	Better sensitivity Better specificity Broadest test menu	Limited availability

Immunoassays & Cross-Reactivity Issues⁴

- Common urine Benzodiazepine immunoassay targets:
 - Oxazepam or Nordiazepam
- Concentrations required to trigger a “positive” Benzodiazepine result:

Drug	100 ng/mL cutoff	% Cross reactivity
7-aminoclonazepam	144 ng/mL	69%
α-hydroxyalprazolam	118 ng/mL	84%
Lorazepam	163 ng/mL	62%
Lorazepam glucuronide	19,615 ng/mL	0.5%
Midazolam	168 ng/mL	60%
α-hydroxymidazolam	140 ng/mL	71%
Temazepam	145 ng/mL	69%
Temazepam glucuronide	>20,000 ng/mL	0.8%

Clinical Case Study #1

- Case History:
 - 55 year old female
- Medical History:
 - Anxiety disorder
- Medications:
 - Lorazepam (Ativan)
- Clinical Evaluation:
 - Anxiety well controlled
 - Orders urine drug testing (UDT) to monitor compliance

Case #1 Continued

- Routine Lab or POCT-based Urine Immunoassay results:
 - January 2019

Immunoassay Screening Test	Urine Cutoff	Result
Amphetamine/Methamphetamine	500 ng/mL	Negative
Barbiturates	200 ng/mL	Negative
Benzodiazepines	100 ng/mL	Negative
Cocaine Metabolite	150 ng/mL	Negative
Phencyclidine (PCP)	25 ng/mL	Negative
THC (Marijuana)	50 ng/mL	Negative
Opiates	300 ng/mL	Negative

Is the Patient Compliant Based on the Urine Test Results?

- Patient prescribed Lorazepam
- Patient Urine Benzodiazepine Immunoassay Result:

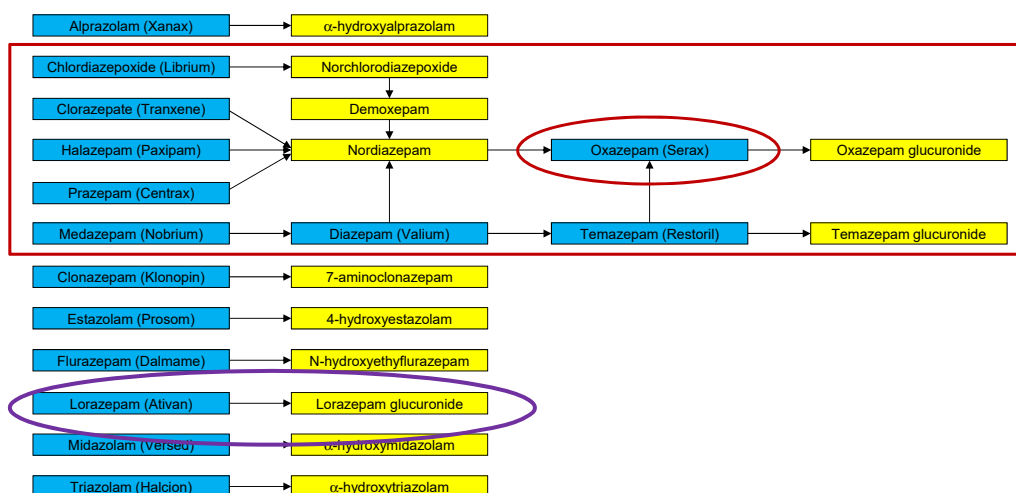
Screening Test	Urine Cutoff	Result
Benzodiazepine	100 ng/mL	Negative

- Remember cross-reactivity w/ Immunoassay:

Drug	100 ng/mL cutoff	% Cross reactivity
Lorazepam	163 ng/mL	62%
Lorazepam glucuronide	19,615 ng/mL	0.5%

- Lorazepam appears in the urine largely as the glucuronidated conjugate

Simplified Benzodiazepine Metabolism



Case #1 Continued; Physician Adds On Order for Benzodiazepine Confirmation Test

- Benzodiazepine LC-MS/MS Confirmation, Urine (BENZU)

Analyte	Urine Detection Limit	Result
7-NH-Clonazepam	100 ng/mL	<100
7-NH-Flunitrazepam	100 ng/mL	<100
Alpha-OH-Alprazolam	100 ng/mL	<100
Alpha-OH-Triazolam	100 ng/mL	<100
OH-ethyl-flurazepam	100 ng/mL	<100
Lorazepam	100 ng/mL	8,250 ng/mL
Nordiazepam	100 ng/mL	<100
Oxazepam	100 ng/mL	<100
Temazepam	100 ng/mL	<100

- Conclusion:
 - Patient is taking Lorazepam (Ativan)

Mayo Clinic's High Resolution Targeted Benzodiazepine Screen (TABSU)

2017 AACC Academy LMPG Evidence-based Recommendation: Definitive Testing⁵

Table 4: Summary of Evidence-Based LMPG Recommendations

#	Recommendation	Grading : Strength of recommendation, Quality of evidence	Target Group		
			Lab	Clinician	Policy [‡]
1	Qualitative definitive tests should be used over immunoassays since they are more effective at identifying relevant over-the-counter medications, prescribed and non-prescribed drugs, and illicit substances in pain management patients.	A, II	X	X	X

High-Resolution Targeted Benzodiazepine Screen TABSU / Targeted Benzodiazepine Screen, Urine

- Features and Benefits:
 - Uses high-resolution accurate mass spectrometry to identify 27 different benzodiazepines and/or metabolites where immunoassays are not adequate
 - Lower detection limits (improved sensitivity)

Drugs Detected in the High-Resolution Targeted Benzodiazepine Screen

Analyte	Cutoff	Analyte	Cutoff	Analyte	Cutoff
Alprazolam	10 ng/mL	Nordiazepam	10 ng/mL	Oxazepam	10 ng/mL
Alpha-Hydroxyalprazolam	10 ng/mL	Flunitrazepam	10 ng/mL	Oxazepam Glucuronide	50 ng/mL
Alpha-Hydroxyalprazolam Glucuronide	50 ng/mL	7-aminoflunitrazepam	10 ng/mL	Prazepam	10 ng/mL
Chlordiazepoxide	10 ng/mL	Flurazepam	10 ng/mL	Temazepam	10 ng/mL
Clobazam	10 ng/mL	2-Hydroxy Ethyl Flurazepam	10 ng/mL	Temazepam Glucuronide	50 ng/mL
N-Desmethyloclobazam	200 ng/mL	Lorazepam	10 ng/mL	Triazolam	10 ng/mL
Clonazepam	10 ng/mL	Lorazepam Glucuronide	50 ng/mL	Alpha-Hydroxy Triazolam	10 ng/mL
7-aminoclonazepam	10 ng/mL	Midazolam	10 ng/mL	Zolpidem	10 ng/mL
Diazepam	10 ng/mL	Alpha-Hydroxy Midazolam	10 ng/mL	Zolpidem Phenyl-4-Carboxylic acid	10 ng/mL

High-Resolution Targeted Benzodiazepine Screen: TABSU / Targeted Benzodiazepine Screen, Urine

- Features and Benefits:
 - Uses high-resolution accurate mass spectrometry to identify 27 different benzodiazepines and/or metabolites where immunoassays are not adequate
 - Lower detection limits (improved sensitivity)
 - Improved test utilization without compromising turn-around-times
 - Significantly reduced need for confirmatory testing required with traditional immunoassay screens
 - Ability to detect “spiked” samples
 - Available with enhanced reports with interpretative comments

Example of Enhanced Report



1-800-533-1710

Targeted Benzodiazepine Screen, U

TABSU

PATIENT NAME VALIDATION, AUTOMATION D					ORDER NUMBER H629001004
PATIENT ID M0000702	DATE OF BIRTH 03/26/1981	AGE 37 Y	SEX Female	REQUESTED BY PROVIDER UNKNOWN	
COLLECTED 11/29/2018, 10:45 AM	RECEIVED 11/29/2018, 10:45 AM	REPORTED 12/7/2018, 1:02 PM			
<small>The collected, received, and reported dates and times on the report are in the time zone of the performing location.</small>					
VALID Test Validation City MN 123456789					

INTERPRETATION

No benzodiazepines were detected. The absence of expected drug(s) and/or drug metabolite(s) may indicate non-compliance, altered pharmacokinetics, inappropriate timing of specimen collection relative to drug administration, diluted/adulterated urine, or limitations of testing.

RESULT(S)

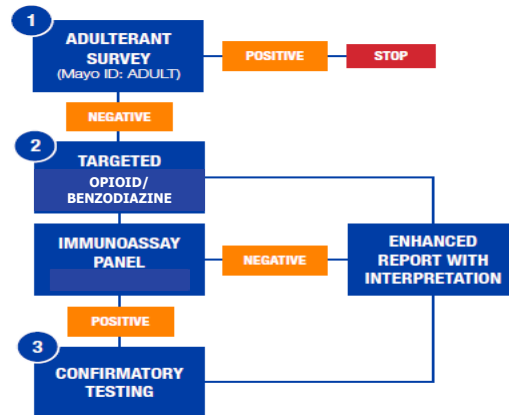
RESULT NAME	RESULT	FLAG	UNITS	REFERENCE VALUES	RESULT COMMENT
Alprazolam	Not Detected		ng/mL	Cutoff: 10	Xanax
Alpha-Hydroxyalprazolam	Not Detected		ng/mL	Cutoff: 10	Metabolite of Alprazolam
Alpha-Hydroxyalprazolam Glucuronide	Not Detected		ng/mL	Cutoff: 50	Metabolite of Alprazolam

Controlled Substance Monitoring Panel (CSMP)

• Profile

- Adulterant Testing:
 - Creatinine, Specific gravity, pH, Oxidant/Nitrite
- Targeted Opioid & Benzodiazepine Screen:
 - 33 Opioids (parent/metabolites)
 - 27 Benzodiazepines (parent/metabolites)
- Immunoassay Screens:
 - Amphetamine/Methamphetamine (Cutoff: 500 ng/mL)
 - Barbiturates (Cutoff: 200 ng/mL)
 - Cocaine metabolite (Benzoylecgonine; Cutoff: 150 ng/mL)
 - Phencyclidine (Cutoff: 25 ng/mL)
 - Tetrahydrocannabinol (Cutoff: 50 ng/mL)

2019 Mayo CSMP Algorithm



Summary

- Objective measures like laboratory tests are needed to:
 - Identify and evaluate recent drug use/abuse
 - Set and monitor clinical goals/expectations
- The new high-resolution targeted benzodiazepine assay:
 - Identifies 27 different benzodiazepines and/or metabolites where immunoassays are not adequate
 - Has lower detection limits (improved sensitivity)
 - Reduces need for confirmatory testing required with traditional immunoassay screens
 - Improves test utilization
 - Available with enhanced reports and interpretative comments
- UDT results need to be interpreted in the context of the test, drug(s) prescribed, specimen type, specimen validity test results, and the patient. Unexpected/unexplained results should be discussed with the patient/laboratory, and additional testing performed if needed

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Thank You