

Clinical Update: December 2019

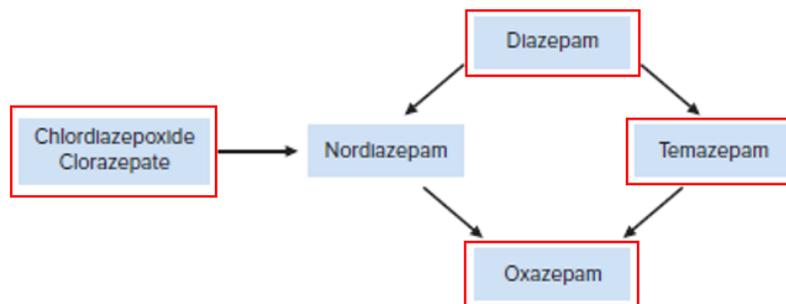
## What Did My Patient Actually Take? An Overview of Benzodiazepine Results

Our series on interpreting unexpected results concludes with a discussion on the interpretation of benzodiazepine results from Aegis Sciences Corporation. Please note that the interpretation of benzodiazepine results differs when using presumptive vs. definitive testing methods, and may differ among laboratories. The information provided here is intended to assist providers with deciphering benzodiazepine results from Aegis, which have undergone definitive testing by liquid chromatography/tandem mass spectrometry prior to reporting as positive.

### **Considerations for Interpreting Unexpected Results**

In the case of **unexpected positive** benzodiazepine results, consider the following drug exposures:

**Chlordiazepoxide (Librax<sup>®</sup>, Librium<sup>®</sup>), Clorazepate (Gen-xene<sup>®</sup>, Tranxene<sup>®</sup>), Diazepam (Valium<sup>®</sup>), Oxazepam, and/or Temazepam (Restoril<sup>®</sup>).** These medications share common metabolites, and distinguishing which compound was ingested may be impossible.<sup>1,2</sup> Note the analytes in red boxes below that are both metabolites and drugs available as a prescription. Because the exact drug ingested may not be distinguishable due to the overlapping metabolic pathways, positive results for Nordiazepam, Oxazepam, and/or Temazepam are reported by Aegis as **Benzodiazepine Metabolites**.



Some commonly prescribed benzodiazepines have unique metabolites, which make identification more straightforward:

- Alprazolam (Xanax<sup>®</sup>):** Metabolizes to  $\alpha$ -hydroxyalprazolam; reported as **Alprazolam**
- Clonazepam (Klonopin<sup>®</sup>):** Metabolizes to 7-aminoclonazepam; reported as **Clonazepam**
- Flurazepam:** Metabolizes to 2-hydroxyethylflurazepam; reported as **Flurazepam**
- Lorazepam (Ativan<sup>®</sup>):** Metabolizes to lorazepam glucuronide; reported as **Lorazepam**

A patient taking alprazolam, clonazepam, flurazepam, or lorazepam *will not* test positive for benzodiazepine metabolites on an Aegis report.

### **Opportunities for Exposure**

**Prescription:** Benzodiazepines are controlled substances, and legitimate prescriptions would show up on the prescription drug monitoring program (PDMP) in most cases. Please note that chlordiazepoxide, when administered with clidinium (Librax<sup>®</sup>), is not a controlled substance in many jurisdictions and may not show up on the PDMP in these states.

**Procedural Administration:** A benzodiazepine may be administered as an anxiolytic or sedative prior to medical procedures. If the medication was directly administered to the patient by the treating provider, record of this may not be part of the patient’s PDMP report. A review of medical records may be necessary to determine the medications given to the patient prior to or during a procedure.

**Hospitalization/Emergency Department Visit:** Patients who arrive at the emergency room with a suspected poisoning or overdose may be given benzodiazepines depending on their presenting symptoms and the source of the toxicity. A benzodiazepine may also be given as an anxiolytic, pre-procedurally, or for treatment of a seizure. If the patient reports a recent hospitalization or emergency department visit, follow-up with the hospital may be necessary to determine what medications were administered to the patient.

**Illicit Exposure:** Sources of illicit exposure may include use of another person’s prescription drug, acquisition of counterfeit or other illicit drugs unknowingly laced with benzodiazepines, or exposure to illicitly manufactured benzodiazepines which may share metabolites with FDA-approved benzodiazepines.<sup>3</sup>

**What medication is the patient prescribed?**

In many cases, the result interpretation may be clarified by correctly indicating the patient’s prescribed medications when ordering testing. Any questions about how to list medications as prescribed on an Aegis laboratory requisition may be directed to the Aegis Client Services department at 1-800-533-7052. In general, the following guidance may be helpful:

Drug Prescribed	Drug to Mark as Prescribed	Expected Result <sup>1,2</sup>
<b>Alprazolam</b>	Alprazolam	Positive for alprazolam and α-OH-alprazolam <ul style="list-style-type: none"> <li>• Parent drug may not be present in all results; only one marker is required for a positive result</li> <li>• If parent drug is present in urine with no α-OH-alprazolam present, please consult the Aegis Clinical Team as multiple clinical factors may be pertinent to result interpretation, and this does not always indicate aberrant patient behavior</li> </ul>
<b>Clonazepam</b>	Clonazepam	Positive for 7-aminoclonazepam
<b>Diazepam</b>	Benzodiazepine <i>(Electronic Requisition)</i> Diazepam <i>(Paper Requisition)</i>	Positive for Benzodiazepine Metabolites <ul style="list-style-type: none"> <li>• Nordiazepam, Temazepam, and/or Oxazepam may be present</li> <li>• Only one marker is required for a positive result</li> </ul>
<b>Flurazepam</b>	Flurazepam <i>(Electronic Requisition)</i> Write in “Other” field <i>(Paper Requisition)</i>	Positive for 2-hydroxyethylflurazepam
<b>Lorazepam</b>	Lorazepam	Positive for Lorazepam
<b>Oxazepam</b>	Benzodiazepine <i>(Electronic Requisition)</i> Oxazepam <i>(Paper Requisition)</i>	Positive for Benzodiazepine Metabolites <ul style="list-style-type: none"> <li>• Only Oxazepam should be present</li> <li>• Presence of other benzodiazepine markers may indicate ingestion of other benzodiazepines</li> </ul>
<b>Temazepam</b>	Benzodiazepine <i>(Electronic Requisition)</i> Temazepam <i>(Paper Requisition)</i>	Positive for Benzodiazepine Metabolites <ul style="list-style-type: none"> <li>• Only Temazepam and/or Oxazepam should be present</li> <li>• Presence of other benzodiazepine markers may indicate ingestion of other benzodiazepines</li> </ul>

**When was the patient's last dose?**

The period of detection for benzodiazepines varies greatly according to the specimen type utilized for testing and the patient's dosing regimen. Benzodiazepines may be detected for a longer period of time in urine compared to oral fluid and blood. In blood, especially, the period of detection is generally limited to very recent use. The detection time may be less in all specimen types in cases of as-needed dosing or ingestion of low doses. In settings of abuse or detoxification, the period of detection may be longer. Diazepam in particular has been noted to be detected longer in the urine of obese patients.<sup>4</sup> Period of detection studies in toxicology are often limited, and special populations of patients are often excluded. If there is a particular scenario involving unexpected results, the Aegis Clinical Team is happy to review available literature to examine possible causes of such results.

**Does the patient have altered gastrointestinal (GI) function or recent GI illness?**

Some patients have short-gut syndrome due to previous surgeries or GI disease or may have a history of gastric bypass surgery. Providers may consider the possibility of reduced absorption of drug and potential impact on unexpected negative results in these patients. Vomiting and diarrhea can disrupt normal absorption and metabolism of medications and reduce excreted amounts to undetectable levels. Providers may also consider recent GI illness in the interpretation of unexpected negative results.

**If evaluating urine results, is the sample dilute?**

Aegis provides special report comments to alert providers when the urine creatinine falls below 20 mg/dL. Urine samples with such a low creatinine level are less concentrated, and urine drug concentrations may fall below the reporting threshold in such samples. Patients who drink a lot of water, consume caffeine, take diuretic medications, have disorders of antidiuretic hormone, or other physiologic disturbances affecting urinary concentration may produce less concentrated urine. Intentional dilution may occur either with intentional ingestion of copious amounts of water or by adding water to the urine sample from the restroom sink or toilet. Such aberrant behavior should be considered in the context of the entire patient presentation with a provider using his or her clinical judgment to assess this possibility. Coloring the toilet water blue prior to sample collection and assessing the urine temperature within 4 minutes of collection (should be between 90°F and 100°F) are additional measures to check for sample tampering.<sup>5-6</sup>

Further information regarding specimen tampering is available in the Aegis Clinical Reference Guide at <https://www.aegislabs.com/resources/clinical-reference-guide/>. Click on the title "Specimen Validity Testing and Specimen Tampering" to download a copy of this chapter.

**Are there concerns with drug and sample stability such as improper storage or delays in shipment?**

If evaluating urine results, the sample pH may be an indicator of sample stability. Although the impact of urine pH would not likely be so significant to cause unexpected negative results, providers may consider that an elevated urine pH may be a natural physiologic response to regulate the body's acid-base balance, or it may also be elevated if the urine was not stored properly prior to shipment. In the case of improper storage, drug degradation contributing to unexpected negative results may be possible.

Clonazepam in particular is more prone to stability issues. Losses of 7-aminoclonazepam in urine averaging 43% have been reported under refrigerated conditions at 2 months.<sup>7</sup> A 76% drop in clonazepam concentration has occurred in an oral fluid specimen stored at room temperature overnight.<sup>8</sup> Complete loss of clonazepam in oral fluid has occurred in 7 days at room temperature.<sup>9</sup> In

oral fluid, losses of 7-aminoclonazepam up to 20% and 33% have been observed at room and refrigerated temperatures, respectively, over a week.<sup>10</sup> Providers may consider these known issues particularly when evaluating unexpected negative clonazepam results. These stability issues along with as-needed dosing and/or low doses may further increase the likelihood of unexpected negative results.

Further information regarding specimen stability is available in the Aegis Clinical Reference Guide at <https://www.aegislabs.com/resources/clinical-reference-guide/>. Click on the title “Drug Stability and Toxicology Testing” to download a copy of this chapter.

### Is the patient on dialysis?

If testing a dialysis patient, testing prior to dialysis is recommended or at least on a non-dialysis day to reduce the possibility of unexpected negative results. Some dialysis patients are able to produce urine, but the urine produced may not be the result of normal filtration and excretion of drug and as such may not be clinically useful for drug compliance testing.

### Point of Care Testing Considerations

Some point-of-care testing (POCT) devices may result in a false positive for benzodiazepines in patients who are taking certain medications.<sup>6,11-17</sup> Cross reactivity can occur with this type of testing among drugs with similar chemical structures.<sup>11</sup> Non-benzodiazepine prescription, illicit, or over-the-counter drugs would **not** cause a false positive for benzodiazepines or benzodiazepine metabolites on Aegis definitive testing. Please see below for a list of drugs which may cause a false positive for benzodiazepines on POCT.<sup>6,11-15</sup> Please refer to the package insert that came with the POCT device being used or contact the manufacturer for more information regarding which drugs may cause false positive results as this information may differ among devices and manufacturers.

IMMUNOASSAY TEST	POTENTIAL DRUGS CAUSING A FALSE POSITIVE OR UNEXPECTED POSITIVE RESULT		
Benzodiazepines	Chlorpromazine Efavirenz Fenoprofen	Flurbiprofen Indomethacin Ketoprofen	Oxaprozin Sertraline Tolmetin

False negative immunoassay results may also occur due to failure of the assay to react to drug-specific markers such as  $\alpha$ -OH-alprazolam, 7-aminoclonazepam, 2-hydroxyethylflurazepam, and lorazepam glucuronide.<sup>6,11,12,16,18-21</sup>

At Aegis, we understand your concerns as you evaluate definitive drug testing results. Unexpected benzodiazepine results may be indicative of noncompliance, drug misuse, or diversion, and we welcome your calls and e-mails for assistance in interpreting these results.

**Please call our clinical team at 1-877-552-3232 if you require additional information.**

NOTICE: The information above is intended as a resource for health care providers. Providers should use their independent medical judgment based on the clinical needs of the patient when making determinations of who to test, what medications to test, testing frequency, and the type of testing to conduct.

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