CLINICAL VIGNETTE

Negative Urine Drug Screen in a Patient with Chronic Benzodiazepine Use

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Case presentation

A 40-year-old male with history of chronic anxiety presents for medication refill and transfer of care. For years, the patient has been taking clonazepam to control his anxiety. He had seen a psychiatrist and psychologist in the past but has not been seen anyone for the past 3 years, despite encouragement from his prior primary care physician. The last clonazepam prescription was given about four months ago, 0.5 mg three times a day, quantity 90 with three refills. In the past month, he has controlled his anxiety with an average use of 0.5 mg of clonazepam twice a day. He has not tried any other medication to control his anxiety. He desired "prn" medications and does not want to take a SSRI as he would then be required to take medication on daily basis. Interestingly, he admits to using clonazepam twice a day, every day, even though he may not be symptomatic and now takes the medication out of habit. In the past, he attempted to wean off clonazepam but was unable to do so because of returning symptoms of anxiety. He denies a history of withdrawal symptoms including seizures, tremors, and palpitations. Other than psychological dependence, he denies any adverse side effects from clonazepam. He denies smoking, illicit drug use, and alcohol use. His job as a teacher is stressful, and he does have some financial hardship. He also reports having limited time to exercise regularly. He is married and expecting his first child in the next month. The rest of the medical history is unrevealing.

A review of the Controlled Substance Utilization Review and Evaluation System (CURES) database is consistent with the patient's controlled substance history for the past three months. Review of the electronic medical record shows sporadic clinic visits, which may not be consistent with daily use of clonazepam within the past three years. There is no urine toxicology to review in the past 3 years.

Because the chronic use of benzodiazepines is generally not appropriate for control of anxiety, the patient was encouraged to slowly taper off of the clonazepam. The risks for dependence, worsening anxiety, overdose, and seizure were explained to the patient. The patient acknowledged the need to taper off this medication, given his dependence. He declined alternative treatments to control his anxiety and referral for therapy. A refill of clonazepam was given for one month with specific instructions given for a taper schedule. Urine drug screen was performed. Results were negative for benzodiazepines, despite his report of medication use that morning.

The patient followed up one month later and had decreased his use of clonazepam from 60 tablets per month to 45 tablets per month. He had self-weaned off more than recommended at the last visit. He had no withdrawal symptoms during this tapering. Another urine drug screen was sent for benzodiazepine confirmation, but unfortunately the urine test was cancelled due to lab error - specifically some urine had leaked from the specimen cup. At the visit's conclusion, the patient looked forward to further tapering of clonazepam and scheduled follow up in one month.

Discussion

Benzodiazepine use is common in the United States, and although typically prescribed for anxiolysis, it is also frequently prescribed for its sedative, antiepileptic, or muscle relaxant qualities. Approximately one in twenty United States adults filled benzodiazepine prescription during the course of the year.[1] In general, benzodiazepines work by enhancing GABA inhibitory effect in the brain similar to that of alcohol. Over time, there is decreased efficacy of GABA receptors, also known as tolerance. Adverse side effects of benzodiazepine are well known and include drowsiness, impaired coordination, concentration, and memory as well as frank irritability. More serious reactions include abuse, dependency, and paradoxical CNS stimulation, which can be interpreted by some patients as anxiety leading to continued use to treat "persistent" symptoms. Recently, a case control study showed chronic benzodiazepine use associated with an increased risk of Alzheimer's disease.[2] Despite concerns with long-term benzodiazepine use and minimal evidence that benzodiazepines retain effectiveness after several months, approximately one-quarter of individuals who are using a benzodiazepine are taking it chronically.[1] Moreover, the combination of benzodiazepine and opiate use increases the risk of respiratory depression. Thus both the California Medical Board and Center for Disease Control have recently recommended against prescribing both drugs concurrently in these cases.[3]

It is worth considering other first line treatments for anxiety, such as SSRI, and avoiding long-term benzodiazepine use.[4] Moreover, to reduce harm, the patient should avoid using alcohol or other illicit drugs while taking a benzodiazepine. Benzodiazepine should not be prescribed to patients with history of alcohol or drug misuse.[4] In addition to obtaining a thorough history and physical exam, one should also consider

monitoring with urine toxicology at least annually in even low-risk patients who are on a controlled substance.

Urine drug screening is a standard of care for prescribed controlled substances. First, it adds objective data to support the clinical history that the patient is taking the medication as prescribed. Second, it may assist in detecting diversion of the medication. Lastly, it may reveal illicit drug use, which may suggest the patient is not being responsible in managing the prescribed controlled substance, thereby increasing the risk of adverse side effects.

To be a useful test, results must be interpreted properly. Prior studies revealed that some primary care physicians may not be proficient in interpreting a urine toxicology screen.[5] As in our case, the patient had a negative drug screen despite chronic use of clonazepam. What does this negative urine drug screen mean? Should the physician be concerned about false negative results in this case? Or should the physician suspect diversion? First, it is important to understand the *type* of test performed.

There are two main types of urine drug screens: antibody based enzyme mediated immunoassays and gas chromatography with mass spectroscopy testing. The first type, immunoassays, are more commonly used as they are cheaper and faster to obtain a result. However, there are many potential false negative and false positive results in each class of drug. This is because individual drugs within a class have different structures, making it difficult for a single antibody to detect all the different types of benzodiazepines. Common benzodiazepines, such as clonazepam and lorazepam often result in false negatives (e.g., the patient is actually taking the substance, but the test results as negative). The immunoassay often uses an antibody to oxazepam, a metabolite of diazepam and chlordiazepoxide.[6,7] This antibody has relatively low cross reactivity with clonazepam and lorazepam and is therefore less likely to be detected reliably. Another reason a benzodiazepine test may be falsely negative is that a dose may not be of a sufficient concentration to reach the detection threshold level in the urine.

False positives can re-occur due to cross-reactivity. Chemical structures of antidepressants like sertraline have some similarity to diazepam and may lead to a false positive result for benzodiazepines (Table 1).[6,8] There may be variability in which substance cross react with a varying threshold of cross reactivity depending upon which drug is tested. Therefore, it is important to review the package insert of the immunoassay offered by the laboratory to be aware of these specifications. And this list, though detailed, should not be considered as exhaustive as there is always a potential for other substances not mentioned to cross react.[6]

A more reliable urine toxicology evaluation is the gas chromatography with mass spectroscopy (GC/MS) test. This is a quantitative test that also allows for identification of the drug detected and not just the class. Not surprisingly, this test is expensive and takes longer to process and should be used if confirmation of a particular medication or concentration of medication is desired. This test also includes metabolite information, which can be useful in certain clinical situations. This provides further objective information if the medication is used as prescribed.

It is important to know the time of the last dose to be able to interpret the results correctly. Urine testing may detect clonazepam if used within 5 days (Table 2). This detection threshold may differ if the medication is used chronically or intermittently. Moreover, other variables may alter the detection window, including individual variations in metabolism, urinary pH, and drug distribution.[6]

In summary, it is important to understand the method of urine toxicology screening in order to use and interpret it correctly. Urine drug screens have become the standard of care to assess compliance, detect diversion, or detect illicit drug use. Our patient should have the confirmatory testing via gas chromatography with mass spectroscopy to help rule out diversion, which is important to reduce the number of pills available in the community and prevent accidental overdose.

Tables

Table 1. False results on Immunoassay of benzodiazepine*

False Positive	False Negative
sertaline, oxaprozin, efavirenz	clonazepam, lorazepam, alprazolam, flunitrazepam, midazolam, chlordiazepoxide

*Antibodies to oxazepam or nordiazepam. Modified table from Appendix A. [6]

Table 2. Estimated detection times of benzodiazepines in urine

Diazepam and/or nordiazepam (Valium)	10 days (up to 30 days for its metabolites)
Alprazolam (Xanax)	5 days
Lorazepam (Ativan)	5 days
Temazepam (Restoril)	5 days
Clonazepam (Klonopin)	5 days
Chlordiazepoxide (Librium)	5 days
Flunitrazepam (Rohypnol)	5 days
Midazolam (Versed)	2 days

*Modified table from data in Appendix B. [6]

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Submitted August 18, 2016