

Buprenorphine Co-positivity with Designer Benzodiazepines in Routine Healthcare Urine Samples

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Background/Introduction

- Novel psychoactive substances (NPS) continue to evolve, with designer benzodiazepines (DBZD) now appearing in online drug forums and surveillance reports.
- DBZD are used as part of upper-downer cycles to achieve sedation and/or amnesia, or to potentiate the effects of opioids or prescription benzodiazepines.
- The combination of prescription benzodiazepines and buprenorphine requires careful monitoring to minimize the risk of accidental injury and resultant increase in healthcare utilization, especially emergency department visits. Due to their unknown potency, DBZD may be more, or less, harmful than their prescription counterparts.
- Identification of DBZD can better inform healthcare providers of their patients' substance use history.

Objectives

- Investigate the rate of buprenorphine detection in designer benzodiazepine positive samples
- Evaluate the positivity rate of specific designer benzodiazepines in urinary specimens
- Assess the need for metabolite testing when developing a testing method for designer benzodiazepines

Methods

This study was IRB approved. DBZD were analyzed in the laboratory as part of a larger NPS panel. Target analytes were included in the method based on information from the US Drug Enforcement Administration and other online resources. Prior to analysis, analytes were extracted from hydrolyzed urine using a liquid-liquid extraction followed by evaporation and reconstitution in mobile phase. Samples were injected onto a liquid chromatography/tandem mass spectrometry (LC-MS/MS) instrument consisting of a Shimadzu Prominence HPLC and Sciex API 4000 MS/MS. The mass spectrometer was operated in positive electrospray ionization mode for scheduled multireaction monitoring (sMRM) analysis. Analytes were chromatographically separated on a Biphenyl column. Upon request by a provider during the study period of January 2021, 3,892 samples were analyzed for bromazolam, clonazolam, 8-aminoclonazolam, diclazepam, delorazepam, etizolam, alpha-hydroxyetizolam, flualprazolam, alpha-hydroxyflualprazolam, flubromazepam, flubromazolam, alpha-hydroxyflubromazolam, nitrazolam, phenazepam, or 3-hydroxyphenazepam, with reporting thresholds ranging from 1-5 ng/mL. Buprenorphine was analyzed separately in hydrolyzed urine, with reporting thresholds of 1 ng/mL for buprenorphine and 2.5 ng/mL for norbuprenorphine. A positive result in all instances included samples where the parent and/or metabolite were detected above the threshold.

Results

| Overall Sample Characteristics | Specimen Tested. No (%) |
|---|-------------------------|
| Number of samples with DBZD test ordered | 3,892 |
| Number of DBZD-positive specimens | 30 (0.7) |
| Number of DBZD samples from males | 14 (46.6) |
| Number of DBZD samples from females | 16 (53.4) |
| Median patient age of DBZD-positive specimens | 39 |

| DBZD and Buprenorphine Positive Samples | 17/30 (56.6) |
|---|--------------|
| DBZD which was present with buprenorphine: | |
| • 8-aminoclonazolam ^a | 9/17 (52.9) |
| • Alpha-Hydroxyflualprazolam ^a | 9/17 (52.9) |
| • Alpha-Hydroxyetizolam ^a | 7/17 (41.1) |
| • Flualprazolam | 5/17 (29.4) |
| • Bromazolam | 1/17 (5.8) |

^a Metabolite

Conclusion/Discussion

- Of 3,892 tests ordered, 30 (0.7%) tested positive for at least one DBZD, with eight samples having >1 DBZD present.
- Of the 30 positive samples, 17 (56.6%) tested positive for buprenorphine.
- In 86.6% of the positive samples, metabolites were the only DBZD markers detected.
- We demonstrate that individuals seeking routine healthcare may test positive for DBZD during office visits and providers may benefit from this knowledge to allow for close monitoring for adverse events from interacting substances.
- Per US FDA guidance, one known interacting drug with prescription benzodiazepines is buprenorphine, which we detected in 56.6% of the 30 DBZD-positive samples.
- Through innovative analytical techniques and education of healthcare providers, the identification of DBZD may potentially play a role in the reduction of adverse events associated with the combination of buprenorphine and benzodiazepines, while facilitating the safer use of buprenorphine for opioid use disorder.

References

1. United States Food and Drug Administration. FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks. United States Food and Drug Administration; September 20, 2017. <https://www.fda.gov/media/107888/download>. Accessed May 7, 2021.
2. Schuman-Olivier Z, Hoepfner BB, Weiss RD, Borodovsky J, Shaffer HJ, Albanese MJ. Benzodiazepine use during buprenorphine treatment for opioid dependence: clinical and safety outcomes. Drug Alcohol Depend. 2013;132(3):580-586. doi:10.1016/j.drugalcdep.2013.04.006