

SOFT-DFC Snapshot – Alprazolam

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SOFT-DFC Snapshots are short reports of critical information about the more common drugs associated with drug-facilitated crimes (DFCs). They are not complete literature reviews about the drug or drug class. One key aspect is their focus on the ability to detect a drug after a single-dose administration, as is often the situation in DFC investigations. As such, these summaries also point out instances in which available data is limited, hoping this will encourage further research studies. Finally, SOFT-DFC Snapshots point to the use of these drugs in actual DFC cases, as cited in the medical and open literature.

Alprazolam is a triazolo analog of the 1,4-benzodiazepine class of central nervous system depressant compounds. The chemical name is 8-chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3- α] [1,4] benzodiazepine. The drug is widely prescribed in the United States, ranging from 30 million prescriptions (2014) to 16.7 million in 2020.¹ A recent global study² found alprazolam to be the third most reported drug in Drug Facilitated Crime cases.

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| Drug Class: | Benzodiazepines |
| Generic Name: | Alprazolam |
| Brand Name(s): | Xanax®, Xanax XR®, Niravam® |
| Dosage Forms: | Oral concentrate (1 mg/mL); oral tablet (0.25 mg; 0.5 mg; 1 mg; 2 mg); oral tablet, disintegrating (0.25 mg; 0.5 mg; 1 mg; 2 mg); oral tablet, extended-release (0.5 mg; 1 mg; 2 mg; 3 mg) |
| FDA Approval: | Alprazolam can be prescribed to treat anxiety disorders and panic disorder (sudden, unexpected attacks of extreme fear and worry about these attacks). It works by decreasing abnormal excitement in the brain. |
| Metabolism/Elimination: | Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxy alprazolam and α -hydroxyalprazolam. The pharmacologically active metabolites have half-lives like alprazolam of approx. 12 hrs. (range 6-27 hr.). Compared to the parent alprazolam concentrations, the plasma concentrations of 4-hydroxy alprazolam and α -hydroxyalprazolam were consistently less than 4%. The reported relative potencies in benzodiazepine receptor binding experiments and animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxy alprazolam and α -hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxyalprazolam and α -hydroxyalprazolam suggest they are unlikely to contribute much to the pharmacological effects of alprazolam. Alprazolam and its metabolites are excreted primarily in the urine. |

It should be noted that adsorption, metabolism, and excretion changes can occur in various populations, such as individuals with impaired hepatic function, alcoholism, and geriatric patients.

Single Dose Studies:

Urine:

The SOFT DFC Committee³ and the AAFS Standards Board⁴ have established the importance of testing urine samples from alleged victims of drug-facilitated crimes for alprazolam's primary urinary metabolite, α -hydroxyalprazolam, at a decision point concentration of 5 ng/mL or lower. Urine is easily collected, straightforward to analyze, and provides a longer window of detection of alprazolam ingestion compared to blood.

Literature on single-dose studies of alprazolam generally pre-date the year 2000; there are few single-dose studies for such a frequently prescribed drug.

One recent study⁵ evaluated eleven healthy volunteers who ingested 10 mg diazepam at the start of the study and 0.5 mg alprazolam on Day 3 of the study. A total of 10 oral fluid samples and 17 urine samples were collected from each participant. T_{max} values were 11 hours. Drug detection times in urine ranged from 0-27 hrs. for alprazolam (median 12) and 26-61 (median 36) for hydroxyalprazolam in urine.

Blood/Plasma/Serum:

A plasma concentration range between 20-40 ng/mL has been proposed for targeting symptoms of panic disorder; higher concentrations correlate with significant central nervous system depression. Twelve volunteers were administered 1 mg of alprazolam, and plasma was collected at various times, demonstrating a C_{max} of 16.5 mg/mL with a T_{max} of 1.25 hours.⁶

Twelve healthy adolescent volunteers (13–17 years) and 12 adult healthy volunteers (20–45 years) received single Xanax XR 1 mg or 3 mg tablets. C_{max} for the 1 and 3 mg groups were 7 – 9 ng/mL and 23 – 24 ng/mL, respectively. T_{max} values for both groups were 8 – 10 hours.⁷

Twelve healthy male volunteers received 1 mg of alprazolam or a placebo on three occasions in a double-blind, randomized, single-dose, three-way crossover study. The three trials were: (a) oral alprazolam and sublingual placebo; (b) an oral placebo and sublingual alprazolam; (c) a placebo by both routes. C_{max} for oral and sublingual administration was 12 and 11.3 ng/mL, respectively, and the T_{max} was 1.8 and 2.8 hours, respectively.⁸

Hair:

Hair analysis allows for the longest detection window of alprazolam compared to blood and urine. Generally, hair analysis is more complex

and less routine for toxicology laboratories. In addition, determining the time of ingestion is far less sensitive and specific than blood or urine. Studies show, however, that following a 0.5 mg oral alprazolam dose, alprazolam was not detected in a hair sample ⁽¹⁰⁾.

That said, hair analysis has been useful in some instances. For example, alprazolam was found in hair segments in two drug-facilitated crimes examined by Kintz.¹¹ Alprazolam was detected at 4.9 and 3.1 pg/mg, which was concluded through repeated doing of alprazolam.

DFC Cases:

A large study examining 1000 sexual assault cases listed alprazolam as identified in 9.3% of urine cases and 7.4% of blood cases.¹² There are limited case-specific reports involving alprazolam. This may be due to the difficulty of determining drug exposure and suspected DFC.

In Alabama, a sexual assault of a student made tabloid headlines in 2015. Four men were charged with sexual assault after the woman was found unconscious in a Tuscaloosa apartment. The subject was voluntarily consuming alcohol with a controlled substance which was reported to be Xanax. Police reported that all four men sexually assaulted the subject while she was unconscious.¹³ In 2015, another media report listed a minor subject who reported using alcohol and Xanax and blacked out. She reported subsequently being subjected to a sexual assault by an adult.¹⁴ It should be noted that these cases are subject to investigation, and toxicology results were not provided in these cases.

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