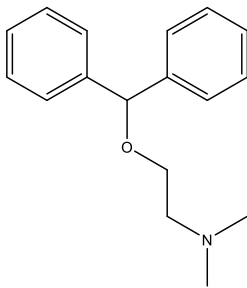


Adulterant Alert

Substance abuse treatment providers, clinicians, outreach workers, and public health clinics should be aware of the following information. The over-the-counter drug, diphenhydramine, is a known cutting agent for illicitly manufactured drugs. Diphenhydramine can produce hallucinogenic, euphoric, and sedating effects. Studies have shown that repeated use of diphenhydramine will lead to tolerance of the sedating effects. When used for its intended purposes, diphenhydramine is considered a safe drug. As a nonprescription drug, diphenhydramine is widely accessible in sleep and cold preparations and has been cited as a substance that can be misused, frequently by adolescents and young adults.

Background: Diphenhydramine (e.g. Benadryl) is an over-the-counter first generation antihistamine approved for allergy treatment by the United States Food and Drug Administration (FDA) in 1946. Diphenhydramine can also be used for its sedative and antiemetic effects. It acts as an antagonist for the histamine 1 (H1) receptor, reversing the effects of histamine in the body and reducing allergic reactions. Due to its ability to cross the blood brain barrier and antagonize the H1 receptors in the central nervous system (CNS), diphenhydramine can cause drowsiness and suppress the medullary cough center. Diphenhydramine also acts as a competitive antagonist for muscarine acetylcholine receptors and as a sodium channel blocker, and higher doses may lead to cardiotoxic effects. It is metabolized in the liver to desmethyldiphenhydramine and diphenylmethoxyacetic acid.

Diphenhydramine



Recommendations for Clinicians

- Be aware that illicit drugs may contain **diphenhydramine**, which can complicate the clinical presentation.
- Be familiar with the signs and symptoms associated with **diphenhydramine** toxicity.
- Be aware that **diphenhydramine** can cause false positives on drug screens for morphine, methadone, PCP and fentanyl urine dip sticks at high concentrations.

Frequent Indicators of Toxicity and Anticholinergic Syndrome

- Delirium
- Agitation
- Restlessness
- Hallucinations
- Ataxia
- Tremor
- Seizure
- Flushed skin
- Elevated body temp
- Mydriasis
- Blurry vision
- Urinary retention
- Tachycardia

Recommendations for MEs & Coroners

- Conduct testing for **diphenhydramine** in all suspected cases involving drugs.

Recommendations for Forensic and Clinical Laboratories

- Include **diphenhydramine** in the routine scope of testing.
- Develop sensitive confirmatory procedures for common adulterating agents, including **diphenhydramine**.
- Consider laboratory analysis of seized drug samples taken from suspected drug overdose investigations.
- Share data on adulterants in drug seizures in your jurisdiction with local health departments, medical examiners and coroners.

Health Impacts: A 2016 study found diphenhydramine accounted for 3.2% of drug overdoses in the United States and ranked among the top 15 drugs most frequently found in drug overdose deaths. In September 2020, the United States FDA issued a warning related to the dangers associated with ingesting diphenhydramine at doses higher than recommended as it can lead to serious heart problems, seizures, coma and death. Individuals who are experiencing diphenhydramine toxicity will present with general CNS depression and an anticholinergic syndrome, and the toxic effects associated with diphenhydramine are dose related. Diphenhydramine-induced QRS widening and QTc prolongation can be observed on an electrocardiogram at high doses.

Death from diphenhydramine has occurred at concentrations above 5,000 ng/mL. Doses of 300-700 mg of diphenhydramine can result in sedation or coma. When taken with opioids or benzodiazepines, diphenhydramine potentiates their analgesic and sedative effects. Chronic use of diphenhydramine can be difficult to identify, since it has similar symptoms to psychiatric disorders, such as major depression and psychosis, which are most common findings with chronic heavy use. Treatment of diphenhydramine poisoning is largely symptomatic and supportive. Physostigmine is a known antidote, however, there is currently a shortage in supply.

In a study of 92,033 overdose deaths during 2019-2020, 9,645 (10.5%) were positive for diphenhydramine and 2,226 (2.4%) had diphenhydramine listed as a cause of death. Diphenhydramine was rarely found as the sole drug in these cases; instead, it was commonly found with opioids. This combination is dangerous due to the enhanced sedation caused by the combination of opioids and diphenhydramine.

The concern of enhanced overdose potential when mixing diphenhydramine with opioids first came to attention in the U.S. in 2005 when a number of adolescents died from a combination of diphenhydramine or acetaminophen mixed with Mexican brown heroin. More recently in 2019-2020, diphenhydramine was found in the fentanyl supply, and as such, is now more common to see overdose deaths involving diphenhydramine associated with fentanyl than any other opioid.

In addition to heroin and fentanyl, diphenhydramine was also commonly found with other opioids, PCP, cocaine, and methamphetamine in the analysis of seized drug extracts. The percent of drug extracts containing diphenhydramine and origination of these samples can be found in Table 1.

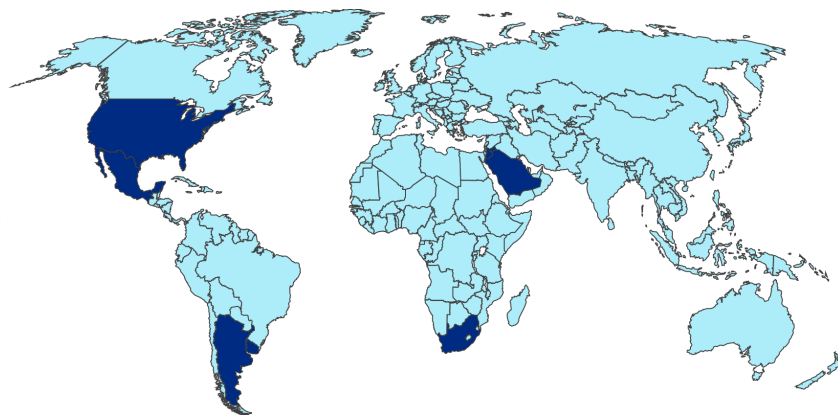


Health Impacts Continued:

Table 1. Frequency diphenhydramine is being detected with other drugs identified in seized drug extracts.

State	% of samples with Diphenhydramine	State	% of samples with Diphenhydramine
West Virginia	23% of fentanyl samples 23% of cocaine samples	Vermont	17% of opioid samples 11% of cocaine samples 22% of methamphetamine samples
Kentucky	42% of opioid samples	Ohio	36% of opioid samples 23% of cocaine samples
Washington DC	30% of PCP samples 30% of fentanyl samples 83% of methamphetamine samples 76% of cocaine samples	Illinois	6% of cocaine samples 74% of opioid samples (Statewide) 90% of opioid samples (Cook County)

Figure 1. Countries reporting diphenhydramine as an adulterant.



In addition to the United States, diphenhydramine has been reported as an adulterant in other countries. Countries including Mexico, Argentina, Uruguay, South Africa, Jordan, Saudi Arabia, and Singapore all have reported diphenhydramine as an adulterant in seized material (Figure 1).

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