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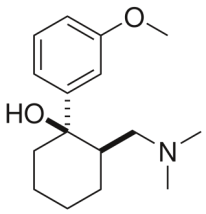
Tramadol: A Toxic Adulterant Found in Illicit Street Drugs.

PUBLIC HEALTH ALERT

Substance abuse treatment providers, clinicians, outreach workers, and public health clinics should be aware of the following information. The prescription drug tramadol is increasingly reported in cases of unintentional and intentional overdoses. Tramadol toxicity can affect multiple organ systems, including the central nervous, cardiovascular, and respiratory systems. In addition to the typical presentation of opioid toxicity, tramadol can also cause seizures. Recently, tramadol has been detected as an adulterant with increasing frequency in seized drug mixtures containing heroin, fentanyl, and methamphetamine. Concomitant use of tramadol with these drugs can increase the risk of serious adverse and sometimes fatal side effects. In a study at Fredric Rieders Family Foundation (FRFF) supported by the Colombo Plan and JMJ Technologies on the presence of toxic adulterants in seized drugs in the United States (n=1,976), tramadol was found in 17.3% percent of the exhibits. Tramadol was most frequently identified in cases from New Hampshire (5.3%), Ohio (2.7%), Vermont (2.5%) and Washington DC (2.1%). Internationally, tramadol has been reported as an adulterant as part of the International Toxic Adulterants Database (ITAD) program in Jordan in synthetic cannabinoid samples in 2020 and in Honduras as an adulterant in cocaine in 2016. Almost half of all countries in Africa have reported non-medical use, seizures or trafficking of tramadol between 2015 to 2019, with most of them located in West, Central and North Africa.

Background: Tramadol is a synthetic opioid analgesic approved in 1995 by the United States Food and Drug Administration (FDA) for moderate to moderately severe pain. Its mechanism of action involves opioid and non-opioid pharmacological activities. Tramadol is a μ-opioid receptor agonist, producing opioid-like effects of analgesia, and respiratory and CNS depression. It also acts as a serotonin and norepinephrine reuptake inhibitor, which can cause excitatory neurological effects. Tramadol is metabolized by CYP2D6 to O-desmethyltramadol, an active metabolite that is more potent and has a longer half-life than the parent drug. Tramadol is approximately equipotent to its structural analog codeine. In 2014, the FDA classified tramadol as a schedule IV controlled substance due to its potential for abuse. Tramadol is available as immediate-release and extended-release tablets. Trade names include ConZip®, Ultram®, Ultracet®, Ryzolt®, and Rybix ODT®.

Tramadol



Recommendations for Clinicians

- Be aware that illicit drugs may contain tramadol, which can complicate the clinical presentation.
- Be familiar with the signs and symptoms associated with tramadol toxicity.
- Be aware that routine hospital drug tests will not disclose the presence of tramadol, which requires a special test.

Frequent Indicators of Toxicity

- Agitation
- Tachycardia
- Hypertension
- Headache
- Itching and rash
- GI irritation
- Nausea
- Vomiting
- Sedation
- CNS depression
- Dizziness
- Seizure

Recommendations for MEs & Coroners

- Conduct testing for tramadol in suspected stimulant or opioid-related fatalities.

Recommendations for Forensic and Clinical Laboratories

- Include tramadol in routine the scope of testing.
- Develop sensitive confirmatory procedures for common adulterating agents, including tramadol.
- 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: Tramadol use has been associated with a greater risk for hypoglycemia. Overdose of tramadol can cause tachycardia, hypertension, and agitation. Coma and respiratory depression have been associated with tramadol doses exceeding 800 mg. Fatalities involving tramadol were reported at higher doses in individuals with concentrations 1.3 and 2.7 mg/L in blood.

Polysubstance use can increase the risk of adverse outcomes. Concomitant use of tramadol with opioids, benzodiazepines, or other CNS depressants can result in deep sedation, respiratory depression, coma, and death. Serotonin syndrome, a potentially life-threatening condition, can occur due to ingestion of large doses of tramadol or in combination with other serotonergic drugs, including antidepressants, antipsychotics, methamphetamine, and fentanyl. Serotonin syndrome may present as an altered mental status, tachycardia, hyperthermia, and neuromuscular hyperactivity. Additionally, and unrelated to serotonin syndrome, individuals exposed to even high therapeutic doses of tramadol may be at increased risk for seizures, especially in individuals with a history of tramadol abuse, chronic tramadol users, or illicit drug users ingesting products adulterated with tramadol. A study of people who recreationally used tramadol found that 54.4% of these individuals had experienced at least one seizure within the three-year study period. Naloxone can reverse the opioid effects, but may increase the risk of seizure, which can be treated with benzodiazepines.

Health providers should be aware of the typical indicators of opioid intoxication as well as seizures and serotonin syndrome when evaluating cases of potential tramadol toxicity or overdose.

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Tramadol Toxicity – Diagnosis and Treatment

Signs & Symptoms of Toxicity or Overdose

Physical	Behavioral
Nausea Vomiting Itchiness Hypotension Bradycardia or tachycardia Respiratory depression Miosis Hypoglycemia Sedation/unconsciousness Seizure Serotonin Syndrome*	Confusion/delirium Euphoria Anxiety Agitation Restlessness

Provider Response

Physical	Behavioral
Maintain adequate ventilation Administer benzodiazepines for the treatment of seizures and serotonin syndrome Administer glucose for hypoglycemia Administer naloxone to reverse respiratory depression	Provide supportive care Administer benzodiazepines for anxiety/agitation

Further Treatment Needed?

Further treatment is rarely required. Serotonin Syndrome is a medical emergency and requires specialized care. Providers should be aware that abstinence or the administration of naloxone can result in opioid withdrawal.

*Serotonin Syndrome, often related to drug-drug interactions, results from the accumulation of serotonin in the body. Symptoms can range from shivering and diarrhea to hyperthermia, fever, muscle rigidity and seizures.

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