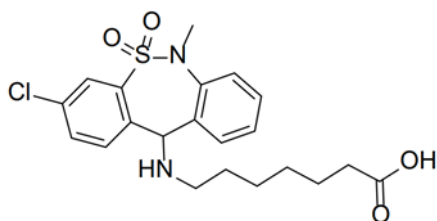


**This notice is to alert substance abuse treatment providers, clinicians, public health agencies and testing labs that Tianeptine, an unapproved atypical antidepressant with opioid activity at higher doses, has been reported for sale in US gas stations and convenience stores, especially throughout the southeast United States. It has the potential to cause adverse opioid-like effects and has been linked to intoxication, overdoses, and death.**

**Background:** Tianeptine, popularly known as “gas station heroin” has been encountered in various forms including bulk powder and counterfeit pills mimicking hydrocodone and oxycodone. Tianeptine has been sold as “ZaZa”, “Tiana”, “Neptune’s Fix” and other brand names. Poison Control Center cases involving tianeptine exposure increased nationwide, from 11 total cases between 2000 and 2013 to 151 cases in 2020. As an antidepressant, tianeptine is prescribed to treat depression and anxiety in some European, Asian, and South American countries, but it is not approved for medical use in the United States. Tianeptine-containing products are marketed as dietary supplements or as “smart drugs” that allegedly enhance cognitive function. Tianeptine induces euphoria at high doses via activation of mu-opioid and dopaminergic receptors. It is also alleged to be useful to manage opioid consumption, with claims that it reduces the effects of opioid withdrawal and craving. Unregulated tianeptine is at an increased risk of contamination with adulterants, which may cause additional or unexpected side effects. Tianeptine is not currently controlled under the Controlled Substances Act, but has been scheduled in several states.

## Tianeptine



### Recommendations for Clinicians

- Since tianeptine activates opioid receptors, know that naloxone should be used in the acute management of tianeptine overdose with the conventional indication of respiratory depression.
- Be familiar with the signs and symptoms associated with **tianeptine** toxicity and withdrawal.
- Report adverse events to the FDA.

### Indicators of Toxicity

#### Effects mimicking opioid toxicity

- Respiratory depression
- Sedation
- Loss of consciousness
- Coma

#### Withdrawal effects

- Agitation
- Nausea
- Vomiting
- Tachycardia
- Hypertension
- Diarrhea
- Tremor
- Diaphoresis

### Recommendations for MEs & Coroners

- Consider testing for **tianeptine** when products suspicious for containing tianeptine are located at the scene, internet browsing history shows searches for tianeptine and/or analysis of seized drug evidence confirms its presence. Be alert for ZaZa, Tianna Red and other apparent supplement products at death scenes.

### Recommendations for Forensic and Clinical Laboratories

- Consider toxicology testing for **tianeptine** when case history supports its use.
- Consider laboratory analysis of seized drug material or commercial products purported to contain **Tianeptine**.
- Share data with local health departments, medical examiners and coroners.

### Health Impacts:

- Tianeptine use carries a risk of misuse, dependence, tolerance, and overdose. A concentration of 15.5 mg/L was reported in a complex suicide case, and a concentration of 5.1 mg/L along with an ethanol concentration of 0.51 g/100mL in another fatality. Toxicological analysis has detected tianeptine in human performance impairment (e.g., intoxication, DUI/D) cases. In three cases submitted by Pennsylvania law enforcement for investigation of driving under the influence of drugs, tianeptine blood concentrations were found to range between 0.50 and 2.9 mg/L. The results of comprehensive toxicology testing performed on these cases are shown below.

**Drug results in three human performance impairment cases where comprehensive toxicology testing was performed.**

#### Case 1

Amphetamine: 170 ng/mL  
Methamphetamine: 380 ng/mL  
Mitragnine: 11 ng/mL  
**Tianeptine: 1600 ng/mL**

#### Case 2

O-desmethylvenlafaxine: 64 ng/mL  
**Tianeptine: 2900 ng/mL**

#### Case 3

**Tianeptine: 570 ng/mL**

### Health Impacts Continued:

Tianeptine misuse has been associated with psychosis in supratherapeutic doses, particularly in individuals with a history of substance abuse or psychotic disorders. In one report, the authors describe a 28-year-old woman with a history of schizoaffective disorder, bipolar type, and polysubstance use who was admitted to inpatient psychiatry for aggressive behavior. She had also been experiencing somatic delusions with disorganized behavior and speech at the time of admission. Her symptoms were previously controlled with monthly long-acting paliperidone. During her admission, the patient reported procuring tianeptine from the Internet and friends to control her anxiety and depression, taking around 100 mg daily. The psychosis reportedly resolved after 2 days of abstinence.

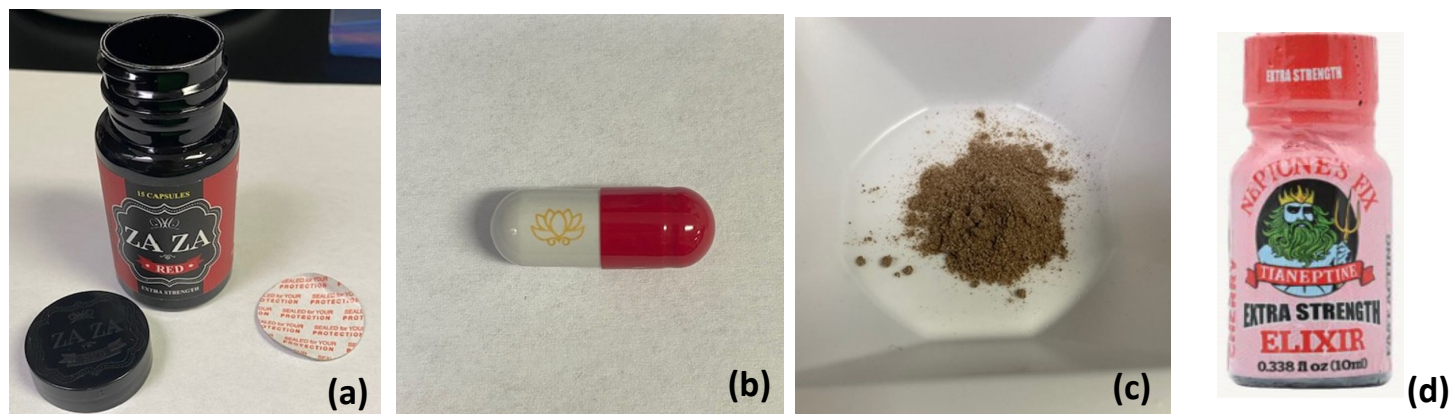
Intentional ingestion of tianeptine as part of a successful suicide attempt has also been reported. In one case, a 26-year-old man was found dead in his apartment next to multiple packets of 12.5-mg tianeptine tablets. A suicide note confirmed the ingestion to be intentional. Analytical testing revealed elevated tianeptine concentrations in the blood, urine, liver, and stomach. The cause of death was attributed to suicidal ingestion of tianeptine in combination with alcohol consumption (serum ethanol concentration: 53 mg/dL).

From 2018 to 2023 tianeptine was detected and quantified in 90 blood samples collected for death investigation purposes. In these cases, tianeptine blood concentrations ranged from 5.0 ng/mL to 47,000 ng/mL (mean: 3,841 ng/mL; median: 1,750 ng/mL). Other substances commonly co-detected in this population included amphetamine, fentanyl, gabapentin, mitragynine, and ethanol.

### Analysis of Tianeptine Containing Exhibits Samples

- An authentic sample of ZAZA was acquired from North Carolina. Labelling on the bottle indicates that the product contains *combretum quadrangulare leaf*, tianeptine and piper methysticum, also known as **Kava**. The contents of the capsule were analyzed at CFSRE via gas chromatography mass spectrometry (GC/MS) and liquid chromatography high resolution mass spectrometry (LC/QTOF-MS). Samples were diluted in solvent or mobile phase prior to analysis.
- Analysis of the product by GC/MS identified a peak consistent with a breakdown product of tianeptine. Results from the LC/QTOF-MS analysis identified tianeptine and the sedative natural product **kavain**, known to be present in the piper methysticum (kava) plant. Interactions between drugs with opioid effects and CNS depressant effects can be significant. In addition, more than 100 cases of liver toxicity related to the use of kava had been reported, some leading to liver transplant and some leading to death.
- The same methodologies were used by CFSRE to test another product labelled “Neptune’s Fix”, a flavored elixir shot associated with a series of severe clinical effects in New Jersey. The product was identified as being available at gas stations and online, and bottles were marked as containing kavain and tianeptine. Patients were described as having altered mental status, tachycardia, hypotension, seizure, and various heart rhythm changes that increase the risk of ventricular arrhythmia. In addition to tianeptine and kavain, some bottles tested positive for the synthetic cannabinoids MDMB-4en-PINACA, and ADB-4en-PINACA. More details were reported recently in the CDC’s [Morbidity and Mortality Weekly Reports \(MMWR\)](#).

**Figure 1.** Images of (a) authentic ZAZA sample obtained from a convenience store in North Carolina; (b) intact capsule and; (c) contents from the capsule once broken open, and (d) Neptune’s Fix bottle.





### **Evaluation of Seized Drug Samples from North Carolina Investigations**

- A total of 59 random seized illicit drug samples from North Carolina were obtained and analyzed to evaluate the potential presence of tianeptine as an adulterant in the illicit drug supply. Twelve (20%) of the samples contained fentanyl, 16 (27%) were positive for cocaine, and 18 (30%) were positive for methamphetamine. Only one sample contained all three of those drugs in a mixture along with other opioids and/or adulterants. A majority of the fentanyl samples were highly lethal. Of the twelve fentanyl samples, seven (58%) contained 2 or more fentanyl compounds. None of these samples however contained tianeptine, suggesting that it is currently present in specific products (see below), and not mixed in with the general drug supply in North Carolina. This, however, should continue to be monitored.
- In the North Carolina samples, 67% of the cases containing fentanyl also contained [xylazine](#). Xylazine is a veterinary tranquilizer known to increase the sedative effects of fentanyl. These samples also contained varying amounts of other active drugs including opioids such as tramadol and heroin, and stimulants including cocaine and methamphetamine that if present in sufficient quantities could enhance the effects on the user and add to the potential lethality of the mixture.
- One North Carolina sample consisted of a combination of two designer benzodiazepines, flualprazolam and [clonazepam](#), the latter posing higher risk than other designer benzodiazepines due to its ability to produce strong sedation and benzodiazepine intoxication at doses higher than 0.5 mg. Note: naloxone is not an antagonist for benzodiazepines.

### **References and Related Articles:**

- Ari M, Oktar S, Duru M. Amitriptyline and tianeptine poisoning treated by naloxone. *Hum Exp Toxicol*. 2010 Sep;29(9):793-5. doi: 10.1177/0960327110372403. Epub 2010 May 24. Erratum in: *Hum Exp Toxicol*. 2010 Sep;29(9):797. PMID: 20498036.
- Bakota EL, Samms WC, Gray TR, Oleske DA, Hines MO. Case Reports of Fatalities Involving Tianeptine in the United States. *J Anal Toxicol*. 2018 Sep 1;42(7):503-509. doi: 10.1093/jat/bky023. Erratum in: *J Anal Toxicol*. 2019 Mar 1;43(2):e1. PMID: 29566235.
- Edinoff AN, Sall S, Beckman SP, Koepnick AD, Gold LC, Jackson ED, Wenger DM, Cornett EM, Murnane KS, Kaye AM, Kaye AD. Tianeptine, an Antidepressant with Opioid Agonist Effects: Pharmacology and Abuse Potential, a Narrative Review. *Pain Ther*. 2023 Oct;12(5):1121-1134. doi: 10.1007/s40122-023-00539-5. Epub 2023 Jul 15. PMID: 37453966; PMCID: PMC10444703.
- Mohr ALA, Logan BK, Fogarty MF, Krotulski AJ, Papsun DM, Kacinko SL, Huestis MA, Roper-Miller JD. Reports of Adverse Events Associated with Use of Novel Psychoactive Substances, 2017-2020: A Review. *J Anal Toxicol*. 2022 Jul 14;46(6):e116-e185. doi: 10.1093/jat/bkac023. PMID: 35445267; PMCID: PMC9282356.
- Counts CJ, Spadaro AV, Cerbini TA, et al. Notes from the Field: Cluster of Severe Illness from Neptune's Fix Tianeptine Linked to Synthetic Cannabinoids — New Jersey, June–November 2023. *MMWR Morb Mortal Wkly Rep* 2024;73:89–90.
- Proença P, Teixeira H, Pinheiro J, Monsanto PV, Vieira DN. Fatal intoxication with tianeptine (Stablon). *Forensic Sci Int*. 2007 Aug 6;170(2-3):200-3. doi: 10.1016/j.forsciint.2007.03.035. Epub 2007 Jul 13. PMID: 17630235.
- Smith KE, Rogers JM, Strickland JC, Epstein DH. When an obscurity becomes trend: social-media descriptions of tianeptine use and associated atypical drug use. *Am J Drug Alcohol Abuse*. 2021 Jul 4;47(4):455-466. doi: 10.1080/00952990.2021.1904408. Epub 2021 Apr 28. PMID: 33909525; PMCID: PMC8380661.
- Wagner ML, Pergolizzi J Jr, LeQuang JAK, Breve F, Varrassi G. From Antidepressant Tianeptine to Street Drug ZaZa: A Narrative Review. *Cureus*. 2023 Jun 20;15(6):e40688. doi: 10.7759/cureus.40688. PMID: 37485121; PMCID: PMC10359047.
- Huppertz LM, Bisel P, Westphal F, et al. (July 2015). "Characterization of the four designer benzodiazepines clonazepam, deschloroetizolam, flubromazolam, and meclonazepam, and identification of their in vitro metabolites". *Forensic Toxicology*. 33 (2): 388–395
- [DEA: Tianeptine \(usdoj.gov\)](#)
- [Tianeptine in Dietary Supplements | FDA](#)
- [Ask the Doctors: What are the Risks and Benefits of Kava: UCLA Health, 2018](#)

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