



EMERGENCY MEETING NOTICE

December 21, 2022 - 8:00 a.m.

LOCATION:

This meeting is being convened telephonically at 8:00 a.m.

Dial-in Number: 614-721-2972 | Conference ID: 379386589#

PURPOSE:

The State of Ohio Board of Pharmacy (Board), pursuant to section 3719.45 of the Ohio Revised Code, proposes the placement of the tianeptine into Schedule I by emergency rule 4729:9-1-01.3.

Pursuant to section 3719.45 of the Ohio Revised Code, the Board, by emergency rule adopted in accordance with division (G) of section 119.03 of the Revised Code, shall add a previously unscheduled compound, mixture, preparation, or substance to schedule I if the Board determines that the compound, mixture, preparation, or substance has no accepted medical use in treatment in this state and poses an imminent hazard to the public health, safety, or welfare.

In determining whether a previously unscheduled compound, mixture, preparation, or substance poses an imminent hazard to the public health, safety, or welfare, the Board shall consider all of the following with respect to the compound, mixture, preparation, or substance:

- (1) Its actual or relative potential for abuse;
- (2) The scope, duration, and significance of that abuse;
- (3) The risk it poses to the public health.

PROPOSED EMERGENCY RULE:

4729:9-1-01.3 – Tianeptine

Pursuant to section 3719.45 of the Revised Code, the state board of pharmacy hereby classifies as a schedule I opiate or opiate derivative any material, compound, mixture, or preparation that contains tianeptine.

77 South High Street, 17th Floor, Columbus, Ohio 43215

T: (614) 466.4143 | F: (614) 752.4836 | contact@pharmacy.ohio.gov | www.pharmacy.ohio.gov





Emergency Scheduling: Temporary Placement of Tianeptine in Schedule I

Section 1: Summary

The State of Ohio Board of Pharmacy (Board), pursuant to section 3719.45 of the Ohio Revised Code, proposes the placement of the tianeptine into Schedule I by emergency rule.

Section 2: Background

Pursuant to section 3719.45 of the Ohio Revised Code, the Board, by emergency rule adopted in accordance with division (G) of section 119.03 of the Revised Code, shall add a previously unscheduled compound, mixture, preparation, or substance to Schedule I if the Board determines that the compound, mixture, preparation, or substance has no accepted medical use in treatment in this state and poses an imminent hazard to the public health, safety, or welfare.

In determining whether a previously unscheduled compound, mixture, preparation, or substance poses an imminent hazard to the public health, safety, or welfare, the Board shall consider all of the following with respect to the compound, mixture, preparation, or substance:

- (1) Its actual or relative potential for abuse;
- (2) The scope, duration, and significance of that abuse;
- (3) The risk it poses to the public health.

Section 3: Evaluation Under the Emergency Scheduling Criteria

(1) The actual or relative potential for abuse.

Tianeptine is an atypical tricyclic antidepressant that is not approved by the U.S. Food and Drug Administration (FDA). The drug (marketed as Coaxil or Stablon) is approved for use



in Europe, Asia, and Latin America.ⁱ In the U.S., tianeptine is known as ZaZa and Tianna Red by some users, who can find it readily available in gas stations, convenience stores, and online.ⁱⁱ

Clinical effects of tianeptine abuse can mimic opioid toxicity and withdrawal due to its strong affinity at the mu-opioid receptors and through increases in extracellular dopamine concentrations throughout cerebral tissue.^{iii iv v vi vii} One study examining the effect of the compound on rats, found that tianeptine produces mu-opioid receptor agonist-like acute adverse effects that include motor impairment, constipation, and respiratory depression.^{viii}

A medical literature review conducted in 2017, found 18 cases of individuals experiencing tianeptine misuse, dependence, and abuse. The review found higher frequency of tianeptine abuse/dependence was observed in women and 30- to 45-year-olds. Most cases ($n = 13$) reported a previous history of substance abuse. The therapeutic dose of tianeptine was exceeded 110-fold (i.e., up to 4125 mg/day) with a mean of about 1469 mg/day. The most prominent phenomena associated with tianeptine abuse and dependence were marked euphoria and withdrawal symptoms perpetuating further drug misuse.^{ix}

A similar review conducted in 2018, resulted in 25 articles that contained references to tianeptine abuse” and “tianeptine dependence” among a total of 65 patients. A majority of patients were male, and age ranged from 19 to 67. Routes of intake included oral, intravenous, and insufflation. In the 15 cases of overdose, 8 combined ingestion with at least one other substance, of which 3 resulted in death. Six additional deaths are reported involving tianeptine (9 total).^x

Specific case reports also demonstrate the abuse potential of tianeptine. A report from 2017 documents the case of a 36-year-old man with a history of major depressive disorder, responsive to sertraline, who turned to the unmonitored use of tianeptine purchased online to treat residual feelings of apathy and boredom. His use of tianeptine was marked by rapidly escalating doses and a significant withdrawal syndrome that made discontinuation of this substance difficult. The authors of the report stated specifically, “this case serves as a reminder that unscheduled pharmaceutical agents are available for misuse by the general population and have the potential to cause significant harm.”^{xi}

According to the U.S. Centers for Disease Control and Prevention (CDC), case reports demonstrate that tianeptine toxicity mimicked opioid toxicity and that naloxone was an effective therapy.^{xii} Tolerance to tianeptine and withdrawal have been reported.^{xiii} Neonatal abstinence syndrome mimicking opioid neonatal abstinence syndrome has occurred after tianeptine dependence during pregnancy.^{xiv}

(2) The scope, duration, and significance of abuse.

To characterize tianeptine exposures in the United States, CDC analyzed all exposure calls related to tianeptine reported by poison control centers to the National Poison Data System (NPDS) from 2000 to 2017. CDC found that tianeptine exposure calls, including those for intentional abuse or misuse, increased across the United States during 2014–2017. Most tianeptine exposures occurred among persons aged 21–40 years and resulted in moderate outcomes. Neurologic, cardiovascular, and gastrointestinal signs and symptoms were the most commonly reported health effects, with some effects mimicking opioid toxicity. A substantial number of tianeptine exposure calls also reported clinical effects of withdrawal. Among 83 tianeptine exposures with noted coexposures, the most commonly reported coexposures were to phenibut, ethanol, benzodiazepines, and opioids.^{xv}

From 2000 to 2017, NPDS received 218 calls related to tianeptine exposure, including one from outside the United States. Tianeptine-only exposures, excluding 29 withdrawal-associated calls, accounted for 114 (52.3%) calls. During the first 14 years of the study period (2000–2013), NPDS received a total of 11 tianeptine exposure calls. From 2014 through 2017, there was a statistically significant increase in calls related to exposure ($p < 0.001$) and intentional abuse or misuse ($p < 0.001$). The total number of tianeptine exposure calls increased from five in 2014 to 38 in 2015, 83 in 2016, and 81 in 2017.^{xvi}



A similar review conducted by Alabama’s poison control centers found an increase in tianeptine toxicity beginning in May 2019. The review found eighty-four cases of atypical tricyclic antidepressants were identified in the study period. Forty-eight cases involving tianeptine met inclusion criteria and were reviewed. Of these, 37 (77%) occurred from

May 2019 to March 2020. Twenty-seven (56%) required medical admission including 17 cases (35%) that were managed in an intensive care unit. Seventeen of the 48 cases resulted from acute tianeptine intoxication. Lethargy was the most common presentation, but some patients also presented with agitation. Thirty-one (65%) of the cases resulted from tianeptine withdrawal, which usually exhibited agitation, anxiety, gastrointestinal distress. Naloxone was used in 4 cases (24%) of the acute intoxication cohort and benzodiazepines were frequently used both in acutely intoxicated patients and in patients experiencing tianeptine withdrawal.^{xvii}

While the drug is approved for use in other countries, many countries have banned or withdrawn this medication from the market. In the country of Georgia, the health authority withdrew tianeptine from the market in June 2010, and the health authorities of Russia and Armenia classified tianeptine as a controlled substance in July 2010.^{xviii} Similar measures were implemented in Ukraine in January 2011. On March 13, 2020, Italy became the first European country to ban tianeptine considering it a Class I controlled substance.^{xix}

Although tianeptine is not approved for use by the FDA, it is readily available for purchase as a dietary supplement or research chemical. Several online discussion forums among users describe the euphoregenic effects of tianeptine. In a 2018 Morbidity and Mortality Weekly Report from CDC, the authors conclude that "...in light of the ongoing U.S. opioid epidemic, any emerging trends in drugs with opioid-like effects raise concerns about potential abuse and public health safety." ^{xx} Currently, the drug is banned or restricted in Michigan, Alabama, Minnesota, Tennessee, Georgia, and Indiana.^{xxi}

It should be noted that there is also a robust online presence ([r/Quittingtianeptine](#)) dedicated to helping individuals quit tianeptine that has 3,870 members. Members of the forum provide information on the negative impacts of the use of this drug:

- *Always available here...5 year habit. Heavy pure sodium user. Almost lost everything. Quit several times only to return. Kicked for good now and slowly putting pieces back together. Praying for anyone trying to get their life back. No matter how big or small your habit is, I know the struggle...^{xxii}*
- *I had been out roughly 3 months when I got into a bad motorcycle accident that demolished my left arm. I had to have surgery in which I went through with no pain medication. Post op was so painful that one day I asked a friend to go pick me up a little kratom just to take the edge off. He came back with ZAZA... he said the guy told him it was just like kratom but a little stronger. It worked amazing for pain relief, plus I loved the way it made me feel. Within 3 months I was up to 3-4 bottles a day. About a month ago I found you guys on reddit and have been desperately searching for a way out...^{xxiii}*

- *Granted it took a 4 day hospital stay due to psychosis and hallucinations. That shit is no joke and I'll never be touching [SIC] it again. If you're trying to quit or have quit keep going ! It's not worth it ! I still feel like shit but each day should get better. Any tip from here out would be appreciated!^{xxiv}*
- *Hey everyone, just wanted to share my experience with this shit drug since this sub has been helping me stay hopeful. 72 hours in with no Tia and still feeling like shit, however I feel like I'm through the thick of the physical symptoms. I'm so thankful I got through that 24-48 hour period, I felt like I was going to die. I started using gas station "Pegasus" capsules about a month ago. Started with a few capsules a day, to one bottle a day in three weeks. The withdrawals consisted of full body RLS, intense sweating, chills, insomnia, muscle and joint aching, insane depression, and worst of all this horrid feeling of building, extremely sharp anxiety in my chest that made me feel like I was going to explode if I didn't move around excessively. Thankfully most of these have subsided greatly. I'm using clonidine and weed, which are helpful to some degree, however they were practically ineffective for the first 24 hours. Anyways, I'm just glad I'm starting to feel better slowly but surely, and hopefully this inspires somebody to quit or to never pick up this shit drug, trust me it's not worth it.^{xxv}*
- *I began taking zaza silvers about 2 weeks ago. Currently I am taking almost a whole bottle (15c) per day. The thing is I'm sick as a dog. I want to stop taking these but I get so sick without them. I can't use the restroom (#1/#2) for the last 2 days & my stomach is protruding at the top. It looks like im [SIC] pregnant but its high in my abdomen. I'm vomiting 2x or more every day. I want to eat but can't because I feel like a balloon & my head is pounding. I've been tracking my temp the last 2 days & it's rising daily. I am having involuntary movements in my hands. Ill [SIC] be holding things & just drop them out of nowhere. I have 4 children who need me. How can I get off this hellish drug?^{xxvi}*
- *Thank you all for sharing your stories. I have been going through a hard time in life, like many of you, and I was looking for something else to help me escape. A few people on another Reddit page started talking about how Great of a high this stuff gives, but you had to be extremely careful. Hearing that I thought I would check out the "dark side" of Tianeptine. This stuff sounds like the greatest and worst thing in the world combined. I've been through WD of all kinds, and multiple substances at once CT. I feel for anyone going through it right now. Sounds like this stuff takes the cake. Im [SIC] staying far away.*

I don't have the self control to take it responsibly. Glad I read some of these threads I literally had it in my cart ready to check out.^{xxvii}

(3) The risk to the public health.

The availability of an unregulated, tricyclic antidepressant without any medical supervision presents a serious risk to public health. Media reports indicate that patients are utilizing tianeptine to either manage withdrawal or initiating use based upon the reported opioid-like effects.^{xxviii} Additionally, reports indicate that such unregulated access leads patients to consuming tianeptine at doses higher than the doses prescribed in the countries where the drug has been approved.^{xxix} Further, the compound is not subject to the same FDA regulatory scheme – including inspections of manufacturing facilities, quality assurance testing, and adverse event monitoring – as other tricyclic antidepressants approved for use in the United States.

According to CDC, case reports demonstrate that tianeptine toxicity mimicked opioid toxicity and that naloxone was an effective therapy.^{xxx} Tolerance to tianeptine and withdrawal have been reported.^{xxxi} Neonatal abstinence syndrome mimicking opioid neonatal abstinence syndrome has occurred after tianeptine dependence during pregnancy.^{xxxii}

A study of internet web postings found that individuals were reporting increased adverse events associated with tianeptine use. Between 2014 and 2020, mentions of positive effects decreased, while mentions of adverse effects and withdrawal increased. Motivations for use included substitution or withdrawal mitigation for other drugs (especially opioids); self-treatment for psychiatric symptoms; and improvement of quality of life, mood, or performance. Descriptions of tolerance, withdrawal, and addiction were evident. Intravenous use was rare and strongly discouraged, with detrimental effects described.^{xxxiii}

Although tianeptine is not approved for use by the FDA, it is readily available for purchase as a dietary supplement or research chemical. Several online discussion forums among users describe the euphoric effects of tianeptine. In a 2018 Morbidity and Mortality Weekly Report from CDC, the authors conclude that “in light of the ongoing U.S. opioid epidemic, any emerging trends in drugs with opioid-like effects raise concerns about potential abuse and public health safety.”^{xxxiv} Currently, the drug is banned or restricted in Michigan, Alabama, Minnesota, Tennessee, Georgia, and Indiana.^{xxxv}

In February 2022, the FDA issued a consumer update on tianeptine products linked to serious harm, overdoses, and death. In the alert, the agency notes that it has identified cases in which people experienced other serious harmful effects from abusing or misusing

tianeptine by itself or with other drugs, including antidepressants and anti-anxiety medicines. These effects included agitation, drowsiness, confusion, sweating, rapid heartbeat, high blood pressure, nausea, vomiting, slowed or stopped breathing, coma, and death.^{xxxvi}

Section 4: Finding of the Board

Section 3719.45 of the Ohio Revised Codes authorizes the State of Ohio Board of Pharmacy, by emergency rule adopted in accordance with division (G) of section 119.03 of the Revised Code, to add a previously unscheduled compound, mixture, preparation, or substance to Schedule I if the Board determines that the compound, mixture, preparation, or substance has no accepted medical use in treatment in this state and poses an imminent hazard to the public health, safety, or welfare.

After a review of all available data, the Board finds tianeptine has no accepted medical use in treatment in this state and poses an imminent hazard to the public health, safety, or welfare.

Based on these findings, the Board hereby issues a resolution requesting the Governor to issue an order pursuant to division (G) of section 119.03 of the Revised Code to file emergency rule 4729:9-1-01.3 of the Administrative Code.

Section 5: Proposed Rule

4729:9-1-01.3 – Tianeptine

Pursuant to section 3719.45 of the Revised Code, the state board of pharmacy hereby classifies as a schedule I opiate or opiate derivative any material, compound, mixture, or preparation that contains tianeptine.

Endnotes

- ⁱ El Zahran T, Schier J, Glidden E, et al. Characteristics of Tianeptine Exposures Reported to the National Poison Data System — United States, 2000–2017. *MMWR Morb Mortal Wkly Rep* 2018;67:815–818. DOI: <http://dx.doi.org/10.15585/mmwr.mm6730a2>.
- ⁱⁱ <https://www.uab.edu/reporter/outreach/uab-in-the-community/item/9574-toxicologist-unravels-the-dangerous-medical-mystery-of-zaza-alabama-s-gas-station-dope>
- ⁱⁱⁱ Characteristics of Tianeptine Exposures Reported to the National Poison Data System — United States, 2000–2017.
- ^{iv} Brink CB, Harvey BH, Brand L. Tianeptine: a novel atypical antidepressant that may provide new insights into the biomolecular basis of depression. *Recent Pat CNS Drug Discov.* 2006;1(1):29–41.
- ^v Sacchetti G, Bonini I, Waeterloos GC, et al. Tianeptine raises dopamine and blocks stress-induced noradrenaline release in the rat frontal cortex. *Eur J Pharmacol.* 1993;236(2):171–175.
- ^{vi} Samuels, B., Nautiyal, K., Kruegel, A. et al. The Behavioral Effects of the Antidepressant Tianeptine Require the Mu-Opioid Receptor. *Neuropsychopharmacol* 42, 2052–2063 (2017). <https://doi.org/10.1038/npp.2017.60>
- ^{vii} Gassaway MM, Rives ML, Kruegel AC, Javitch JA, Sames D. The atypical antidepressant and neurorestorative agent tianeptine is a μ -opioid receptor agonist. *Transl Psychiatry.* 2014 Jul 15;4(7):e411. doi: 10.1038/tp.2014.30. PMID: 25026323; PMCID: PMC4119213.
- ^{viii} Baird, T.R., Akbarali, H.I., Dewey, W.L. et al. Opioid-like adverse effects of tianeptine in male rats and mice. *Psychopharmacology* 239, 2187–2199 (2022). <https://doi.org/10.1007/s00213-022-06093-w>
- ^{ix} Janusz Springer & Wiesław Jerzy Cufała (2018) Tianeptine Abuse and Dependence in Psychiatric Patients: A Review of 18 Case Reports in the Literature, *Journal of Psychoactive Drugs*, 50:3, 275-280, DOI: 10.1080/02791072.2018.1438687
- ^x Rahul Lauhan, Alan Hsu, Al Alam, Kristin Beizai, Tianeptine Abuse and Dependence: Case Report and Literature Review, *Psychosomatics*, Volume 59, Issue 6, 2018, Pages 547-553, ISSN 0033-3182, <https://doi.org/10.1016/j.psym.2018.07.006>.
- ^{xi} Gupta S, Wallace R, Slosower J. Online Sales of Unscheduled Pharmaceutical Agents: A Case Report of Tianeptine Use in the United States. *J Addict Med.* 2017 Sep/Oct;11(5):411-412. doi: 10.1097/ADM.0000000000000342. PMID: 28742625.
- ^{xii} Dempsey SK, Poklis JL, Sweat K, Cumpston K, Wolf CE. Acute Toxicity From Intravenous Use of the Tricyclic Antidepressant Tianeptine. *J Anal Toxicol.* 2017 Jul 1;41(6):547-550. doi: 10.1093/jat/bkx034. PMID: 28541419; PMCID: PMC6075028.
- ^{xiii} Kisa C, Bulbul DO, Aydemir C, Goka E. Is it possible to be dependent to Tianeptine, an antidepressant? A case report. *Prog Neuropsychopharmacol Biol Psychiatry.* 2007 Apr 13;31(3):776-8. doi: 10.1016/j.pnpbp.2007.01.002. Epub 2007 Jan 16. PMID: 17270334.
- ^{xiv} Bence C, Bonord A, Rebillard C, Vaast P, Alexandre C, Jardri R, Rolland B. Neonatal Abstinence Syndrome Following Tianeptine Dependence During Pregnancy. *Pediatrics.* 2016 Jan;137(1). doi: 10.1542/peds.2015-1414. Epub 2015 Dec 11. PMID: 26659818.
- ^{xv} El Zahran T, Schier J, Glidden E, et al. Characteristics of Tianeptine Exposures Reported to the National Poison Data System — United States, 2000–2017. *MMWR Morb Mortal Wkly Rep* 2018;67:815–818. DOI: <http://dx.doi.org/10.15585/mmwr.mm6730a2>
- ^{xvi} El Zahran T, Schier J, Glidden E, et al. Characteristics of Tianeptine Exposures Reported to the National Poison Data System — United States, 2000–2017. *MMWR Morb Mortal Wkly Rep* 2018;67:815–818. DOI: <http://dx.doi.org/10.15585/mmwr.mm6730a2>
- ^{xvii} William Rushton, Brian Whitworth, Julie Brown, Michael Kurz & Jessica Rivera (2021) Characteristics of tianeptine effects reported to a poison control center: a growing threat to public health, *Clinical Toxicology*, 59:2, 152-157, DOI: 10.1080/15563650.2020.1781151
- ^{xviii} Durmus N, Ozbilen G, Kasap Y, et al. Risk management in tianeptine abuse in Turkey: a national experience. *Bulletin of Clinical Psychopharmacology* 2013;23:149–54.
- ^{xix} <https://www.gazzettaufficiale.it/eli/id/2020/03/30/20A01820/sg>
- ^{xx} El Zahran T, Schier J, Glidden E, et al. Characteristics of Tianeptine Exposures Reported to the National Poison Data System — United States, 2000–2017. *MMWR Morb Mortal Wkly Rep* 2018;67:815–818. DOI: <http://dx.doi.org/10.15585/mmwr.mm6730a2>.
- ^{xxi} <https://www.vice.com/en/article/88q3va/tianeptine-gas-station-heroin-legal-in-most-states>
- ^{xxii} https://www.reddit.com/r/QuittingTianeptine/comments/zl17c5/if_you_feel_alone_with_no_support/
- ^{xxiii} https://www.reddit.com/r/QuittingTianeptine/comments/z3vc7y/desperate_for_change/

-
- xxiv https://www.reddit.com/r/QuittingTianeptine/comments/zh4la6/15_days_off_zaza_silver/
- xxv https://www.reddit.com/r/QuittingTianeptine/comments/zapwty/72hrs_clean_hopeful_but_struggling/
- xxvi https://www.reddit.com/r/QuittingTianeptine/comments/z7gopv/just_started_taking_tianeptine_something_is_wrong/
- xxvii https://www.reddit.com/r/QuittingTianeptine/comments/znm664/i_was_about_to_order_some_tianeptine_until_i/
- xxviii <https://www.vice.com/en/article/88q3va/tianeptine-gas-station-heroin-legal-in-most-states>
- xxix <https://www.fda.gov/consumers/consumer-updates/tianeptine-products-linked-serious-harm-overdoses-death>
- xxx Dempsey SK, Poklis JL, Sweat K, Cumpston K, Wolf CE. Acute Toxicity From Intravenous Use of the Tricyclic Antidepressant Tianeptine. *J Anal Toxicol*. 2017 Jul 1;41(6):547-550. doi: 10.1093/jat/bkx034. PMID: 28541419; PMCID: PMC6075028.
- xxxi Kisa C, Bulbul DO, Aydemir C, Goka E. Is it possible to be dependent to Tianeptine, an antidepressant? A case report. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007 Apr 13;31(3):776-8. doi: 10.1016/j.pnpbp.2007.01.002. Epub 2007 Jan 16. PMID: 17270334.
- xxxii Bence C, Bonord A, Rebillard C, Vaast P, Alexandre C, Jardri R, Rolland B. Neonatal Abstinence Syndrome Following Tianeptine Dependence During Pregnancy. *Pediatrics*. 2016 Jan;137(1). doi: 10.1542/peds.2015-1414. Epub 2015 Dec 11. PMID: 26659818.
- xxxiii Kirsten E. Smith, Jeffery M. Rogers, Justin C. Strickland & David H. Epstein (2021) When an obscurity becomes trend: social-media descriptions of tianeptine use and associated atypical drug use, *The American Journal of Drug and Alcohol Abuse*, 47:4, 455-466, DOI: 10.1080/00952990.2021.1904408
- xxxiv El Zahran T, Schier J, Glidden E, et al. Characteristics of Tianeptine Exposures Reported to the National Poison Data System — United States, 2000–2017. *MMWR Morb Mortal Wkly Rep* 2018;67:815–818. DOI: <http://dx.doi.org/10.15585/mmwr.mm6730a2>.
- xxxv <https://www.vice.com/en/article/88q3va/tianeptine-gas-station-heroin-legal-in-most-states>
- xxxvi <https://www.fda.gov/consumers/consumer-updates/tianeptine-products-linked-serious-harm-overdoses-death>