Permanent Scheduling Action: Placement of Tianeptine in Schedule I

Section 1: Summary

The State of Ohio Board of Pharmacy (Board), pursuant to section 3719.44 of the Ohio Revised Code, proposes the placement of the tianeptine into Schedule I.

Section 2: Background

Pursuant to section 3719.44 the Board may add or transfer a compound, mixture, preparation, or substance to Schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

In making a determination to add an unscheduled compound, the Board is required to consider the following 8 criteria:

(1) The actual or relative potential for abuse;
(2) The scientific evidence of the pharmacological effect of the substance;
(3) The state of current scientific knowledge regarding the substance;
(4) The history and current pattern of abuse;
(5) The scope, duration, and significance of abuse;
(6) The risk to the public health;
(7) The potential of the substance to produce psychic or physiological dependence liability; and
(8) Whether the substance is an immediate precursor.

Section 3: Evaluation Under the 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 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. Most patients were male and ranged in age 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 scientific evidence of the pharmacological effect of the substance.

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.[xv] [xvi] [xvii] [xviii] [xix] 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.[xx] Neonatal abstinence syndrome mimicking opioid neonatal abstinence syndrome has occurred after tianeptine dependence during pregnancy.[xxi]

Additional evidence demonstrates that tianeptine mimics opioid toxicity due to reports of tianeptine toxicity being reversed with naloxone. Dempsey and others (2017) document a case report of a 36-year-old male intentionally injected tianeptine powder intravenously and, as a result, became unresponsive. The authors noted that "his toxicity was successfully reversed with two doses of naloxone 0.4 mg IV."[xxii]

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.[xxiii]

(3) The state of current scientific knowledge regarding the substance.

Tianeptine is an atypical antidepressant approved for use in Europe, Asia, and Latin America. The drug has not been approved by the United States Food and Drug Administration (FDA) for any medical use nor are there any commercial uses for tianeptine in the United States.

As stated previously, the 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.[xxiv] [xxv] [xxvi] [xxvii] [xxviii] 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.[xxix] Neonatal abstinence syndrome mimicking opioid neonatal abstinence syndrome has occurred after tianeptine dependence during pregnancy.[xxx]

According to Lauhan and others (2018), the package insert from Servier (one of the manufacturers approved to market the drug in other countries) cites increase in

spontaneous activity of pyramidal cells in the hippocampus, acceleration of their recovery after functional inhibition, and increased rate of serotonin re-uptake as the mechanism of action.[xxxi]

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(4) The history and current pattern of abuse.

The history and current pattern of abuse can be illustrated by a recent review of exposure calls related to tianeptine reported by poison control centers to the National Poison Data System (NPDS) from 2000 to 2017. 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.[xxxiii]

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.[xxxiv]

While the drug is approved for use in other counties, 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.[xxxv] 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.[xxxvi] Tianeptine has been described to have a similar risk for diversion as diazepam, ranking first among various antidepressants for doctor-shopping in France.[xxxvii]

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 euphorigenic 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." [xxxviii] Currently, the drug is banned or restricted in Michigan, Alabama, Minnesota, Tennessee, Georgia, and Indiana.[xxxix]

(5) 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.[xl]

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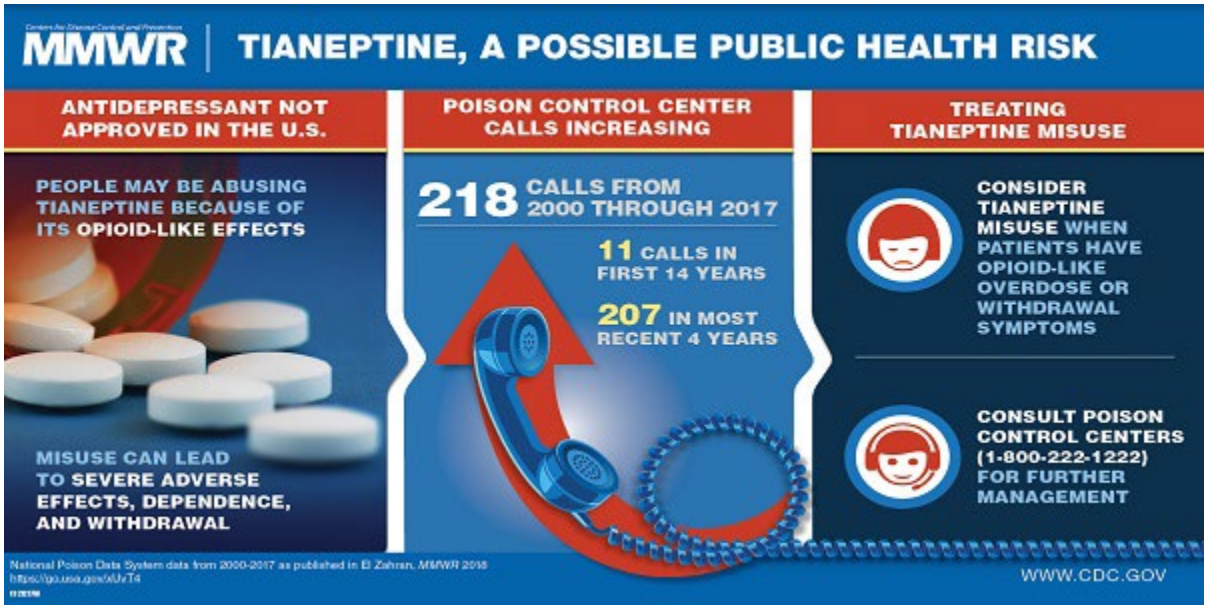

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While the drug is approved for use in other counties, many countries have banned or withdrawn this medication from the market. In the country of Georgia, the health authority withdrew tianeptine from the market in June 2010, and the health authorities of Russia and Armenia classified tianeptine as a controlled substance in July 2010.[xliii] 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.[xliv] Tianeptine has been described to have a similar risk for diversion as diazepam, ranking first among various antidepressants for doctor-shopping in France.[xlv]

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epidemic, any emerging trends in drugs with opioid-like effects raise concerns about potential abuse and public health safety." [xlvi] Currently, the drug is banned or restricted in Michigan, Alabama, Minnesota, Tennessee, Georgia, and Indiana.[xlvii]

It should be noted that there is also a robust online presence (r/Quittingtianeptine) dedicated to helping individuals quit tianeptine that has 3,931 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...*[xlviii]

- *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…*[xlix]

- *Granted it took a 4 day hospital stay due to psychosis and hallucinations. That shit is no joke and I'll never be tou hing [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!*[l]

- *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.*[li]

- *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?* [lii]

- *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.* [liii]

(6) 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.[liv] 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.[lv] 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.[lvi] Tolerance to tianeptine and withdrawal have been reported.[lvii] Neonatal abstinence syndrome mimicking opioid neonatal abstinence syndrome has occurred after tianeptine dependence during pregnancy.[lviii]

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.[lix]

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(7) The potential of the substance to produce psychic or physiological dependence liability.

While tianeptine is approved for use in other counties, many countries have banned or withdrawn this medication from the market due to concerns regarding addiction and other adverse events. 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.[lxiii] 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.[lxiv] Tianeptine has been described to have a similar risk for diversion as diazepam, ranking first among various antidepressants for doctor-shopping in France.[lxv] Currently, the drug is banned or restricted in Michigan, Alabama, Minnesota, Tennessee, Georgia, and Indiana.[lxvi]

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Specific case reports also demonstrate the ability of tianeptine to produce psychic or physiological dependence liability. 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."[lxix]

A robust online presence (r/Quittingtianeptine) dedicated to helping individuals quit tianeptine illustrates the dependence liability of the drug. The online forum has 3,931 members. Members of the forum—excerpts provided above—provide information on the negative impacts of the use of this drug and the difficulties in discontinuation of the use of the drug.[lxx]

(8) Whether the substance is an immediate precursor.

This substance is not known to be an immediate precursor.

Section 4: Finding of the Board

Pursuant to section 3719.44 the Board may add or transfer a compound, mixture, preparation, or substance to Schedule I when it appears that there is a high potential for abuse, that it has no accepted medical use in treatment in this state, or that it lacks accepted safety for use in treatment under medical supervision.

After a review of all available data, the Board finds tianeptine has a high potential for abuse and that it has no accepted medical use in treatment in this state.

Section 5: Resolution of the Board

Based on these findings, the Board hereby authorizes the filing of an amendment to rule 4729:9-1-01 of the Administrative Code with the Common Sense Initiative and the Joint Committee on Agency Rule Review to classify as a schedule I opiate or opiate derivative any material, compound, mixture, or preparation that contains tianeptine.

The Board further authorizes the amendment of paragraph (G) to update the incorporation by reference to the date the rule is filed with JCARR.

Endnotes

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[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.
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[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
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[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
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[xv] Characteristics of Tianeptine Exposures Reported to the National Poison Data System — United States, 2000–2017.
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