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Review Article

Tianeptine: Unveiling the Dangers of "Gas Station Heroin" Disguised as a Dietary Supplement

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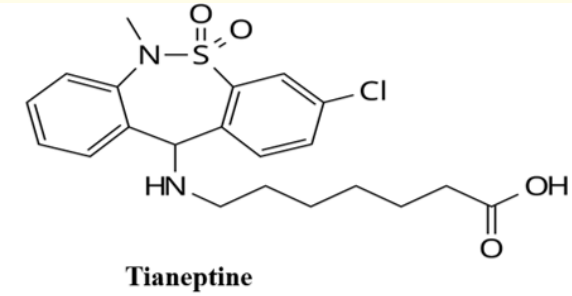
Abstract

Tianeptine, also known as "gas station heroin", is an opioid agonist and an antidepressant. In some countries, tianeptine is used as an oral antidepressant at a typical labeled dose of 12.5 mg three times daily. Tianeptine has been shown to be a moderately potent agonist for the mu-opioid receptor (MOR) and to a lesser extent the delta-opioid receptor (DOR). The antidepressant efficacy of tianeptine appears to be related to its MOR activity and its action on glutamate-mediated pathways of neuroplasticity. Because it is an opioid agonist with significant potential for abuse, high doses of tianeptine can produce opioid-like euphoria, tolerance, dependence, and withdrawal symptoms consistent with other opioid agonists. In the United States, tianeptine is an unapproved drug sold unlawfully as an unregulated dietary supplement. Despite explicit warnings from the FDA against its sale and distribution, tianeptine is frequently available at convenience stores, gas stations, vape shops, and online retailers. Tianeptine is often used recreationally, but it has also been used by some consumers to self-treat a variety of conditions or disorders. In recent years, case reports of recreational abuse of tianeptine have increased significantly. Reports of tianeptine abuse describe consumers ingesting high daily doses of tianeptine (from 50 mg to 10 g), leading to either withdrawal, intoxication, or death from an overdose. Due to the increase in tianeptine abuse, which can lead to serious harm, including death, several States have banned products containing tianeptine and have designated tianeptine as a controlled substance. The FDA has also been working on protecting the public from tianeptine products, including warning consumers and health care professionals about the serious adverse events that are associated with tianeptine abuse and helping detain tianeptine shipments at the U.S. borders. Health care professionals need to be proactive in understanding and addressing the recreational abuse of tianeptine as a growing threat to public health. Health care providers must encourage patients and consumers to avoid all products containing tianeptine, including those claiming to treat a medical condition or disorder. Health care professionals must also provide patients and the public with accurate and reliable information about tianeptine products and the underlying dangers of tianeptine abuse.

Keywords: *Tianeptine; Gas Station Heroin; Supplement; Dietary Supplement; Nootropic Supplement; Opioid; Opioid Agonist; MOR Agonist; Abuse; Withdrawal; Dependence; Respiratory Depression; Overdose; Opioid Use Disorder; Naloxone; Buprenorphine*

Introduction

Tianeptine, an atypical tricyclic antidepressant and a selective agonist at the mu-opioid receptor (MOR), was first synthesized by researchers in France as an analog of the tricyclic antidepressants (TCAs) [1]. Although tianeptine has a tricyclic structure that resembles that of other TCAs, the tricyclic structure of tianeptine differs from conventional TCAs by the seven-membered sultam ring system and the carboxylic acid tail. Unlike the selective serotonin reuptake inhibitors (SSRIs) and the structurally related TCAs, tianeptine was initially thought to act as a selective serotonin reuptake enhancer (SSRE), stimulating the uptake of serotonin without apparent activity at any serotonin receptors or monoamine transporters [2]. New evidence confirmed, however, that the mechanism of action of the antidepressant tianeptine is unrelated to serotonergic neurotransmission [1].



Figure

Years after the disclosure of its synthesis, tianeptine was first approved in France as a prescription oral antidepressant in the 1980s [3]. Today, tianeptine is approved and used as an antidepressant in more than 60 countries in Europe, Asia, and South America, under different trade names (such as Coaxil, Stablon, and Tatinol) [4]. Clinical evidence also suggested that the utility of tianeptine may extend beyond the treatment of depression. Tianeptine has demonstrated some efficacy as a treatment for anxiety, asthma, irritable bowel syndrome (IBS), convulsions, fibromyalgia, and attention-deficit hyperactivity disorder (ADHD) [5-9]. A number of human clinical trials are currently investigating the use of tianeptine, as monotherapy or in combination therapy, for the treatment of a variety of disorders including treatment-resistant depression, bipolar depression, postmastectomy pain after breast cancer surgery, and brain fog symptoms related to COVID-19 [10].

In countries where tianeptine is an approved antidepressant drug, the typical labeled dose to treat depression is 12.5 mg orally three times daily [1]. Because tianeptine is an opioid with potential for abuse, higher doses can produce opioid-like euphoria, dependence, and withdrawal symptoms consistent with other mu-opioid receptor (MOR) agonists. In recent years, an increasing number of case reports in the medical literature have shown that tianeptine is indeed being used recreationally around the world at doses far beyond what is considered therapeutically relevant or safe [11-14]. As a result, some countries have restricted how tianeptine is prescribed and dispensed or revised the drug label to warn of possible addiction [15].

In the United States (U.S.), tianeptine is not approved (and was never approved) by the Food and Drug Administration (FDA) for any use [16,17]. Despite the lack of FDA approval, tianeptine is widely available in the United States as a dietary supplement and a nootropic cognitive enhancer. Tianeptine, which is often called "gas station heroin" because of its availability in gas station stores, is sold at gas stations, convenience stores, vape shops, and through online retailers. Products containing tianeptine are available under a variety of names including, but not limited to, ZaZa, Tia, Tianaa, ZaZa Red, TD Red, Neptune's Fix, and Pegasus [18]. Tianeptine is often used

recreationally, but it has also been used to self-treat a variety of ailments [1,19,20]. Recreational misuse of tianeptine can lead to opioid-like euphoria, addiction, respiratory depression, and withdrawal symptoms [1,4]. Case reports in the medical literature describe U.S. consumers ingesting daily doses on the order of 1.3 to 250 times (50 mg to 10,000 mg) the daily tianeptine dose typically recommended in labeled foreign drug products [11-13,21-24]. Cases of accidental and intentional tianeptine overdose have been documented [1]. In addition, data from the FDA and poison control centers revealed a significant overall increase in cases of tianeptine abuse in the United States. The National Poison Data System (NPDS) reported 11 tianeptine exposure calls between 2000 and 2017 and 207 calls between 2014 and 2017, and the FDA reported 151 cases in 2020 [4,13,16].

Due to the increasing number of adverse events involving tianeptine products, which can lead to serious harm, including death, and the serious and continuing risk these products pose to both young and old consumers in the U.S., some States have banned products containing tianeptine and have designated tianeptine as a Schedule I or II controlled substance [4]. In addition, the FDA has taken several steps to protect consumers from tianeptine products, including warning consumers about severe side effects, issuing warning letters to companies distributing and selling unlawful tianeptine products, and placing products on import-alert to help detain tianeptine shipments at the U.S. borders [16]. In this article, we aimed to summarize the pharmacological and toxicological profiles of tianeptine, highlight the abuse of tianeptine products as a growing threat to public health, and discuss what health care professionals should be doing to protect patients and consumers from the underlying dangers of tianeptine products.

Pharmacology of tianeptine

Tianeptine is an atypical tricyclic antidepressant approved in the late 1980s for the treatment of major depressive disorder (MDD) in many European, Asian, and Latin American countries. Although it is not approved for any use by the FDA, tianeptine is sold in the U.S. as a dietary supplement at gas stations, smoke shops, and health stores. While structurally it is considered a tricyclic compound, tianeptine has a distinctive pharmacodynamic profile that separates it from other tricyclic antidepressants as it does not exhibit affinity for monoamine transporters or receptors [1]. In recent years, significant attention has been directed toward the pharmacological activity of tianeptine at the mu-opioid receptors, due to reports of misuse and toxicity associated with unregulated use in the U.S. [1,4].

Early studies suggested that tianeptine's mechanism of action is serotonergic. Tianeptine was thought to act as a selective serotonin reuptake enhancer (SSRE), stimulating the uptake of serotonin without affecting the release, binding, or uptake of any other neurotransmitter along with an apparent lack of amine oxidase activity [2]. However, follow-up studies indicated that tianeptine has low affinity for serotonin transporters and no clinically significant serotonergic effects, confirming that an enhancement of serotonin uptake may not be the primary mechanism for the antidepressant effects of tianeptine. These follow-up studies concluded that an involvement of serotonin in the antidepressant effects of tianeptine is unlikely [4].

Recent studies have provided strong evidence supporting a glutamatergic mechanism as the primary mechanism for the antidepressant effects of tianeptine. Specifically, tianeptine has been shown to act by influencing the expression of synaptic plasticity via modulation of the phosphorylation state of glutamate receptors and modulation of glutamatergic neurotransmission [1,4]. Long-term tianeptine administration was examined at hippocampal CA3 commissural associational (c/a) glutamate receptor ion channels (NMDA and AMPA) and was shown to normalize the amplitude ratio of NMDA to AMPA/kainate receptor-mediated currents and prevent the stress-induced attenuation of NMDA-excitatory postsynaptic currents. This effect was attenuated by administration of a kinase inhibitor, indicating that tianeptine acts via a postsynaptic phosphorylation cascade at the CA3 c/a synapse. By modulating glutamatergic neurotransmission, tianeptine is able to promote improved neuroplasticity and stress resilience and restore glutamatergic balance that can be disrupted in depressive states [4].

Tianeptine has also been shown to act as an opioid. Tianeptine is a moderately potent but highly efficacious and selective agonist at the mu-opioid receptor (MOR) [4,25]. Tianeptine has weaker activity at the delta-opioid receptor (DOR) and no appreciable activity at

the kappa-opioid receptor (KOR). The active human metabolite of tianeptine (MC5), which is a 3-fold weaker agonist than tianeptine at MOR, mimics the behavioral effects of tianeptine in a MOR-dependent manner [4]. Animal studies revealed that both the analgesic and the antidepressant effects of tianeptine are MOR-dependent [26]. The MOR activity of tianeptine induces dopaminergic release, enhancing the antidepressant efficacy of tianeptine through activation of the mTOR pathway. The MOR activity of tianeptine is also responsible for the opioid-like effects (euphoria, addiction, respiratory depression, withdrawal symptoms, etc.) that tianeptine produces when used at supratherapeutic doses. The opioid-like effects of tianeptine have significant clinical implications for its misuse and abuse potential [1,4]. These findings validate MOR as a significant CNS target for tianeptine and confirm that MOR is at least partially involved in the antidepressant efficacy of tianeptine [27].

Tianeptine is available on the market as the racemic mixture of the two enantiomers of tianeptine, the (−)-enantiomer and the (+)-enantiomer [28]. The absolute stereochemistry of each enantiomer is yet to be determined. MOR binding studies revealed that only marginal differences in MOR binding exist between the two enantiomers of tianeptine [4]. Data from serotonin uptake studies, however, showed a major difference between the two enantiomers of tianeptine. The (−)-enantiomer of tianeptine has the best activity in terms of increasing the neuronal uptake of serotonin *in vivo*; the (+)-enantiomer is much less active. The (+)-enantiomer did not appear to significantly inhibit the activity of the (−)-enantiomer [29,30].

Toxicology of tianeptine

Tianeptine is an atypical tricyclic antidepressant and an opioid agonist. When used as an oral antidepressant, the typical therapeutic adult dose of tianeptine is 12.5 mg three times daily. At therapeutic doses, clinical studies revealed that tianeptine is well tolerated. These studies reported a relative lack of adverse effects with tianeptine therapy compared to classical TCAs [3]. Unlike therapy with classical TCAs, therapeutic doses of tianeptine did not alter cognitive functions to any significant extent [31,32]. In addition, tianeptine therapy did not affect driving skills and was shown to decrease the risk of falling in the elderly [33].

In the United States, tianeptine is an unapproved and unregulated drug sold unlawfully as a supplement under names like ZaZa or Tianaa Red. Tianeptine is often used recreationally, but it has also been used by some patients to self-treat a variety of ailments [1,19,20]. Doses taken recreationally may exceed 1000-3000 mg per day. At these high doses of tianeptine, users report opioid-like euphoria, physical dependence, and withdrawal symptoms consistent with other opioid agonists [34]. Unlike many of the opioid agonists that are used recreationally, however, tianeptine may not be identified in routine drug screening panels. Recreational use of tianeptine products is associated with many adverse effects including constipation, diarrhea, dizziness, drowsiness, headache, insomnia, nausea, vomiting, agitation, asthenia, confusion, coma, respiratory depression, hypertension, liver damage, myalgias, tachycardia, seizure, and tremors. Several case reports of tianeptine abuse have also documented a wide spectrum of serious adverse events at supratherapeutic doses (from 87.5 mg to 10g), including psychosis, respiratory depression, and death due to overdose, often in the setting of polypharmacy or co-ingestion with sedatives or alcohol [13,14,19,35-37].

Numerous case reports related to tianeptine abuse and misuse in the U.S. have been documented in the medical literature. For example, a case report in 2020 described a 28-year-old woman with a history of schizoaffective disorder, bipolar type, and polysubstance use who was involuntarily admitted and presented with psychosis, hallucinations and delusions after consuming supratherapeutic doses of tianeptine. This case report highlighted the neuropathic risks associated with tianeptine abuse [11]. In other case reports, a 28-year-old male and a 30-year-old male died in Texas from respiratory depression as a result of tianeptine intoxication. Postmortem toxic blood levels of tianeptine were found to be 2.0 mg/L for the 28-year-old and 8.4 mg/L for the 30-year-old, demonstrating the lethality of tianeptine when abused [38]. At least two cases of suicide associated with tianeptine use have already been documented, further emphasizing the danger of tianeptine when used at high doses [39,40].

Tianeptine is frequently used chronically and, if stopped abruptly, users may experience withdrawal symptoms similar to those associated with opioid discontinuation. Recent clinical and toxicological data have established tianeptine's capacity to induce tolerance, dependence, and severe withdrawal symptoms. Withdrawal symptoms include agitation, anxiety, insomnia, diarrhea, cravings, myalgias, and sweating. In one poison control center study, 65% of tianeptine related calls involved withdrawal, and more than half required hospitalizations [41]. Management of withdrawal usually involves supportive care with benzodiazepines to alleviate anxiety and agitation, IV ondansetron, and IV fluids. Naloxone and buprenorphine-naloxone have been shown to reverse tianeptine-induced respiratory depression, and have been successfully used to manage withdrawal and dependence. For example, a case report described a 36-year-old man experiencing opioid-like toxicity with respiratory depression and miosis after injecting tianeptine intravenously who was able to reverse his symptoms with naloxone [42].

Many case reports of tianeptine withdrawal have been documented in the literature. For example, a 38-year-old male with a past medical history of anxiety, opioid use disorder, seizures, and cerebral vasoconstriction syndrome secondary to substance use experienced encephalopathy and had symptoms of tachycardia, hypotension, and cyanosis after ingesting multiple substances including 8 to 20 g of tianeptine daily, cough syrup, duloxetine 20 mg daily, mouthwash, cocaine, and kratom. He was treated with methylene blue for methemoglobinemia and buprenorphine-naloxone SL 4mg/1mg twice daily with additional doses of 2 mg/0.5 mg every 2 hours and IV buprenorphine every 6 hours for opioid withdrawal symptoms that resolve within 3 days [43]. A recent 2024 case report described a 67-year-old male with a past medical history of polysubstance misuse, chronic hyponatremia, major depressive disorder, and anxiety who presented to the Emergency Department with lightheadedness, lethargy, constipation, urinary retention, chest pain, shortness of breath, palpitations, headaches, blurry vision, fever, chills, and anorexia after stopping a self-selected tianeptine supplement for 12 hours. The patient received supportive care with IV ondansetron and two liters of normal saline for managing tianeptine withdrawal. On the second day of admission, the patient reported improvement in symptoms and was discharged [44].

Discussion

Tianeptine is an atypical tricyclic antidepressant and an opioid agonist. It is used as an antidepressant in many European, Asian, and Latin American countries. In these countries, the typical antidepressant dose of tianeptine is 12.5 mg orally three times daily. Because tianeptine is an opioid agonist with significant potential for abuse, higher doses can produce opioid-like euphoria, tolerance, dependence, and withdrawal symptoms consistent with other opioid agonists. In recent years, increasing reports of tianeptine abuse and dependence have been documented in the literature. These reports revealed that tianeptine is being used recreationally around the world at doses far beyond what is considered therapeutically relevant or safe. As a result, some countries have restricted how tianeptine is prescribed and dispensed or revised the drug label to warn of possible addiction [11-15].

In the United States, tianeptine (also known as "gas station heroin") is an unapproved drug sold unlawfully as an unregulated dietary supplement under a variety of names such as ZaZa, TD Red, Neptune's Fix, and Pegasus. Tianeptine is not approved by the FDA for any use, is not generally recognized as safe for use in food, and does not meet the statutory definition of a dietary ingredient. In addition, tianeptine is not currently scheduled under the U.S. Controlled Substances Act. Despite explicit warnings from the FDA against its sale and distribution, tianeptine is frequently available at convenience stores, gas stations, vape shops, and online retailers [36]. Tianeptine is often used recreationally, but it has also been used by some consumers to self-treat a variety of medical conditions [1,19,20]. Although it is well recognized to be an opioid by recreational users, tianeptine is falsely perceived on social media as being less dangerous than other opioids or substances of abuse and is taken in doses much higher than the typical prescription dose recommended in labeled foreign drug products [11-13,20-24].

Case reports of tianeptine abuse in the U.S. have been increasing steadily in recent years. The FDA Center for Food Safety and Applied Nutrition (CFSAN) Adverse Event Reporting System (CAERS) received more reports of tianeptine abuse in 2022 than in the previous 3

years combined [35]. These case reports describe U.S. consumers ingesting high daily doses of tianeptine (from 50 mg to 10g), leading to either acute effects from tianeptine withdrawal, acute effects from tianeptine intoxication, or death from an intentional or unintentional tianeptine overdose. In many instances, tianeptine was taken concurrently with other substances [12]. Naloxone and/or buprenorphine have been shown to reverse tianeptine-induced respiratory depression, and have been successfully used to manage tianeptine withdrawal and dependence [24,42,45].

Due to the significant increase in tianeptine abuse in the U.S., which can lead to serious harm, including death, at least 9 States have banned products containing tianeptine and have designated tianeptine as a Schedule I or Schedule II controlled substance [4]. The FDA has also been working on protecting U.S. consumers from tianeptine products, including warning consumers and health care professionals about the serious adverse events that are associated with tianeptine abuse, issuing warning letters to companies distributing and selling unlawful tianeptine products, and helping detain tianeptine shipments at the U.S. borders [16]. In addition, the FDA has warned that manufacturers of tianeptine products are making inaccurate and unproven claims regarding the use of tianeptine to improve brain function or treat anxiety, opioid use disorder, and other health ailments. While it is closely following the distribution and sale of tianeptine products, the FDA is strongly encouraging health care professionals to fully appreciate the magnitude of the underlying dangers of these products, and to provide the public with accurate and reliable information about the underlying dangers of tianeptine abuse. The goal is to protect public health by educating patients and consumers about tianeptine and the underlying dangers of tianeptine products.

Health care professionals must encourage patients and consumers to avoid all products containing tianeptine, including those claiming to treat an ailment or disorder. Health care providers need to counsel patients and consumers regarding the risks of tianeptine and remind them that just because a substance is conveniently sold does not mean it is safe. Health care professionals should provide person-centered and trauma-informed care to patients and consumers, even if they are not ready to stop using tianeptine. Health care professionals should also consider talking with patients and consumers about evidence-based treatment options for opioid use disorder, depression, anxiety, or pain, and about how to access overdose reversal medicines, including over-the-counter naloxone nasal spray. In addition, health care providers should educate patients and consumers on overdose risk-prevention strategies (such as avoiding mixing substances) and, if needed, refer them to local harm reduction agencies or other trusted community-based organizations available to connect them to needed resources. Health care providers who believe a patient/consumer is experiencing an adverse event from a tianeptine-containing product should contact Poison Help at 1-800-222-1222 (www.poisonhelp.org) for guidance regarding clinical management.

Health care providers are encouraged to report adverse events following use of tianeptine-containing products to the FDA either online at the FDA's MedWatch (www.fda.gov) or by calling 1-888-INFO-FDA (1-888-463-6332). Health care providers can also encourage patients and consumers to report adverse events following use of tianeptine products to the FDA by visiting the FDA's MedWatch website. When reporting adverse events following use of tianeptine to the FDA, health care providers and patients/consumers must include as much information as possible regarding the product suspected to have caused the adverse events. Important information includes anything found on the product label (e.g. product name, dosage form, active ingredients, strength/concentration, lot number, expiration date, name and phone number of manufacturer or distributor). If possible, submitting photos of product labeling is highly encouraged. In addition, information regarding where the product was purchased (website or retail store name/address), will certainly help FDA investigators with sampling and testing of products.

Conclusion

Tianeptine, also known as "gas station heroin", is an opioid agonist and an antidepressant. In the United States, tianeptine is an unapproved drug sold unlawfully as an unregulated supplement. In recent years, case reports of recreational abuse of tianeptine have been increasing steadily. Due to the increase in tianeptine abuse, which can lead to serious harm, including death, several States have banned products containing tianeptine and have designated tianeptine as a Schedule I or Schedule II controlled substance. The FDA has

also taken a number of steps at the federal level to protect the public from tianeptine products. Health care providers must encourage patients and consumers to avoid all products containing tianeptine, including those claiming to treat a medical condition or disorder. Health care professionals must also provide patients and the public with accurate and reliable information about tianeptine and the underlying dangers of tianeptine abuse.

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