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REVIEW

Tianeptine, an Antidepressant with Opioid Agonist Effects: Pharmacology and Abuse Potential, a Narrative Review

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ABSTRACT

Tianeptine is an antidepressant drug approved for the treatment of major depressive disorder in countries other than the US. It is classified as an atypical tricyclic antidepressant and has shown potential benefits in addressing anxiety and irritable bowel disease. However, it is important to note that tianeptine is not approved for any use by the United States Federal Drug Administration (FDA). Despite its lack of approval by the FDA, tianeptine has been distributed online and at small retail locations. The term "gas station drugs" refers to a wide range of substances typically available for purchase from gas stations, corner stores, bodegas, mini marts, smoke shops, and the Internet. These substances may be produced commercially by drug manufacturers or in clandestine laboratories to mimic the effects of more well-known illicit/controlled substances such as marijuana, cocaine, opioids, etc. Tianeptine has made its way to convenience stores and gas station shelves, branded as "Zaza" and "Tianna Red." It can also be obtained online from independent vendors without a prescription. Misuse of tianeptine can lead to euphoric, opioid-like highs with the potential for chronic users to develop dependence and tolerance. Overdose and use in suicide attempts have also

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been documented. This manuscript is a narrative review, highlighting the dangers of tianeptine and other gas station drugs and underscoring the urgent need to regulate these substances.

Keywords: Tianeptine; Zaza; Opioid agonists; Overdose; Gas station supplements; Suicide

Key Summary Points

Why did we carry out this study?

Tianeptine is an atypical tricyclic antidepressant used in other countries for treating major depressive disorder; however, it is not approved for use in the United States.

Tianeptine has agonist activity at opioid receptors and can be misused for its euphoric highs.

This study was carried out to see what the literature says about the scope of the problem with tianeptine use, given its easy accessibility.

What was learned in the study?

Overdose and use in suicide attempts occur when used in combination with other substances.

Tolerance and withdrawal can occur in those who use the substance.

Treatment options for opioid use may include medications such as buprenorphine, among others.

Further studies should be conducted to gain a deeper understanding of this substance.

INTRODUCTION

Major depressive disorder (MDD) is one of the most pervasive psychiatric diagnoses in the United States [1]. Worldwide, it is responsible for the most significant proportion of disease burden related to disability, measured as years lost to disability (YLD) [2]. Despite its immense prevalence and decades of research dedicated to understanding its etiologies, MDD remains controversial in public health, psychology, and medicine. Treatment of MDD is complex, and must be tailored to the individual. First-line pharmacotherapies for MDD include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and serotonin modulators (SMs), among others [3].

Tianeptine is an atypical tricyclic antidepressant that is approved in some European, Asian, and Latin American countries primarily for the treatment of MDD. Additionally, it has been used to treat anxiety and irritable bowel syndrome. Tianeptine was developed to help increase serotonin uptake in the brain; it can also act as a full agonist at the mu-opioid receptor. As a full agonist, it produces a euphoric high and carries a significant risk of overdose. Furthermore, its short half-life can lead to rapid withdrawal, increasing its potential for addiction and misuse.

Despite its lack of FDA approval, tianeptine has made its way to the shelves of convenience stores and gas stations, branded as “Zaza” and “Tianna Red.” It can also be obtained online from independent vendors without a prescription. Of note, this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. This manuscript is a narrative review, highlighting the dangers of tianeptine and other “gas station drugs” and underscoring the urgent need to regulate these substances.

No human subjects/ data were involved in the construction of this manuscript outside of the original studies in this review. We thank the subjects that were involved in those studies. No IRB approval was required for this review.

TIANEPTINE

Tianeptine was first developed as an antidepressant in the 1980s [4]. Previously classified as a tricyclic antidepressant due to its structural similarity, tianeptine is molecularly and mechanistically unique from other antidepressants and is therefore classified as an atypical tricyclic antidepressant [4]. Almost unintuitively, tianeptine was thought to *stimulate* rather than *inhibit* the reuptake of 5-hydroxytryptophan (5-HT) in the synaptic cleft; its therapeutic effects were partially due to neuronal remodeling and plasticity [5, 6]. This theory has since been disproven and will be discussed later in this picture. Interestingly, tianeptine weakly interacts with the mu- and delta-opioid receptors, producing many similar clinical effects as other opioid agonists [4, 6]. Further discussion of tianeptine's mechanisms of action and off-target effects are highlighted below.

While not marketed in the United States, tianeptine is prescribed for treating MDD in some European, Asian, and Latin American countries [4, 5, 7]. There is significant inconsistency in the literature regarding tianeptine's potential for abuse, addiction, and withdrawal. A 2018 study published in Madrid reported that tianeptine use does not produce tolerance, dependence, or withdrawal, noting that the drug has a low potential for abuse. They further suggested that tianeptine could even be administered to patients who require prolonged use of morphine for its dependence-inhibiting effects [4]. In partial agreement, an analysis by Bailey et al. that reviewed all accessible tianeptine clinical trial data reported that tianeptine is effective as an antidepressant, allowing for improved functionality compared to standard first-line antidepressant medications. However, it also acknowledged tianeptine's potential for abuse and dependence when ingested at high doses due to its mu-opioid receptor agonist effects [8]. While studies agree that tianeptine, at its therapeutic dose, is effective at treating depression, its opioid-like characteristics can induce euphoria at high enough doses [8]. In countries where tianeptine is prescribed to treat depression, 25 to 50-mg daily doses are standard. However, When taken recreationally, doses can reach up to 3000 mg daily [9].

As its pharmacology has been elucidated over the past several years, namely its activity at the opioid receptor, there has been a growing interest in tianeptine misuse in the United States [6]. Despite lacking FDA approval for any purpose in the United States, tianeptine can still be found in certain convenience stores and gas stations [6]. It can also be obtained online from independent vendors without a prescription [9]. Tianeptine's unregulated production and distribution have made it difficult to monitor. However, using online forums like *Reddit*, Smith et al. were able to use social media posts to gather information on current, former, and prospective tianeptine users via personal blog posts [10]. They found that tianeptine users were more likely to be polydrug users, and tianeptine is often co-ingested with other drugs marketed online as "cognitive enhancers" or dietary supplements [10]. A novel finding from this study is that recreational tianeptine users overwhelmingly conceptualized the drug as an opioid and were motivated to use tianeptine related to additional perceived benefits [10].

Pharmacologic Considerations of Tianeptine

Serotonergic Mechanisms

Preclinical studies have yielded conflicting data regarding tianeptine's direct serotonin system neuromodulation ability. The serotonin reuptake transporter (SERT) is a target of many standard first-line pharmacologic treatments for MDD, including SSRIs and SNRIs. While these drugs increase the concentration of 5-HT in the synaptic cleft by inhibiting its reuptake at SERT, it is postulated that tianeptine's mechanism is the complete opposite—that it instead *stimulates* serotonin reuptake due to the presence of a specific amino acid in its side chain [5, 8]. More recent studies employing advanced technology have contradicted this theory, demonstrating that the drug exhibits low affinity for 5-HT transporters and does not exert significant effects on 5-HT neurotransmission [4, 11].

Glutamatergic Mechanisms

Glutamate has been implicated in neural mechanisms related to the pathophysiology of MDD [12]. Several clinical models have shown that glutamate levels are decreased in various brain regions in people with MDD compared to those without the disease [12]. Tianeptine is thought to stabilize glutaminergic signaling and exerts opposing effects on *N*-methyl-D-aspartate (NMDA) and aminomethylphosphonic acid (AMPA) receptors; these interactions potentiate anti-depressive effects [4, 8, 11]. It is now known that tianeptine's primary mechanism of action is glutamate modulation [4, 11]. This mechanism of action is where the anti-depression action occurs rather than in the serotonin system.

Opioid Receptor Interactions

Tianeptine is a full mu- and weak delta-opioid receptor agonist. Its opioid-like actions trigger dopamine release, producing euphoria-inducing effects and has a high potential for abuse [6, 8, 13]. One downstream effect of mu-opioid receptor activation is the upregulation of mTOR, which stimulates the glutaminergic pathway and thus enhances tianeptine's therapeutic properties [6, 8, 13].

Pharmacokinetics and Pharmacodynamics

Although the mechanisms responsible for tianeptine's clinical efficacy have only recently been elucidated, its basic pharmacokinetics have been established through decades of preclinical studies. With a half-life of only 2.5 h, tianeptine is quickly absorbed in the gastrointestinal tract. It becomes highly bound to albumin once in the bloodstream, thus having a low volume of distribution [4, 8]. It is hepatically metabolized into MC3 and the biologically active MC5, which functions similarly to its parent compound [4, 7, 8]. Since tianeptine is really cleared, its half-life is markedly increased in elderly patients and those with kidney disease. In countries where tianeptine is routinely prescribed, dose adjustments must be made in kidney failure patients, especially since hemodialysis is ineffective for a tianeptine overdose [6, 8].

As previously mentioned, tianeptine is mechanistically distinct from other antidepressant drug classes. While tianeptine's regulation of glutaminergic signaling is mainly responsible for its anti-depressive actions, most of the controversy surrounding tianeptine use involves the drug's opioid-like qualities. There are inconsistent data regarding the misuse potential of tianeptine, namely, whether its chronic use confers tolerance and withdrawal symptoms similar to that of other opioids in humans.

A 2017 *Nature* study performed on rodent models demonstrated that mice chronically treated with tianeptine experienced similar analgesia to those treated with morphine without displaying any evidence of tolerance or withdrawal after administration of naloxone [14]. Thus, the authors concluded that tianeptine might have specific downstream targets distinct from those of morphine, which could inform the future development of novel therapy [14]. Various case reports and social media forums detailing reports of tianeptine withdrawal, addiction, and overdose call these findings into question and warrant further discussion [4, 6, 9, 10, 13, 15].

Gas Station Treatment History and Relation to Tianeptine

The term "gas station drugs" refers to a wide range of substances typically available from gas stations and corner stores, bodegas, mini-marts, etc. They are also widely available for purchase over the Internet. These substances may be produced commercially by drug manufacturers or in clandestine laboratories and aim to mimic the effects of more well-known illicit/controlled substances such as marijuana, cocaine, opioids, etc. [16]. The first reports of these drugs in the US occurred in December of 2008 when the first shipment of a substance called "spice", a synthetic cannabinoid that mimics the effects of Δ9-tetrahydrocannabinol (THC), was seized in Dayton, Ohio [16]. Since then, many new drugs have emerged on the shelves of gas stations,

available for anyone to purchase legally, even individuals under 18. Unfortunately, many of these drugs are legally sold until their deleterious consequences create enough public outrage to push for reactive regulatory action. This was the case for the synthetic cannabinoid known as spice which the Federal Drug Administration (DEA) banned in 2011 [17]. A similar story can be told for synthetic cathinones, more commonly known as bath salts. These drugs started appearing in the US a couple of years after spice and were ultimately banned by the DEA after several associated fatalities [17]. New "gas station drugs" are continually emerging. Of these substances, the most prominent still being sold across the country today include delta 8/10 TCH, TCH acetate (TCH O), Royal Honey, Rhino Products, and Kratom [18].

Among the most recent drugs emerging in the US are tianeptine products [19]. They are sold in stores commonly under the names ZaZa Red or Tianna Red, although they can also be found under other names. The drug has earned the nickname "gas station heroine" due to its agonistic activity on mu-opioid receptors and potential for similar abuse [20]. Similar to other "gas station drugs," the increasing incidence of individuals experiencing harmful effects brought attention to the use of tianeptine within the community. WBRC, a media station in Birmingham, AL, recently reported that tianeptine was cited in nearly 1000 poison control center calls and three deaths [21]. Those involved in the recent outbreak included teenagers who could legally buy tianeptine-containing drugs [22].

The widespread availability and ease of access to gas station drugs has been one of the biggest problems regarding the harm these substances have caused across various communities. Adding to the issue is the way that they are marketed. They often claim to deliver highly sought-after benefits such as improved mood, energy, and sexual performance, as well as controlling appetite or muscle pain [22]. In the case of tianeptine-containing substances, they are commonly advertised as nootropics that provide cognitive enhancement [21]. The manufacturers have even gone so far as to claim that they can reduce the symptoms of opioid withdrawal. However, the drugs can also be addictive, trading one addiction for another [17, 19].

While tianeptine is not yet banned, the FDA has advised all consumers to avoid the drug, and state governments will likely begin banning the sale and possession of tianeptine due to the recent increase in drug misuse [21]. Many people have purchased these drugs under the assumption that they are safe simply because they are legal to buy in stores [17]. Although numerous gas station drugs are presently legal, it is primarily due to manufacturers being able to make slight alterations to the chemical structure to evade legal restrictions once they are deemed illegal [22]. In addition to making it harder for the FDA to keep track of each new drug, changing the chemical structure can also enhance the drug's addictive properties, making it more harmful than its predecessor [22]. Other methods to avoid removal from the market include labeling the products "not for human consumption" and smuggling the products into the country as misbranded imports [18]. Given the ease of slightly altering the chemical structure of a drug and manipulating the labeling of a product, it is likely that "gas station drugs" will remain widely available for anyone to obtain for the foreseeable future [21].

Tianeptine in the Literature

Much of the recent literature regarding tianeptine comes from case reports and review articles. Several available studies have been conducted to determine the role of tianeptine as a drug of misuse. Analysis of tianeptine use in the United States is limited, with most publications originating from other countries [23]. Further research is needed to understand the implications of unregulated tianeptine use fully.

Demographics and Risk Factors for Tianeptine Misuse

Research into the demographics associated with tianeptine use is sparse, and there appears to be some disagreement amongst the reviews

currently available. Misuse potential seems to be greater among younger individuals. An article by Lauhan et al. reported that 77% of cases involved individuals 35 years of age or below [23]. Springer and Cubała reported that about 89% of cases were of individuals between the ages of 30 and 45. Authors suggest this misuse is partly related to its anxiolytic effects, with supratherapeutic dosing used to placate the withdrawal symptoms of other substances [24]. A history of substance use was also prevalent among those who used tianeptine. Lauhan et al. reported that 63% of patients had a history of substance use, compared with nearly 89% of patients in the review by Springer and Cubała [23, 24].

There is no consensus in the literature concerning the risk of misuse by male and female gender. In Lauhan et al., males appeared at greater risk of tianeptine misuse in 76% of reviewed cases [23]. In the 2018 article by Springer and Cubała, however, 75% of cases involved females [24].

Laboratory Analysis of Tianeptine

Before discussing this new drug of misuse further in the available, methods of detection need to be described. In the case of a 67-year-old woman found dead by planned complex suicide, liquid chromatography with photodiode array and mass spectrometry (LC-DAD-MS) was used to quantify tianeptine levels in the postmortem samples. Analysis revealed tianeptine concentrations in the blood at 5.1 mg/ml, urine at 2.0 mg/ml, liver at 23 mg/g, and 22 mg in 200 ml of stomach contents [25].

In Bakota et al., the detection of tianeptine was performed through liquid chromatography time-of-flight mass spectrometry (LC-TOF-MS), using 5 mM ammonium formate with 0.01% formic acid in water as the aqueous mobile phase and 0.01% formic acid in methanol as the organic mobile phase. The injection volume of solution was 4 µl at a flow rate of 0.6 ml/min. Quantitation was performed through liquid chromatography-tandem mass spectrometry (LC-MS-MS) using a binary gradient of 0.1% formic acid in water and 0.1% formic acid in acetonitrile. The authors noted the difficulty in recovering tianeptine because it comprises both active acidic and basic groups. However, fragmentation was not impeded, and two ion transitions were successfully acquired. The authors concluded that LC-TOF-MS is effective in identifying tianeptine in a sample and LC-MS-MS in accurately quantifying tianeptine levels in the serum [9].

In a case report by Dempsey et al., LC-MS-MS was also used to detect tianeptine, with a mobile phase consisting of water and 20 mM ammonium formate and methanol and 20 mM ammonium formate. The sample injection volume was 10 µl at a 0.6 ml/min flow rate. Tianeptine was successfully detected and quantitated against the control. This highlights the possibility of using several methods to identify tianeptine in a given sample [26].

More recently, a study by Abdullatef et al. offered an alternative method for determining and quantifying tianeptine in bulk and pharmaceutical formulations. The authors used the quenching effect of tianeptine on vilazodone to evaluate the presence and quantity of tianeptine spectrofluorimetrically. Working standard solutions of both drugs in methanol were created, and tianeptine was mixed with 250 µg/ml vilazodone to form a tianeptine concentration of 10–100 ng/ml. This solution was used to produce appropriate calibration curves. A 1000 µg/ml concentration of tianeptine in methanol was created from 12.5-mg tablets to be tested against the standard via spectrofluorimetry. The authors reported success in determining and quantitating tianeptine concentrations from the sample with high fidelity. Given the rapidity, reliability, low cost, and high sensitivity of the test, it is suggested that it may help analyze biological samples in the clinical setting [27].

Adverse Effects in Case Reports

Now that we know how to detect it, the adverse effects seen in the literature can be discussed. Tianeptine misuse has been associated with psychosis in supratherapeutic doses, particularly in individuals with a history of substance

abuse or psychotic disorders. Such a case was reported in early 2020 [28]. The authors describe a 28-year-old woman with a history of schizoaffective disorder, bipolar type, and polysubstance use who was involuntarily 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. Standard urine toxicology results were negative. 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, and the patient was discharged on day 10 of admission. It was posited that increased dopaminergic transmission through the nucleus accumbens resulted in the positive symptoms of psychosis in this patient. As a side note, this case reinforces the importance of an appropriate review of all medications and supplements during the diagnostic process of psychosis [28].

There also appears to be a euphoric effect associated with tianeptine misuse, where euphoria and dependency are produced from activating the mu-opioid receptor and dopaminergic pathways. Given its potential for misuse, it may be prudent to maintain close monitoring of tianeptine use for the duration of treatment. In a review of 18 case reports, 16 displayed classic symptoms of substance dependence, including increasing dosage and tolerance. Withdrawal symptoms were also reported, although it is unclear whether these were part of a true withdrawal syndrome or simply some of the known side effects of tianeptine [24].

Unregulated tianeptine is at a higher risk of contamination with adulterants, which may cause additional or atypical side effects. Another case of tianeptine misuse was reported in late 2018, in which a 44-year-old male presented for suicidal ideation and progressively worsening depression for the previous 2 weeks. He had a history of polysubstance use and generalized anxiety disorder. He reported increasing use of tianeptine alongside baclofen and occasionally alcohol to control his anxiety. He ultimately increased use to a dose of 150 mg three or four times daily, noting a brief sensation of euphoria after administration. A urine drug screen was positive for barbiturates, which was thought to be an adulterant. Withdrawal symptoms improved with inpatient benzodiazepine detoxification. Gabapentin was prescribed along with mirtazapine to improve anxiety symptoms. In this case, the contamination of tianeptine with an adulterant is notable. The authors warn of an increased risk of tianeptine adulterants in the United States, citing lack of regulation, and raise concerns over the potentially life-threatening side effects when administered alongside sedatives [23].

Cases of non-fatal intoxication with tianeptine have been published in the literature. In one such case, a 36-year-old male was reported to have intentionally injected an unknown amount of tianeptine powder to "see the future" and subsequently became unresponsive. He was successfully reversed with 1 mg IV naloxone administered by emergency responders, two additional 0.4 mg IV doses, and a 0.2 mg/h naloxone infusion administered in the emergency department. Serum and urine samples were reportedly collected around 2 h after admission. Serology studies showed an elevated ethanol concentration of 133 mg/dl and a mildly elevated ALT of 69 IU/l. Urine analysis revealed a creatinine of 0.11 mg/dl and a 2 ng/ml tianeptine concentration. The authors suspected the lower urine level of tianeptine may be explained by the high rate of drug metabolism, low excretion in the urine, low urine creatinine, and a short time between exposure and specimen collection [26].

Intentional ingestion of tianeptine as part of a successful suicide attempt has also been reported in the literature. The case of a 26-year-old man found dead in his apartment next to multiple packets of 12.5-mg tianeptine tablets and a suicide note was published in 2007, which confirmed the ingestion to be intentional. Autopsy analysis using LC-DAD-MS revealed elevated tianeptine concentrations in the blood, urine, liver, and stomach. Serum ethanol levels were also elevated at 53 mg/dl. Examiners attributed the cause of death to suicidal

ingestion of tianeptine in combination with alcohol consumption. This article provides a basis for understanding the use of tianeptine in the setting of fatal intoxication [25].

Although reports in the literature of fatal tianeptine overdose are rare, a review of two cases of fatal tianeptine intoxication in the U.S. was published in early 2018 [9]. In both cases, the authors found post-mortem serum concentration of tianeptine different than in previously reported non-fatal intoxication. In the first case, serum tianeptine concentration was measured at 2.0 mg/l, less than in previously reported fatal intoxication [25]. However, significant levels of the tianeptine metabolite MC5 were identified using the time-of-flight spectrum, indicating the possibility of a much higher serum tianeptine concentration at one point during intoxication. The authors also noted the potential drug tolerance for affecting this and previously reported cases, potentially obscuring results. In the second case, serum levels were reported at 8.4 mg/l, in line with other cases of fatal intoxication. Ethanol and alprazolam were also identified in quantities consistent with a state of post-mortem decomposition and therapeutic dosing, respectively [9].

Tianeptine has also been used as part of complex suicide. A 67-year-old woman was found deceased in her bathtub after apparent suicide involving electrocution, wrist cutting, and drug overdose. An autopsy revealed a tianeptine blood concentration of 15.5 and 956 mg/l in the stomach contents, significantly greater than in other cases of tianeptine intoxication [9, 25, 26]. Nordiazepam and oxazepam, the metabolites of the benzodiazepine prazepam, morphine, codeine, and paracetamol, were found during an analysis of blood and stomach contents. Morphine, paracetamol, and prazepam metabolites were considered within therapeutic limits, while codeine concentration was slightly below the therapeutic range. A history of depression and multiple suicide attempts were noted in the review. In this instance, the state of decomposition reportedly made a definitive cause of death exceptionally difficult. However, the authors deemed the measured concentrations of tianeptine on autopsy potentially lethal. Complex suicide involving the above combination appears unusual, and the use of tianeptine is rare [29].

Management of Tianeptine Misuse and Overdose in the Literature

Now that the adverse effects have been discussed, how can clinicians treat this new drug of misuse? The opioid agonist effects of tianeptine may present a significant risk for overdose, especially in those with a high misuse potential. Naloxone is an FDA-approved treatment for opioid overdose and therefore is an appropriate choice for reversing the effects of a tianeptine overdose. A combination of buprenorphine and naloxone also appears useful in treating tianeptine withdrawal in a case report by Trowbridge and Walley, where a 24-year-old man with a history of undiagnosed anxiety presented for detoxification from tianeptine. He had been purchasing tianeptine online for over 2 years, initially taking a 12.5-mg dose thrice daily. He began to experience withdrawal symptoms, and to avoid these symptoms, he gradually increased his dose to 100 mg every 2 h. He attempted to decrease his dose but could not successfully detox due to the withdrawal effects. The patient was initially started on mirtazapine and clonidine for symptom control but returned the following week unable to complete his taper off tianeptine. Adjuvant risperidone was added, and his mirtazapine increased, which helped the patient discontinue tianeptine use. However, he continued to experience anxiety along with depression and recurrent withdrawal symptoms, relapsing less than a week later. A combination of buprenorphine and naloxone was initiated at 2 and 0.5 mg twice daily with a resolution of most symptoms and no additional cravings [30].

Naloxone has also been used in the acute management of tianeptine overdose. Initiation of 1 mg IV naloxone with two additional 0.4 mg doses and 0.2 mg/h naloxone infusion was used to successfully reverse tianeptine overdose in a 36-year-old male [26]. This observation is supported in animal models. In a study by Baird et al. using rat models of drug misuse,

Table 1 Summary of tianeptine clinical studies

Author, year published, and citation	Study title and description	Results	Conclusions
Abdullatef et al. (2020) [27]	"Spectrofluorimetric determination of tianeptine using its quenching effect on Vilazodone" An experimental study in which authors formulated a method for determining and quantifying tianeptine in a pharmaceutical sample	The quenching effect of tianeptine on vilazodone was used to analyze tianeptine via spectrofluorimetry. Tianeptine concentration in a known sample was measured against calibration curves. The method was successful in the accurate determination and quantification of tianeptine concentration	A rapid, low-cost, highly sensitive test for evaluating tianeptine was created using vilazodone and spectrofluorimetry. This may be useful in the clinical setting
Bakota et al. (2018) [9]	"Case Reports of Fatalities Involving Tianeptine in the United States" A case report of two separate fatalities involving tianeptine intoxication in Texas. The authors developed a method of detecting and quantifying tianeptine in a given sample	Significantly elevated levels of tianeptine were detected in samples taken from both individuals. LC-TOF-MS and LC-MS-MS were successfully used to detect and quantify tianeptine in a sample	Authors report the first two known fatalities due to tianeptine intoxication in the U.S. LC-TOF-MS is an effective method for detecting tianeptine presence. At the same time, LC-MS-MS accurately quantifies tianeptine in a sample
Dempsey et al. (2017) [26]	"Acute Toxicity from Intravenous Use of the Tricyclic Antidepressant Tianeptine" Case report of a 36-year-old male who presented after an IV injection of tianeptine powder and became unresponsive	The patient was reversed with multiple doses of naloxone. LC-MS-MS successfully quantified levels of tianeptine in the patient's urine sample at 2 ng/ml	Naloxone was effective in reversing the effects of tianeptine. LC-MS-MS helps quantify tianeptine in a urine sample. The low urine level of tianeptine may be due to the rapid metabolism of the drug
Karim and Ioannou (2020) [28]	"Tianeptine Abuse Leading to an Episode of Psychosis: A Case Report and Literature Review" A case report of a 28-year-old female taking supratherapeutic doses of tianeptine who presented with an episode of psychosis	The patient had a history of schizoaffective disorder bipolar type and was reportedly self-administering tianeptine in doses of up to 100 mg daily. Symptoms of psychosis resolved after 2 days of abstinence	Tianeptine may precipitate psychosis. Clinicians should review all substances ingested by the patient when taking a history

Table 1 continued

Author, year published, and citation	Study title and description	Results	Conclusions
Lauhan et al. (2018) [23]	"Tianeptine Abuse and Dependence: Case Report and Literature Review" A case report of a 44-year-old male with the escalating use of tianeptine, followed by a comprehensive literature review	The patient experienced difficulty discontinuing tianeptine use. A barbiturate was identified as an adulterant in this case. Controlled administration of lorazepam and diazepam in combination with gabapentin and mirtazapine was effective. The detailed literature review identified the most significant instances of tianeptine abuse in younger ages, males, and those with a history of substance abuse	Tianeptine may produce dependence and withdrawal effects in patients. Adulterants may be present in tianeptine procured from unregulated sources. Inpatient benzodiazepine tapers may be used if outpatient medication tapers fail
Pélissier-Alicot et al. (2008) [29]	"Planned complex suicide: an unusual case" Case report of a 67-year-old woman who died in a planned complex suicide involving electrocution, wrist-cutting, and tianeptine overdose	An autopsy revealed massive ingestion of tianeptine and therapeutic or sub-therapeutic concentrations of other drugs. A hairdryer with the victim was found in the bathtub, suggestive of electrocution. The advanced state of decomposition complicated the identification of a cause of death	Tianeptine may be implicated in complex suicide. However, complex suicide makes accurately identifying the cause of death difficult, necessitating an interdisciplinary approach
Proença et al. (2007) [25]	"Fatal intoxication with tianeptine (Stablon)" Case of a 26-year-old man who died by apparent suicidal ingestion of tianeptine and alcohol intoxication	Analysis of the blood, urine, liver, and stomach contents at autopsy revealed concentrations of tianeptine levels with intoxication. Serum ethanol was also elevated. LC-DAD-MS was used in the quantitation of tianeptine concentrations	Serum tianeptine concentration was in line with previous reports of fatal tianeptine intoxication. The cause of death was ruled as suicidal ingestion of tianeptine with concurrent alcohol use. LC-DAD-MS was effectively used in quantitation

Table 1 continued

Author, year published, and citation	Study title and description	Results	Conclusions
Springer and Cubała (2018) [24]	"Tianeptine Abuse and Dependence in Psychiatric Patients: A Review of 18 Case Reports in the Literature" Review 18 cases of tianeptine abuse to identify any patterns in the literature	A detailed literature search returned 18 cases of tianeptine abuse. The majority of observed cases involved individuals ages 30–45 and females. Common symptoms of dependence were identified in 16 of the 18 cases. A history of substance abuse was identified in 13 of the 18 cases	Major risk factors for tianeptine abuse include younger age, female sex, and history of substance abuse. Caution should be used when prescribing tianeptine to groups at higher risk of developing dependence and abuse
Trowbridge and Walley (2019) [30]	"Use of Buprenorphine-Naloxone in the Treatment of Tianeptine Use Disorder" Case report of a 24-year-old male who was presented for failed detoxification from tianeptine	The patient had been purchasing tianeptine online to treat his anxiety but had gradually increased the dose due to worsening withdrawal symptoms and failed attempts at detoxification. He was successfully treated with buprenorphine/naloxone with the cessation of most symptoms	Long-term use of tianeptine may devolve into a dependency disorder. The presentation may be similar to opioid use disorder and should be treated with appropriate medical therapies
Wagstaff et al. (2001) [32]	"Tianeptine" A review of the chemical and therapeutic properties of tianeptine	Tianeptine enhances serotonin uptake in the brain and undergoes significant extrarenal metabolism. It is as efficacious as common SSRIs and TCAs but with a side effect profile closer to SSRIs. Typical side effects may include GI upset, headaches, dizziness, and changes in dreaming	Tianeptine is an effective antidepressant with a favorable drug profile and may have utility in special population groups, including elderly patients and those with chronic alcohol use disorder

respiratory depression associated with supratherapeutic doses of tianeptine was reversed when naloxone was administered. The authors noted that naltrexone effectively prevented tianeptine-dependent motor dysfunction [31].

Benzodiazepine tapers may assist in controlled withdrawal if the patient experiences difficulty completing a tianeptine taper. Lauhan et al. reported successfully using an inpatient benzodiazepine taper in a 44-year-old man who had previously failed outpatient tianeptine taper. The patient was initially administered 0.5 mg of oral lorazepam before being switched to diazepam and received 30 mg of diazepam over the 2 days of inpatient care [23]. Table 1 is

a summary of the studies involving tianeptine in the available literature.

CONCLUSIONS

Tianeptine is a drug that is approved in other countries for the treatment of MDD. It has no clinical use or clinical approval in the United States by the FDA. This drug can be obtained online or at small retail locations such as gas stations or mini-marts. Its action at the mu-opioid receptor can produce an opioid-like euphoric high and is associated with a short half-life of only around 2½ h. The interaction with opioid receptors is weak, but tolerance and dependence have been seen in the limited literature. Tianeptine has been used in both overdoses and suicide attempts. Overdoses of the substance have been successfully treated with the use of naloxone.

Despite increasing reports of tianeptine, few studies guide treating patients who use this substance. Case reports have suggested success in treating tianeptine use similar to opioid use, with naloxone for acute overdose and buprenorphine to treat dependence. Furthermore, unregulated distribution has made monitoring usage rates, adverse effects, and gathering information about those who use tianeptine extremely challenging. This situation has underscored social media's value in supplementing clinical knowledge when traditional sources are limited. Continued study is necessary to understand the dangers and guide medical treatment for tianeptine and other "gas station" drugs so that they may be appropriately regulated.

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REFERENCES

1. Major Depression [Internet]. National Institute of Mental Health (NIMH). [cited 2023 Jan 22].

Available from https://www.nimh.nih.gov/health/statistics/major-depression

2. Smith K. Mental health: a world of depression. Nature. 2014;515(7526):180–1.

3. Ruberto VL, Jha MK, Murrough JW. Pharmacological treatments for patients with treatment-resistant depression. Pharm Basel Switz. 2020;13(6):116.

4. Alamo C, García-Garcia P, Lopez-Muñoz F, Zaragozá C. Tianeptine, an atypical pharmacological approach to depression. Rev Psiquiatr Salud Ment. 2019;12(3):170–86.

5. Preskorn SH. Tianeptine: a facilitator of the reuptake of serotonin and norepinephrine as an antidepressant? J Psychiatr Pract. 2004;10(5):323.

6. Rushton W, Rivera J. Tianeptine: a new frontier in surveillance and understanding through social media. Am J Drug Alcohol Abuse. 2021;47(4):411–3.

7. Nutrition C for FS and A. Tianeptine in dietary supplements. FDA [Internet]. 2020 Jun 22 [cited 2023 Mar 4]; Available from https://www.fda.gov/food/dietary-supplement-products-ingredients/tianeptine-dietary-supplements

8. Bailey SJ, Almatroudi A, Kouris A. Tianeptine: an atypical antidepressant with multimodal pharmacology. Curr Psychopharmacol [Internet]. 2018 Jan 2 [cited 2023 Mar 5];6(2). Available from http://www.eurekaselect.com/152697/article

9. Bakota EL, Samms WC, Gray TR, Oleske DA, Hines MO. Case reports of fatalities involving tianeptine in the United States. J Anal Toxicol. 2018;42(7):503–9.

10. Smith KE, Rogers JM, Strickland JC, Epstein DH. When obscurity becomes a trend: social-media descriptions of tianeptine use and associated atypical drug use. Am J Drug Alcohol Abuse. 2021;47(4):455–66.

11. Tianeptine: new description of the mechanism of action and change of technical data sheet. Elsevier Enhanced Reader [Internet]. [cited 2023 Mar 19]. Available from https://reader.elsevier.com/reader/sd/pii/S217350502100011X?token=0A6A7A2CB1D74049B774D95FB8891A2439596A9B08A7FE370 7DB14FFE902CAA6231D91F78CF398C91331846CA8EC2 EB8&originRegion=us-east-1&originCreation=20230319173426

12. Moriguchi S, Takamiya A, Noda Y, Horita N, Wada M, Tsugawa S, et al. Glutamatergic neurometabolic levels in major depressive disorder: a systematic review and meta-analysis of proton magnetic resonance spectroscopy studies. Mol Psychiatry. 2019;24(7):952–64.

13. Michienzi AE, Borek HA. Emerging agents of substance use/misuse. Emerg Med Clin North Am. 2022;40(2):265–81.

14. Samuels BA, Nautiyal KM, Kruegel AC, Levinstein MR, Magalong VM, Gassaway MM, et al. The behavioral effects of the antidepressant tianeptine require the mu-opioid receptor. Neuropsychopharmacology. 2017;42(10):2052–63.

15. Commissioner O of the. Tianeptine products linked to serious harm, overdoses, death. FDA [Internet]. 2022 Feb 10 [cited 2023 Jan 22]. Available from https://www.fda.gov/consumers/consumer-updates/tianeptine-products-linked-serious-harm-overdoses-death

16. Synthetic Drugs | CADCA [Internet]. [cited 2022 Dec 29]. Available from https://www.cadca.org/synthetic-drugs#_ftn6

17. Stovall M. Mark Stovall: gas station drugs: the hidden danger around every corner [internet]. The Dispatch. 2022 [cited 2022 Dec 29]. Available from https://cdispatch.com/opinions/2022-10-14/mark-stovall-gas-station-drugs-the-hidden-danger-around-every-corner/

18. Gas Station Drugs—Southern Medical Association [Internet]. 2022 [cited 2022 Dec 29]. Available from https://sma.org/gas-station-drugs/

19. Warren A. State health officials sounding alarm on 'gas station heroin' [internet]. https://www.wlbt.com. 2022 [cited 2022 Dec 29]. Available from https://www.wlbt.com/2022/03/25/state-health-officials-sounding-alarm-gas-station-heroin/

20. Alyssa. What is gas station dope? Banyan Pompano [Internet]. Banyan Treatment Center. 2022 [cited 2022 Dec 29]. Available from https://www.banyantreatmentcenter.com/2022/05/31/what-is-gas-station-dope-pompano/

21. Nikki. Gas station drugs can contain addictive substances hidden in plain sight [Internet]. APCB-ham. 2022 [cited 2022 Dec 29]. Available from https://apcbham.org/2022/06/06/gas-station-drugs-can-contain-addictive-substances-hidden-in-plain-sight/

22. Jorandby. Update on "Gas Station Heroin" and other legal drugs. Psychology Today [Internet]. 2022 [cited 2022 Dec 29]. Available from https://www.psychologytoday.com/us/blog/use-your-brain/202208/update-gas-station-heroin-and-other-legal-drugs

23. Lauhan R, Hsu A, Alam A, Beizai K. Tianeptine abuse and dependence: case report and literature review. Psychosomatics. 2018;59(6):547–53.

24. Springer J, Cubała WJ. Tianeptine abuse and dependence in psychiatric patients: a review of 18 case reports in the literature. J Psychoactive Drugs. 2018;50(3):275–80.

25. Proença P, Teixeira H, Pinheiro J, Monsanto PV, Vieira DN. Fatal intoxication with tianeptine (Stablon). Forensic Sci Int. 2007;170(2–3):200–3.

26. Dempsey SK, Poklis JL, Sweat K, Cumpston K, Wolf CE. Acute toxicity from intravenous use of the tricyclic antidepressant tianeptine. J Anal Toxicol. 2017;41(6):547–50.

27. Abdullatef OA, Morshedy S, Khalifa YM, Talaat W. Spectrofluorimetric determination of tianeptine using its quenching effect on vilazodone. Spectrochim Acta A Mol Biomol Spectrosc. 2021;15(251): 119412.

28. Karim A, Ioannou C. Tianeptine abuse leading to an episode of psychosis: a case report and literature review. J Psychiatr Pract. 2020;26(2):146–8.

29. Pélissier-Alicot AL, Gavaudan G, Bartoli C, Kintz P, Piercecchi-Marti MD, Desfeux J, et al. Planned complex suicide: an unusual case. J Forensic Sci. 2008;53(4):968–70.

30. Trowbridge P, Walley AY. Use of buprenorphine-naloxone in the treatment of tianeptine use disorder. J Addict Med. 2019;13(4):331–3.

31. Baird TR, Akbarali HI, Dewey WL, Elder H, Kang M, Marsh SA, et al. Opioid-like adverse effects of tianeptine in male rats and mice. Psychopharmacology. 2022;239(7):2187–99.

32. Wagstaff AJ, Ormrod D, Spencer CM. Tianeptine. CNS Drugs. 2001;15(3):231–59.