

Navigating the Nomenclature of a Purported “Dietary Supplement”: A Cautionary Tale for Consumers and Practitioners Regarding Tianeptine or “Gas Station Heroin”

Keith R. Martin

Center for Nutraceutical and Dietary Supplement Research, College of Health Sciences, University of Memphis, Memphis, TN, USA

Email: krmrtin4@memphis.edu

How to cite this paper: Martin, K.R. (2023) Navigating the Nomenclature of a Purported “Dietary Supplement”: A Cautionary Tale for Consumers and Practitioners Regarding Tianeptine or “Gas Station Heroin”. *Health*, **15**, 1338-1351.
<https://doi.org/10.4236/health.2023.1512087>

Received: September 16, 2023

Accepted: December 23, 2023

Published: December 26, 2023

Copyright © 2023 by author(s) and Scientific Research Publishing Inc.
This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).
<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

Dietary supplement sales have surpassed \$30 billion per year with their use becoming and remaining extremely popular amongst the general public. There are numerous bioactive components, both nutritive and non-nutritive, in dietary supplements with considerable efficacy in promoting health. However, there are many ways disallowed ingredients may enter the supplement pipeline with potentially toxic effects. Dietary supplements can be regulated (either pre- or post-market) as a drug, dietary supplement, a nutraceutical, new dietary ingredient (NDI), generally recognized as safe (GRAS) food ingredient, a food additive, or a food. A pharmaceutical drug (medication) is used to treat, cure, prevent, or diagnose a disease and is regulated by the FDA pre-market only and allowed by medical prescription, whereas the other labeling designations are largely regulated post-market. One such molecule with a labeling problem is tianeptine, which has global use as an efficacious, prescribed drug, while at the same time being considered a non-drug and potentially dangerous adulterant often referred to as gas station heroin. In this paper, we critically evaluate the use and labeling of this compound and attempt to clarify the conundrum surrounding its legal or illegal use. Tianeptine is effective and efficacious as an antidepressant in those responding poorly to selective serotonin reuptake inhibitors (SSRIs) and exhibits many medicinal characteristics of tricyclic antidepressants with fewer opioid-like side effects. As a result, sixty-six countries permit use of tianeptine as a prescription drug. At higher doses, tianeptine has recently been shown to exhibit significant potential for abuse and dependency along with toxicity. As such, the US does not recognize tianeptine as an FDA-approved drug or as a dietary supple-

ment, nutraceutical, new dietary ingredient (NDI), GRAS ingredient, or a food. Instead, tianeptine is a synthetic adulterant of a dietary supplement and considered technically an unapproved food additive. In conclusion, tianeptine, although viewed as a safe dietary supplement by many, is illegal in the US despite benefits to many but toxicity to others that make it vital that consumers and healthcare providers learn to critically evaluate and navigate the often confusing nomenclature of a purported dietary supplement to convey to the public whether it is efficacious, safe, and legal.

Keywords

Tianeptine, SSRI, Tricyclic Antidepressant, Dietary Supplement, Pharmaceutical, Nutraceutical, GRAS, NDI

1. Introduction

Dietary supplement sales have reached the multibillions and their use is extremely popular amongst the general public in promoting health with an estimated one half of the population consuming at least one dietary supplement [1] [2]. There is no doubt that there are many bioactive components in supplements, both nutritive and non-nutritive, and many efficacious and useful components that do in fact promote health. However, inadequate oversight of these product ingredients can sometime allow, whether intentionally or not, the introduction of chemicals into the dietary supplement pipeline, which may affect efficacy and/or safety while the product remains on the market. Unintentional inclusion of a chemical would be considered contamination and intentional addition of illegal disallowed potentially toxic ingredients to products would constitute adulteration. Toxicants are synthetic, human-made, chemicals, whereas toxins are poisons produced within living cells or organs of plants, animals, and bacteria.

2. Problems with Adulteration of Dietary Supplements

Introduction of an undesired, illegal, and/or unapproved ingredient into a dietary supplement or food can occur via contamination or adulteration. The former is accidental and the latter intentional. From 2007 through 2016, 776 adulterated dietary supplements were identified by the FDA and 146 dietary supplement manufacturers and/or distributors were identified. The majority of these products were marketed for sexual enhancement (353 [45.5%]), weight loss (317 [40.9%]), or muscle building (92 [11.9%]), with 157 adulterated products (20.2%) containing >1 unapproved ingredient [2]. Some 28 products were specifically identified in up to three warnings by the FDA more than a half year apart with 19 (67.9%) returning to the market with even more unapproved ingredients in the subsequent marketed product [2]. At a time when 150 million Americans spend over \$20.5 billion on dietary supplements, many posit that the FDA has

responded too slowly and reluctantly to governmental action and mandates to implement the law and needs to do more to ensure that safe and efficacious products enter the market [3] [4]. Immersion into the market places considerable burden on healthcare providers and uninformed consumers as to safety, efficacy, and/or toxicity of readily available products.

3. Discovery and Initial Legitimate Use of Tianeptine

Tianeptine was discovered and patented by The French Society of Medical Research in the 1960s and used in Europe as an antidepressant to treat patients who responded poorly to selective serotonin reuptake inhibitors (SSRIs) [5] [6]. This synthetic molecule exhibited many similar, beneficial characteristics of tricyclic antidepressants such as fluoxetine and amitriptyline (**Figure 1**) via mu opioid receptor binding with downstream effects on pathways that is currently unclear but nonetheless effective in treating depression and anxiety, as well as asthma, irritable bowel syndrome (IBS), and purportedly improved mood but with fewer sedative, anticholinergic, and cardiovascular side effects and complications than traditional antidepressants [7] [8] [9] [10]. The mu receptors neuromodulate different physiological functions, primarily nociception but also stress, temperature, respiration, endocrine activity, gastrointestinal activity, memory, mood, and motivation [11] [12]. Mu-opioid receptors (MORs) bind opioids. However, opioid receptors are a very large family of receptors that include, in addition to MORs, delta-opioid receptors (DORs), kappa opioid receptors (KORs), and nociceptin receptors (NORs), also referred to as opioid-receptor-like receptor 1 (ORL1), which appear to have a critical role in the development of tolerance to mu-opioid agonists used as analgesics [13]. Current research suggests that tianeptine produces its antidepressant effects through the modulation of glutamate receptor activity, *i.e.*, AMPA and NMDA receptors, and affect the release of brain-derived neurotrophic factor (BDNF), which impacts neural plasticity [14]. More recent studies by support the role of tianeptine in the modulation of glutamatergic activity in the amygdala, the emotional region of the brain associated with memories [15]. In 2010, tianeptine was patented by Biophore India Pharmaceuticals and approved for prescription because clinical data showed at the time it was an effective antidepressant with acceptable safety and tolerability. It is currently used in 66 countries, but not in New Zealand, Canada, the United Kingdom or the US [16]. This, however, has not impeded the ease of availability, growing use and popularity in the US.

4. Rise in Popularity and Recognition as an Adulterant

Some experts attribute tianeptine's rise in popularity in the U.S. in part to a 2014 study in the medical journal *Translational Psychiatry* [12], which found that the drug exhibited effects similar to those of opioids and specifically MORs much like schedule 2 prescription drugs already on the market [12]. With these emerging reports of potency and efficacy, the FDA reported a marked increased

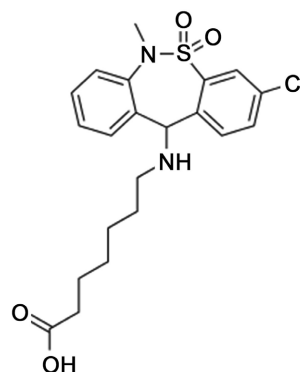


Figure 1. Chemical structure of tianeptine.

in imports starting around 2015. Subsequently, dietary supplements with names such as Tianaa, Za Za, Coaxil, Salymbra, Stablon, Tatinol, Tiana Red or Tiana, Tianeurax, Tynept, Zaza Red, and Zinosal appeared on the market online and, in particular at quick service convenience stores and/or gas stations, allowing purchase by anyone including minors although unapproved and illegal for use in the US. This ultimately generated the phrase “gas station heroin” based on ease of acquisition at convenience stores, *i.e.*, gas stations, and the capacity of tianeptine to bind mu opioid receptors as schedule 2 drugs do, e.g., heroin, although requiring higher doses (>100 mg) [13]. As a note, this compound and the supplement blend that it adulterates have not been reported to contain heroin but instead the mixture containing tianeptine mimics the opioid-like effects, which may be rescued with the opioid antagonist naloxone if overdosed [17]. Dissemination of the potential beneficial actions and opioid-like effects, use has considerably increased as well as self-regulated dosages markedly exceeding that suggested for efficacy against depression (25 - 50 mg/day). Users quickly realized that megadoses (>100 mg) could elicit opioid-like effects and, as a result, substance abuse commenced with some consumers taking megadoses each day [18] [19]. Moreover, many commercial tianeptine products contain 100 times the normal therapeutic dose, and without rigorous regulation, individuals are unknowingly consuming high doses that can lead to dangerous side effects and dependency [20]. Ultimately, public focus shifted from benefits to the negative impact and it was realized that tianeptine was highly addictive and those attempting to cease dosing experienced serious withdrawal side effects and reports of severe opioid-induced effects occurred [16] [21]. This resulted in hundreds of reports to Poison Control Centers (Figure 2) and to the FDA regarding serious adverse events [22] [23] [24]. Ultimately governmental action entailed advisement to discontinue use (with appropriate medical assistance) or avoidance of the product altogether.

5. Is Tianeptine a Drug with Pharmaceutical Activity?

Tianeptine can attenuate symptoms of depression-associated anxiety with sufficient tolerance and minimal sedation and/or cognitive impairment [25]. These

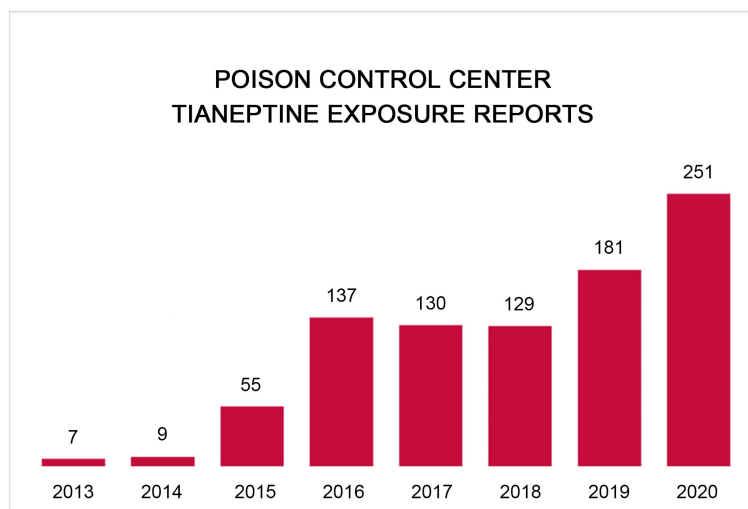


Figure 2. The number of reports generated by year by the PoisonControl-Center regarding Tianeptine exposure leading to adverse effects. Reprinted with permission.

effects have been attributed, in large part, to neurobiological properties such as prevention and reversal of stress-associated structural and cellular modifications to the brain and modulation of impaired neurotransmission by the excitatory amino acid glutamic acid or glutamate [26] [27] [28]. In the hippocampal region of the brain, tianeptine interferes with stress-induced dendritic atrophy, improves neurogenesis, reduces undesired cell death, and normalizes metabolite levels and volume of the hippocampus [29]. Moreover, tianeptine acts as a mu-opioid receptor (MOR) and a weak delta-opioid receptor (DOR) agonist that triggers the modulation of the glutaminergic system, which is responsible for antidepressant and anxiolytic effects [12] [30]. MORs are broadly exhibited throughout the hippocampus in the brain, which may activate glutamatergic neurons and synapses through several mechanisms [30]. Tianeptine increases the availability of dopamine in the nucleus accumbens, which can foster glutamate release at presynaptic dopamine receptors on glutamatergic presynaptic terminals [30]. These beneficial effects have been observed also in the amygdala and cortex of the brain and could mitigate and/or reverse stress-induced dysfunction in neuronal and synaptic signaling. The collective neurobiological properties of tianeptine may explain efficacious antidepressant activity and anxiolytic outcomes in patients with depression, as well as the purported absence of adverse effects on cognitive function and memory [6]. From the early study of tianeptine, there have many similar reports of beneficial pharmacological effects of consumption leading to its ongoing prescription in some countries [31] [32]. However, recent research activities have demonstrated a dangerous downside to its use leading ultimately to a conundrum.

Since 1938, submission of a New Drug Application (NDA) is the mandatory means for drug sponsors to formally propose to the FDA a new pharmaceutical, viz., drug, for approval and commercialization in the U.S. The application for an

Investigational New Drug (IND) is supported with robust data collected in animal studies and human clinical trials demonstrating efficacy and effectiveness, without toxicity at intended doses. Tianeptine has not undergone this process and is not approved as a drug by the FDA for any use in health management in the US and, as a result, is not scheduled as a drug according to FDA statutory regulations. However, in numerous individual US states, tianeptine is classified as a Schedule II drug, a legally protected term, meaning it may lead to severe psychological or physical dependence and is, therefore, banned [18] [33]. Other examples of schedule 2 drugs include morphine, methamphetamine, cocaine, methadone, hydrocodone, fentanyl, and phencyclidine (PCP) [34]. The drug—banned in Alabama, Michigan, Mississippi, Tennessee, Georgia, Indiana, and Ohio—is unapproved and unregulated by the FDA though other countries in Europe, Asia and Latin America have approved tianeptine as a prescription drug to treat depression and anxiety legally in clinical practice. These observations may introduce confusion when considering the legal definition of a drug by the FDA (Drugs@FDA Glossary of Terms) [FDA]:

- recognized by an official pharmacopoeia (USP) or formulary.
- intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- other than food intended to affect the structure or any function of the body.
- intended for use as a medical component but not a device, component, part or accessory of a device.
- biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).

Depending on a product's ingredients and the claims with which a product is marketed, it is regulated as a drug, dietary supplement, food ingredient, or food [35] [36]. Generally, if a product is marketed as a dietary supplement but claims to diagnose, mitigate, treat, cure, or prevent a specific disease or diseases, then it is regulated as a drug under the purview of the FDA and must undergo a rigorous process of testing and validation.

6. Is Boactive Tianeptine a Dietary Supplement or New Dietary Ingredient (NDI)?

The Dietary Supplement Health and Education Act (DSHEA) of 1994 defined by statute the terms “dietary ingredient” and “new dietary ingredient”. To be a “dietary ingredient”, an ingredient in a dietary supplement must be one of the following: vitamin, mineral, herb or other botanical, amino acid, a dietary substance for use by humans to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any dietary ingredient from the other categories listed above [35] [36]. To that end, tianeptine is not a dietary supplement by itself nor is it an NDI although products may be adulterated with it under the FD&C Act.

A new “New Dietary Ingredient” or NDI is an ingredient that meets the defi-

inition of a “dietary ingredient” but was not marketed in the United States before October 15, 1994 (pre-passage of DSHEA) [37]. Tianeptine, however, has been determined to violate statutory law regarding the definition of a food additive. Any component not naturally part of the human diet must be approved by the FDA, as an NDI, before being introduced into the food supply. Some components rely on history of use, length of use, and lack of adverse effects or events to promote and/or support their ingredient and/or product so that it is known generally as GRAS or *generally recognized as safe* based on supportive documentation [37] [38]. Collection and submission of supporting materials must be made to the FDA for this determination and is an alluring option for many dietary supplement producers and retailers [39].

Under section 413(a)(2) of the FD&C Act (21 U.S.C. 350b(a)(2)), the manufacturer or distributor of an NDI that has not been present in the food supply as an article used for food, or a dietary supplement containing such an NDI, must submit a premarket safety notification to FDA at least 75 days before introducing the product into interstate commerce [37]. This guidance is intended to help manufacturers and distributors of dietary ingredients and dietary supplements decide whether to submit a premarket safety notification to FDA (commonly referred to as NDI notifications) for a product that is or contains an NDI, which will allow execution of review more efficiently and response more quickly.

Tianeptine does not fall within this category either and violates the FD&C Act and is considered an illegal, unapproved food additive or adulterant. As a result, many dietary supplement manufacturers have committed the additional resources necessary to obtain GRAS status for their supplements from the FDA rather than risk prohibition post-market [37]. Once reviewed by the FDA, the FDA can issue a statement of “No Objection” (to the application), which permits acceptance into the food supply. Tianeptine is not GRAS under its conditions of use in the specific dietary supplement product. Because tianeptine does not qualify as a dietary ingredient or NDI and is not GRAS or otherwise exempt from the food additive definition, the product is adulterated because it contains an unsafe food additive.

7. Might Tianeptine Be a Nutraceutical?

The term “nutraceutical” is not defined by US law and, as such, nutraceuticals are largely unregulated pre-market, since they exist in the same category as dietary supplements and food additives established by the FDA, under the authority of the FD&C Act. The word “nutraceutical” is a blending of the words “nutrition” and “pharmaceutical” to denote mixtures and/or molecules that are derived from natural food sources, and not synthetically produced non-dietary compounds, *i.e.*, tianeptine, and are already consumed in the diet but in much higher amounts, but not excessive, than in the average diet [40]. A non-drug nutraceutical is a pharmaceutical alternative in that the product is isolated or purified from foods and generally sold in medicinal forms not usually associated

with food because it has physiological benefit or provides protection against chronic disease. In short, pharmaceuticals are the result of clinical trials aimed at treating specific diseases. Nutraceuticals are food-based, naturally occurring substances provided often in higher amounts than normally consumed in the diet used for the mitigation, prevention, and treatment of diseases. Given these definitions, tianeptine, at least in the US, is neither a pharmaceutical, viz., drug, nor a nutraceutical.

Since these initial reports, considerable clarity has emerged regarding the use and misuse of tianeptine. All the while, tianeptine is illegally marketed as a dietary supplement or as an ingredient in a dietary supplement in products sold under names like Za Za Red, Pegasus, T-D Red and Tianna [41]. Numerous creative strategies have been attempted to circumvent the obvious concerns with toxicants. For example, tianeptine has many different names as mentioned previously, so ingredient labels must be read carefully before taking any supplement. Look for tianeptine, tianeptine sodium or tianeptine sulfate listed in the ingredients or supplement facts noting that the product may be in both powder and pill form. As one might expect, the product is sold in vibrant, bright-colored bottles with advertising claims that it helps improve brain function, treats anxiety, depression, pain, and opioid use disorder [41]. Moreover, to bypass the FD&C Act, tianeptine is typically sold as “not for human consumption” or “for research purposes only” or simply added as an adulterated, perhaps undisclosed, ingredient in a marketed dietary supplement.

The US FDA does not consider tianeptine to be a substance that meets the statutory definition of a dietary ingredient (supplement), nutraceutical, or FDA-approved drug and is instead considered an unsafe and unapproved food additive or adulterant. Yet, some companies are illegally marketing and selling products containing tianeptine to consumers. Moreover, dangerous and unproven claims are proffered that tianeptine can improve brain function and treat anxiety, depression, pain, opioid use disorder, and other conditions that have not been evaluated by a regulatory agency or committee regarding veracity. The relatively recent emergence of a significant number of adverse events, calls to Poison Control Centers, and problems with dependency, addiction, and withdrawal symptoms from tianeptine have been alarming and have prompted immediate action [18].

Some supplement manufacturers are promoting potentially toxic compounds—often with unproven drug claims and purposely manipulating the statutory definitions of what defines a dietary supplement, which, as likely intended, can confuse and/or mislead consumers. Most products when stripped free of the adulterant tianeptine, are legitimate, legally marketed dietary supplements. Ultimately, potentially illegal activities place the collective dietary supplement industry at risk by confusing consumers, harming patients and debasing reputable dietary supplement products by associating them with the activities of disallowed components. In this case, these companies are targeting unaware, vulnerable patients

who may be seeking alternative treatments to serious medical conditions like opioid use disorder.

8. Tianeptine Use as an Increasing Public Health Risk

The U.S. Centers for Disease Control and Prevention (CDC) warned that clinical effects of tianeptine abuse and withdrawal can mimic opioid toxicity and withdrawal. The CDC also reported there has been a rise in tianeptine exposure calls to U.S. Poison Control Centers from 2014-2017, suggesting an emerging public health risk (**Figure 2**) due to significant health effects, including neurologic, cardiovascular, and gastrointestinal signs and symptoms, and some effects mimicking opioid toxicity and withdrawal [20] [42]. However, growing misuse and abuse have mandated intervention into the availability and use of tianeptine. As a result, the FDA issued its first official warning in 2018 to two dietary supplement companies that had been openly selling products containing tianeptine. As observed in online marketing, the previous appearance of tianeptine in product labels now is absent from many products from companies that were contacted by the FDA. The piercing question now is whether the tianeptine has been removed from the product or simply the name from the label?

9. What Can a Health Care Professional Do?

In the US tianeptine abuse has increased nearly 25-fold between 2014 and 2019 due largely to misleading claims that it safely reduces anxiety, depression, pain, and helps mitigate opioid-associated addiction. Patients receiving FDA-approved medication assisted treatments (MAT) for opioid dependence markedly reduce risk of death from all causes by half. However, using products with unsubstantiated claims such as tianeptine may prevent those addicted to opioids from pursuing approved, safe, and effective treatments ultimately prolonging recovery and increasing the risk of mortality.

It is imperative that health care providers (including doctors, dentists, pharmacists, and dietitians) solicit and consumers reveal information regarding dietary supplement and nutraceutical use, frequency of use, and dose used. The Office of Dietary Supplements (ODS) within the NIH website has a useful printable form for documenting and noting the name, dose, frequency, and the reason for use for dietary supplements. Consumers can then share and consult with healthcare providers, ideally prior to consumption, who can help determine which supplements, if any, might be valuable for client or patient. More importantly, obtaining a health care provider's approval prior to replacing or adding on supplements to prescribed FDA-approved medicines is also important. Additionally, prior to any type of surgical procedure, consultation with a health care provider regarding routinely used supplements should be undertaken since this can markedly affect outcome and prognosis.

A dietary supplement's safety depends on many things, such as its chemical composition, mechanism of action, e.g., SSRI, mu opioid receptor agonist, etc.,

form and route administered, and the amount consumed. Some suggested questions about dietary supplements are listed below:

- What are its potential benefits for me? Why am I taking this?
- How, when, and for how long should I take the supplement?
- Does it have any safety and/or toxicity risks?
- What is the appropriate dose to take?

Reducing the number of Americans who are addicted to opioids (currently at >2,000,000) and cutting the rate of new addiction is a priority for the FDA and includes promoting more widespread innovation and access to opioid addiction treatments. New safe and effective MATs are becoming more available. Health care professionals and consumers are encouraged to report any adverse events related to these products to a primary caregiver and the FDA.

There are many other recommendations for healthcare providers regarding course of action with suspected tianeptine use and misuse. Providers who suspect tianeptine exposure in any client should call a Poison Control Center for advice regarding diagnosis, treatment, and prevention of toxicity [43]. One-on-one treatment should include monitoring of blood pressure and heart rate, supportive care, and an EKG evaluation if the expertise is present until more advanced care is available [44]. During typical counseling sessions, providers are urged to counsel clients regarding the risks of tianeptine even if the client is not ready to cease use. At this point, it is also helpful to inform patients about potential overdose risk from mixing substances, e.g., other opioids. In particular, convey the message clearly and strongly that convenience and availability, as found with gas stations, does not prove safety or legality. In advanced cases of poisoning or overdose, administration of over-the-counter naloxone, an opioid antagonist, is advised particularly if an individual has slow, ineffective respiration [45]. Depending on the available resources, healthcare professionals should refer clients or patients to local drug prevention organizations or other reliable, community-based providers that may direct clients to additional needed resources associated with drug use.

10. Conclusion

In conclusion with so many supplements on the market (upwards of 29,000) and the current mechanism of governmental regulation with largely post-market review, it is imperative that health professionals stay abreast of dietary supplement and nutraceutical use by patients, clients, etc. and scientific reports of potential problems. Initially emergence of adverse events via social media should be viewed cautiously but does alert one to follow up with reputable scientific sources such as the ODS, NIH, Consumer Reports, FDA, FTC, etc. as to the nature of the purported adverse effect, toxicant, adulterant, drug, etc. [37]. Health care providers and public health officials should also proactively report adverse effects to the FDA MedWatch reporting system and contact Poison Control Centers for clinical guidance with perhaps initially a focus on the adverse effects associated with

tianeptine. This is indeed a compelling case seemingly centered on scientific semantics. That is, tianeptine has compelling evidence to suggest clear benefit against anxiety and depression and effective evidence-based outcomes with limited toxicity when used as legally prescribed. However, some countries have not evaluated tianeptine as a drug and disallow its prescription. Moreover, the increased misuse of this compound has highlighted its potential lack of safety and likelihood of abuse and misuse.

Acknowledgements

The author thanks the College of Health Sciences for support with this manuscript.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

- [1] Pawar, R.S. and Grundel, E. (2017) Overview of Regulation of Dietary Supplements in the USA and Issues of Adulteration with Phenethylamines (PEAs). *Drug Testing and Analysis*, **9**, 500-517. <https://doi.org/10.1002/dta.1980>
- [2] Tucker, J., Fischer, T., Upjohn, L., Mazzera, D. and Kumar, M. (2018) Unapproved Pharmaceutical Ingredients Included in Dietary Supplements Associated with US Food and Drug Administration Warnings. *JAMA Network Open*, **1**, e183337. <https://doi.org/10.1001/jamanetworkopen.2018.3337>
- [3] Bailey, R.L., Gahche, J.J., Lentino, C.V., *et al.* (2011) Dietary Supplement Use in the United States, 2003-2006. *The Journal of Nutrition*, **141**, 261-266. <https://doi.org/10.3945/jn.110.133025>
- [4] Burdock, G.A. (2006) The Importance of GRAS to the Functional Food and Nutra-ceutical Industries. *Toxicology*, **221**, 17-27. <https://doi.org/10.1016/j.tox.2006.01.012>
- [5] Kasper, S. and Olie, J.P. (2002) A Meta-Analysis of Randomized Controlled Trials of Tianeptine versus SSRI in the Short-Term Treatment of Depression. *European Psychiatry*, **17**, 331-340. [https://doi.org/10.1016/S0924-9338\(02\)00651-X](https://doi.org/10.1016/S0924-9338(02)00651-X)
- [6] Brink, C.B., Harvey, B.H. and Brand, L. (2006) Tianeptine: A Novel Atypical Anti-depressant That May Provide New Insights into the Biomolecular Basis of Depression. *Recent Patents on CNS Drug Discovery*, **1**, 29-41. <https://doi.org/10.2174/157488906775245327>
- [7] Wagstaff, A.J., Ormrod, D. and Spencer, D.M. (2001) Tianeptine: A Review of Its Use in Depressive Disorders. *CNS Drugs*, **15**, 231-259. <https://doi.org/10.2165/00023210-200115030-00006>
- [8] McEwen, B.S. and Olie, J.P. (2005) Neurobiology of Mood, Anxiety, and Emotions as Revealed by Studies of a Unique Antidepressant: Tianeptine. *Molecular Psychiatry*, **10**, 525-537. <https://doi.org/10.1038/sj.mp.4001648>
- [9] Wilde, M.I. (1996) Tianeptine: A Review of Its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Depression and Coexisting Anxiety and Depression. *Drugs*, **49**, 411-439.

- <https://doi.org/10.2165/00003495-199549030-00007>
- [10] Zoladz, P.R., Park, C.R., Munoz, C., Fleshner, M. and Diamond, D.M. (2008) Tianeptine: An Antidepressant with Memory-Protective Properties. *Current Neuropharmacology*, **4**, 311-321. <https://doi.org/10.2174/157015908787386096>
- [11] Allain, F., Ehrlich, A.T., McNicholas, M., Gross, F., Ma, W., Kieffer, B.L. and Daroq, E. (2023) Chronic Tianeptine Induces Tolerance in Analgesia and Hyperlocomotion via Mu-Opioid Receptor Activation in Mice. *Frontiers in Psychiatry*, **14**, Article 1186397. <https://doi.org/10.3389/fpsy.2023.1186397>
- [12] Gassaway, M.M., Rives, M.L., Kruegel, A.C., Javitch, J.A. and Sames, D. (2014) The Atypical Antidepressant and Neurorestorative Agent Tianeptine is a μ -Opioid Receptor Agonist. *Translational Psychiatry*, **4**, e411. <https://doi.org/10.1038/tp.2014.30>
- [13] Herman, T.F., Cascella, M. and Muzio, M.R. (2023) Mu Receptors. StatPearls, Treasure Island. <https://www.ncbi.nlm.nih.gov/books/NBK551554/>
- [14] Reagan, L.P., Hemndry, R.M., Rezbikov, L.R., Piroli, G.G., Wood, G.E., McEwen, B.S. and Grillo, C.A. (2007) Tianeptine Increases Brain-Derived Neurotrophic Factor Expression in the Rat Amygdala. *European Journal of Pharmacology*, **565**, 68-75. <https://doi.org/10.1016/j.ejphar.2007.02.023>
- [15] Kole, M.H.P., Swan, L. and Fuchs, E. (2022) The Antidepressant Tianeptine Persistently Modulates Glutamate Receptor Currents of the Hippocampal CA3 Commissural Associational Synapse in Chronically Stressed Rats. *European Journal of Neuroscience*, **6**, 807-816. <https://doi.org/10.1046/j.1460-9568.2002.02136.x>
- [16] Smith, E., Rogers, J., Strickland, J.C. and Epstein, D.H. (2021) When an Obscurity Becomes a Trend: Social-Media Descriptions of Tianeptine Use and Associated Atypical Drug Use. *The American Journal of Drug and Alcohol Abuse*, **47**, 455-466. <https://doi.org/10.1080/00952990.2021.1904408>
- [17] Ari, M., Oktar, S. and Duru, M. (2010) Amitriptyline and Tianeptine Poisoning Treated by Naloxone. *Human & Experimental Toxicology*, **29**, 793-795. <https://doi.org/10.1177/0960327110372403>
- [18] Samuels, B.A., Nautiyal, K.M., Kruegel, A.C., *et al.* (2017) The Behavioral Effects of the Antidepressant Tianeptine Require the Mu-Opioid Receptor. *Neuropsychopharmacology*, **42**, 2052-2063. <https://doi.org/10.1038/npp.2017.60>
- [19] Lauhan, R., Hsu, A., Alam, A. and Beizai, K. (2018) Tianeptine Abuse and Dependence: Case Report and Literature Review. *Psychosomatics*, **59**, 547-553. <https://doi.org/10.1016/j.psym.2018.07.006>
- [20] Evans, E.A. and Ma, S. (2014) Abuse and Misuse of Antidepressants. *Substance Abuse and Rehabilitation*, **5**, 107-120. <https://doi.org/10.2147/SAR.S37917>
- [21] Edinoff, A.N., Sall, S., Beckman, S.P., Koepnick, A.D., Gold, L.C., Jackson, E.D., Wenger, D.M., Cornett, E.M., Murnane, K.S., Kaye, A.M. and Kaye, A.D. (2023) Tianeptine, an Antidepressant with Opioid Agonist Effects: Pharmacology and Abuse Potential, a Narrative Review. *Pain and Therapy*, **12**, 1121-1134. <https://doi.org/10.1007/s40122-023-00539-5>
- [22] Baird, T.R., Akbarali, H.I., Dewey, W.L., Elder, H., Kang, M., Marsh, S.A., Peace, M.R., Poklis, J.L., Santos, E.J. and Negus, S.S. (2022) Opioid-Like Adverse Effects of Tianeptine in Male Rats and Mice. *Psychopharmacology*, **239**, 2187-2199. <https://doi.org/10.1007/s00213-022-06093-w>
- [23] El Zahran, T., Schier, J., Glidden, E., Kieszak, S., Law, R., Bottei, E., Aaron, C., King, A. and Chang, A. (2018) Characteristics of Tianeptine Exposures Reported to the National Poison Data System—United States, 2000-2017. *Morbidity and Mortality*

- Weekly Report*, **67**, 815-818. <https://doi.org/10.15585/mmwr.mm6730a2>
- [24] Marraffa, J.M., Stork, C.M., Hoffman, R.S. and Su, M.K. (2018) Poison Control Center Experience with Tianeptine: An Unregulated Pharmaceutical Product with Potential for Abuse. *Clinical Toxicology*, **56**, 1155-1158. <https://doi.org/10.1080/15563650.2018.1476694>
- [25] Guelfi, J.D., Duloire, C., Le Moine, P. and Tafani, A. (2002) Clinical Safety and Efficacy of Tianeptine in 1858 Depressed Patients Treated in General Practice. *Neuropsychobiology*, **25**, 140-148. <https://doi.org/10.1159/000118824>
- [26] McEwen, B.S., Magarinos, A.M. and Reagan, L.P. (2002) Structural Plasticity and Tianeptine: Cellular and Molecular Targets. *European Psychiatry*, **17**, 318-330. [https://doi.org/10.1016/S0924-9338\(02\)00650-8](https://doi.org/10.1016/S0924-9338(02)00650-8)
- [27] McEwen, B.S. and Chattarji, S. (2004) Molecular Mechanisms of Neuroplasticity and Pharmacological Implications: The Example of Tianeptine. *European Neuropsychopharmacology*, **14**, S497-S502. <https://doi.org/10.1016/j.euroneuro.2004.09.008>
- [28] McEwen, B.S., Chattarji, S., Diamond, D.M., Jay, T.M., Reagan, L.P., Svenningsson, P. and Fuchs, E. (2010) The Neurobiological Properties of Tianeptine (Stablon): From Monoamine Hypothesis to Glutamatergic Modulation. *Molecular Psychiatry*, **15**, 237-249. <https://doi.org/10.1038/mp.2009.80>
- [29] Kasper, S. and McEwen, B.S. (2008) Neurobiological and Clinical Effects of the Antidepressant Tianeptine. *CNS Drugs*, **22**, 15-26. <https://doi.org/10.2165/00023210-200822010-00002>
- [30] Andras, S. (2008) "Atypical" Antidepressive Mechanisms: Glutamatergic Modulation and Neuroplasticity in Case of Tianeptine. *Neuropsychopharmacologia Hungarica*, **10**, 305-313.
- [31] García-Alberca, J.M., Gris, E., de la Guía, P. and Mendoza, S. (2022) Effects of Tianeptine Treatment on Depression and Cognitive Function in Patients with Alzheimer's Disease: A 12-Month Retrospective Observational Study. *Journal of Alzheimer's Disease*, **88**, 707-720. <https://doi.org/10.3233/JAD-215630>
- [32] Alamo, C., Garcia-Garcia, P., Lopez-Munoz, F. and Zaragoza, C.P. (2019) Tianeptine, an Atypical Pharmacological Approach to Depression. *Revista de Psiquiatría y Salud Mental*, **12**, 170-186. <https://doi.org/10.1016/j.rpsm.2018.09.002>
- [33] Kisa, C., Bulbul, D.O., Aydemir, C. and Goka, E. (2007) Is It Possible to Be Dependent to Tianeptine, an Antidepressant? A Case Report. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, **31**, 776-778. <https://doi.org/10.1016/j.pnpbp.2007.01.002>
- [34] Drug Enforcement Administration and Department of Justice (2020) Drugs of Abuse. A DEA Resource Guide.
- [35] Bailey, R.L. (2020) Current Regulatory Guidelines and Resources to Support Research of Dietary Supplements in the United States. *Critical Reviews in Food Science and Nutrition*, **60**, 298-309. <https://doi.org/10.1080/10408398.2018.1524364>
- [36] Dickinson, A. (2011) History and Overview of DSHEA. *Fitoterapia*, **82**, 5-10. <https://doi.org/10.1016/j.fitote.2010.09.001>
- [37] Mister, S. and Hathcock, J. (2012) Under the Law, FDA Must Grant Different Standards for New Dietary Ingredients and Food Additives. *Regulatory Toxicology and Pharmacology*, **62**, 456-458. <https://doi.org/10.1016/j.yrtph.2012.01.006>
- [38] Burdock, G.A. (2000) Dietary Supplements and Lessons to Be Learned from GRAS. *Regulatory Toxicology and Pharmacology*, **31**, 68-76. <https://doi.org/10.1006/rtph.1999.1369>

-
- [39] Burdock, G.A. and Carabin, I.G. (2004) Generally Recognized as Safe (GRAS): History and Description. *Toxicology Letters*, **150**, 3-18.
<https://doi.org/10.1016/j.toxlet.2003.07.004>
- [40] Kalra, E.K. (2003) Nutraceutical-Definition and Introduction. *AAPS PharmSci*, **5**, Article No. 25. <https://doi.org/10.1208/ps050325>
- [41] Dellaleau, B., Dulcire, C., Le Moine, P. and Kamoun, A. (1988) Analysis of the Side Effects of Tianeptine. *Clinical Neuropharmacology*, **11**, S83-S89.
- [42] Wagner, M.L., Pergolizzi, J., LeQuang, J.K., Breve, F. and Varrassi, G. (2023) From Antidepressant Tianeptine to Street Drug ZaZa: A Narrative Review. *Cureus*, **15**, e40688. <https://doi.org/10.7759/cureus.40688>
- [43] Rushton, W., Whitworth, B., Bron, J., Kurz, M. and Rivera, J. (2021) Characteristics of Tianeptine Effects Reported to a Poison Control Center: A Growing Threat to Public Health. *Clinical Toxicology*, **59**, 152-157.
<https://doi.org/10.1080/15563650.2020.1781151>
- [44] Hargett, J.L., Lowry, P.F. and Lee, K.N. (2023) Nursing Implications for Tianeptine Use and Misuse. *Journal of Addictions Nursing*, **34**, 158-161.
<https://doi.org/10.1097/JAN.0000000000000535>
- [45] Trowbridge, P. and Walley, A.Y. (2019) Use of Buprenorphine-Naloxone in the Treatment of Tianeptine Use Disorder. *Journal of Addictions Nursing*, **13**, 331-333.
<https://doi.org/10.1097/ADM.0000000000000490>