Journal of Medical Toxicology (2025) 21:30–41
https://doi.org/10.1007/s13181-024-01053-6

ORIGINAL ARTICLE

Tianeptine Exposures Reported to United States Poison Centers, 2015–2023

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Received: 23 August 2024 / Revised: 6 December 2024 / Accepted: 12 December 2024 / Published online: 26 December 2024

Abstract

Introduction Tianeptine is an atypical tricyclic antidepressant not approved for medical use in the US but is found in dietary supplements. This study investigates single-substance tianeptine exposures reported to US poison centers.

Methods We analyzed cases involving tianeptine reported to the National Poison Data System from 2015 to 2023.

Results There were 892 single-substance tianeptine exposures reported to US poison centers from 2015 to 2023, and the rate of exposures increased 1,400% from 2015 to 2023, including a 525% increase from 2018 to 2023. Most exposures were associated with moderate (51.5%) or major (12.0%) effects, and 40.1% required medical admission, including 22.9% to a critical care unit. Individuals 50 years and older were more likely to experience major effects (RR: 1.70, 95% CI: 1.13–2.56) or require medical admission (RR: 1.43, 95% CI: 1.20–1.72) than younger individuals. Tianeptine abuse accounted for 40.1% of exposures and was more likely to be associated with moderate or major effects (RR: 1.18, 95% CI: 1.06–1.31) than exposures not attributed to abuse. Withdrawal accounted for 22.5% of tianeptine exposures. Tianeptine exposure rates were highest in the US South. Alabama enacted legislation to regulate tianeptine as a controlled substance in 2021. Alabama's tianeptine exposure rate increased by 1,413.7% from 2018 to 2021, followed by a 74.6% decrease from 2021 to 2023, while the rate in other southern states continued to increase.

Conclusions This study demonstrates the toxicity and rapid increase of tianeptine exposures reported to US poison centers. Uniform regulation of tianeptine across all states may offer an important strategy to help mitigate this public health problem.

Keywords Dietary Supplements · Adverse Drug Events · Toxicity · Tricyclic Antidepressant · Poisoning · Public Policy

Abbreviations

CI	confidence interval
FDA	United States Food and Drug Administration
NPDS	National Poison Data System
PC	poison center
RR	risk ratio
US	United States

Introduction

Tianeptine is an atypical tricyclic antidepressant with anxiolytic properties. Although it is approved for use in some European, Asian, and Latin American countries, tianeptine is not approved for medical use in the United States (US), and the US Food and Drug Administration (FDA) has declared it an "unsafe food additive, and dietary supplements containing tianeptine are adulterated under the Federal Food, Drug, and Cosmetic Act" [1]. Despite this, dietary supplements containing tianeptine are available online or at smoke shops, gas stations, and convenience stores in the form of pills, powders, and shots [2, 3].

Supervising Editor: Matthew R. Dernbach, MD

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Tianeptine's clinical effects are due to mu-opioid receptor agonism and indirect modulation of the glutamatergic system [4, 5], and include antidepressant and anxiolytic effects, opioid-like euphoria in high doses, tolerance with chronic use, and toxicity during recreational abuse [6–8]. At higher doses, delta-opioid receptor agonism may play a role [4]. It is sometimes marketed as a mood enhancer or as a treatment for pain, opioid use disorder, or depression, which may delay individuals from receiving safer, approved medical treatments for these disorders [1, 9, 10].

In 1994, the Dietary Supplement Health and Education Act amended the Federal Food, Drug, and Cosmetic Act and defined FDA's regulatory authority over dietary supplements [11]. Unlike drugs, the FDA does not have the authority to approve the safety and effectiveness of dietary supplements before they appear in the marketplace. Although the distribution and sale of adulterated dietary supplements is prohibited by law, the FDA must initially rely on manufacturers and distributors to ensure the safety of their products. If they fail to do so, the FDA may take postmarket regulatory action to protect consumers. Evidence of inadequate federal regulation of tianeptine products includes documentation of the (1) variation of tianeptine dose compared with the product label, (2) contamination with other potentially toxic substances, (3) lack of child-resistant packaging, and (4) absence of warnings about dependence and serious side effects, such as central nervous system depression and opioid-like withdrawal, which have been associated with hospitalization and death [3, 12–15]. The FDA has issued multiple recall notifications, warning letters to manufacturers and distributors, consumer alerts, and press releases [1, 16–19]. In addition, at least 12 US states have designated tianeptine as a controlled substance as of January 2024 [20].

Tianeptine was identified as an emerging public health risk after reports to US PCs increased from 2014 to 2017 [8]. Articles related to tianeptine published since 2018 have focused on state-level data [3, 21, 22] or case reports [14, 15, 23–25]. The objective of this study was to investigate the evolving characteristics and trends of single-substance tianeptine exposures reported to US PCs from 2015 to 2023.

Methods

Data Sources

Data for this study were obtained from the National Poison Data System (NPDS), which is a data warehouse maintained by America's Poison Centers that receives data in near real-time from regional PCs in the US [26, 27]. Data are received and managed by Specialists in Poison Information at each PC, which undergo a series of quality control measures to ensure completeness and accuracy [26]. National population estimates were obtained from the US Census Bureau and were used to calculate population-based rates [28–31]. This study was determined to be exempt from approval by the institutional review board at the authors' institution.

Case Selection Criteria

Single-substance tianeptine exposures reported to US PCs from January 1, 2015, through December 31, 2023, were identified using the NPDS product code for tianeptine. Exposure cases were excluded if the medical outcome was documented as "unrelated effect" ($n = 20$), leaving 892 exposures for analysis.

Study Variables

Age groups were categorized as < 20 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, > 59 years, and unknown. The NPDS classified the highest level of health care received as: (1) no healthcare facility treatment received, (2) treated/evaluated and released, (3) admitted to a critical care unit, (4) admitted to a non-critical care unit, (5) admitted to a psychiatric facility, (6) patient refused referral/did not arrive at a healthcare facility, or (7) patient lost to follow-up/left against medical advice/unknown. Cases admitted to a critical care unit or non-critical care unit were combined into a category representing medical admissions during analyses. Exposures with an "unknown" management site were included in the "lost to follow-up/left against medical advice/unknown" category, and this category was considered as unknown during analyses.

We grouped reason for exposure into the following categories: (1) unintentional, (2) suspected suicide, (3) intentional misuse, (4) abuse, (5) intentional – unknown, (6) withdrawal, (7) other (which includes adverse reactions), and (8) unknown. The NPDS defines abuse as "an exposure resulting from the intentional improper or incorrect use where the patient was likely attempting to gain a high, euphoric effect or some other psychotropic effect, including recreational use of a substance for any effect." [32] Intentional misuse is defined as "an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect." [32] Withdrawal is defined as "a person experiencing symptoms from a decline in blood concentration of a pharmaceutical or other substance after discontinuing therapeutic use or abuse of that substance or withdrawal triggered by administration of another drug." [32].

The categories used in this article for related clinical effects are based on NPDS definitions. They include moderate central nervous system depression (defined as "a state of unconsciousness in which the patient will arouse to loud verbal or painful stimuli") and major central nervous system

depression (defined as "a state of unconsciousness in which the patient cannot be awakened with a stimulus") [32].

Medical outcomes were categorized by the NPDS as: (1) no effect, (2) minor effect (some signs or symptoms that were minimally bothersome and resolved quickly), (3) moderate effect (signs or symptoms that were more pronounced, more prolonged, or more systemic than minor effect), (4) major effect (signs or symptoms that are life-threatening or result in substantial disability or disfigurement), (5) death, (6) not followed (includes minimal clinical effects possible and judged as a non-toxic exposure), or (7) unable to follow (judged as a potentially toxic exposure) [32]. States were grouped into the following census regions: Midwest, Northeast, South, and West [33]. Other variables that were analyzed in this study included sex, year, chronicity, related clinical effects, and performed therapies.

Statistical Analysis

Data were analyzed using SPSS Statistics 29.0 (IBM Corporation, Armonk, New York) and SAS 9.4 (SAS Institute, Inc. Cary, North Carolina). Tianeptine exposure rates per 100,000 population were calculated based on age-, sex-, and region-specific population estimates from the US Census Bureau for the years 2015–2023 [28–31]. Rates for the southern region of the US were calculated with and without inclusion of Alabama because of the disproportionately large number of tianeptine exposures reported from Alabama. A post-hoc analysis employed the Mann-Whitney U test to test the difference between the medians of the average rates of tianeptine exposures during the first four years of the study period (2015–2018) compared with the last four years (2020–2023). The level of statistical significance was alpha < 0.05. Based on our retrospective cohort study design, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated to assess the magnitude of the relationships between key factors and outcomes, including abuse and medical outcome or highest level of health care received, and age group and medical outcome or highest level of health care received.

Results

General Characteristics

There were 892 tianeptine exposures reported to US PCs from 2015 to 2023, averaging 99 per year or approximately one exposure every 3.5 days. More than one-third (36.6%) of exposures were among individuals 30–39 years old, followed by 20–29 years old (22.3%) and 40–49 years old (20.0%) (Table 1). Most exposures involved males (69.5%) or occurred at a residence (92.2%). Acute exposures accounted for 45.4% of cases, followed by chronic (36.3%) and acute-on-chronic (18.3%) exposures.

Reason for Exposure

Almost two-thirds (65.2%) of tianeptine exposures were intentional, including 40.1% attributed to abuse (Table 1). More than one-fifth (22.5%) of exposures were associated with withdrawal. Unintentional exposures accounted for only 4.8% of exposures. Abuse was the most common reason for exposure in each age group, followed by withdrawal, although suspected suicide and withdrawal accounted for an equal proportion of exposures (9.7%) among <20-year-olds. The proportion of abuse-related exposures generally decreased with increasing age group.

Abuse-related exposures were associated with moderate effects in more than half (53.4%, $n = 165$) of cases and major effects in 15.2% ($n = 47$) of cases. Abuse-related exposures were more likely to be associated with moderate or major effects than exposures not attributed to abuse (RR: 1.18, 95% CI: 1.06–1.31). Further, 25.1% ($n = 77$) and 16.6% ($n = 51$) of abuse-related exposures were admitted to a critical care unit and non-critical care unit, respectively. The association of abuse with medical admission was not statistically significant (RR: 1.12, 95% CI: 0.94–1.34). Approximately half of abuse-related exposures were acute events (50.5%, $n = 149$), followed by chronic (29.8%, $n = 88$) and acute-on-chronic (19.7%, $n = 58$).

Most exposures related to suspected suicide were associated with moderate effects (56.8%, $n = 46$), followed by major effects (20.1%, $n = 17$), minor effects (17.3%, $n = 14$), and none resulted in death. Most suspected suicide-related exposures were associated with medical admission to a critical care unit (35.9%, $n = 28$) or non-critical care unit (20.5%, $n = 16$), while 11.5% ($n = 9$) were admitted to a psychiatric facility as their highest level of care and approximately one-third (32.1%, $n = 25$) were treated/evaluated and released.

Almost half of withdrawal-related cases were associated with moderate effects (48.5%, $n = 82$), followed by minor effects (31.9%, $n = 54$) and major effects (3.6%, $n = 6$). Although more than half (60.1%, $n = 101$) of withdrawal cases were treated/evaluated and released, 15.5% were admitted to a critical care unit ($n = 26$) and 16.7% were admitted to a non-critical care unit ($n = 28$). Individuals 30–39 years old accounted for almost half (47.7%, $n = 42$) of withdrawal cases associated with moderate or major effects and almost half (46.3%, $n = 25$) associated with medical admission. Compared with exposures related to other reasons for exposure, withdrawal cases were less likely to be associated with moderate or major effects (RR: 0.80, 95%

Table 1 Characteristics of Tianeptine Exposures Reported to the National Poison Data System by Age Group, 2015–2023

Characteristics	Age Groups							
	< 20 Years *n* (%)[a]	20–29 Years *n* (%)[a]	30–39 Years *n* (%)[a]	40–49 Years *n* (%)[a]	50–59 Years *n* (%)[a]	> 59 Years *n* (%)[a]	Unknown *n*	Total *n* (%)[a]
Sex								
Male	29 (90.6)	150 (78.1)	222 (70.7)	107 (62.2)	61 (60.4)	31 (63.3)	19	619 (69.5)
Female	3 (9.4)	42 (21.9)	92 (29.3)	65 (37.8)	40 (39.6)	18 (36.7)	12	272 (30.5)
Unknown	0	0	1	0	0	0	0	1
Exposure Site								
Residence[b]	30 (96.8)	179 (95.7)	295 (97.4)	156 (96.3)	89 (92.7)	46 (93.9)	27	822 (96.1)
Other[c]	1 (3.2)	8 (4.3)	8 (2.6)	6 (3.7)	7 (7.3)	3 (6.1)	0	33 (3.9)
Unknown	1	5	12	10	5	0	4	37
Reason for Exposure								
Unintentional[d]	6 (19.4)	9 (4.8)	6 (2.0)	9 (5.6)	4 (4.3)	3 (6.4)	4	41 (4.8)
Intentional	21 (67.7)	129 (69.0)	196 (64.7)	96 (60.0)	60 (63.8)	33 (70.2)	19	554 (65.2)
Suspected suicide	3 (9.7)	21 (11.2)	26 (8.6)	15 (9.4)	13 (13.8)	4 (8.5)	0	82 (9.6)
Intentional - Misuse	2 (6.5)	22 (11.8)	30 (9.9)	19 (11.9)	10 (10.6)	7 (14.9)	2	92 (10.8)
Abuse	14 (45.2)	79 (42.2)	126 (41.6)	56 (35.0)	33 (35.1)	18 (38.3)	15	341 (40.1)
Intentional - Unknown	2 (6.5)	7 (3.7)	14 (4.6)	6 (3.8)	4 (4.3)	4 (8.5)	2	39 (4.6)
Withdrawal	3 (9.7)	33 (17.6)	83 (27.4)	41 (25.6)	21 (22.3)	8 (17.0)	2	191 (22.5)
Other[e]	1 (3.2)	16 (8.6)	18 (5.9)	14 (8.8)	9 (9.6)	3 (6.4)	3	64 (7.5)
Unknown reason	1	5	12	12	7	2	3	42
Chronicity								
Acute	18 (66.7)	87 (50.3)	124 (43.8)	54 (38.0)	36 (45.0)	17 (39.5)	16	352 (45.4)
Acute-on-chronic	5 (18.5)	29 (16.7)	46 (16.3)	34 (23.9)	12 (15.0)	12 (27.9)	4	142 (18.3)
Chronic	4 (14.8)	57 (32.9)	113 (39.9)	54 (38.0)	32 (40.0)	14 (32.6)	8	282 (36.3)
Unknown	5	19	32	30	21	6	3	116
Highest Level of Health Care Received								
No HCF treatment received	3 (10.0)	10 (5.6)	6 (2.1)	7 (4.4)	3 (3.2)	2 (4.7)	12	43 (5.4)
Treated/evaluated and released	18 (60.0)	96 (53.9)	146 (52.1)	76 (48.1)	38 (40.9)	14 (32.6)	1	389 (48.7)
Medical admission[f]	9 (30.0)	57 (32.0)	108 (38.6)	71 (44.9)	47 (50.5)	27 (62.8)	1	320 (40.1)
Admitted to a CCU	6 (20.0)	34 (19.1)	59 (21.1)	37 (23.4)	29 (31.2)	18 (41.9)	0	183 (22.9)
Admitted to a non-CCU	3 (10.0)	23 (12.9)	49 (17.5)	34 (21.5)	18 (19.4)	9 (20.9)	1	137 (17.2)
Admitted to psychiatric facility	0 (0.0)	8 (4.5)	16 (5.7)	2 (1.3)	3 (3.2)	0 (0.0)	0	29 (3.6)
Patient refused referral/ did not arrive at HCF	0 (0.0)	7 (3.9)	4 (1.4)	2 (1.3)	2 (2.2)	0 (0.0)	2	17 (2.1)
Patient lost to follow-up/ left against medical advice/ unknown	2	14	35	14	8	6	15	94
Medical Outcome								
No effect	6 (20.0)	10 (5.6)	15 (5.2)	2 (1.3)	0 (0.0)	3 (6.4)	4	40 (4.9)
Minor effect	8 (26.7)	43 (24.3)	77 (26.7)	42 (26.3)	20 (21.3)	9 (19.1)	1	200 (24.7)
Moderate effect	11 (36.7)	91 (51.4)	153 (53.1)	87 (54.4)	51 (54.3)	25 (53.2)	0	418 (51.5)
Major effect	2 (6.7)	20 (11.3)	31 (10.8)	18 (11.3)	17 (18.1)	9 (19.1)	0	97 (12.0)
Not followed[g]	3 (10.0)	13 (7.3)	12 (4.2)	11 (6.9)	6 (6.4)	1 (2.1)	10	56 (6.9)
Unable to follow[h]	2	15	27	12	7	2	16	81
US Region								
Midwest	7 (21.9)	25 (13.0)	46 (14.6)	23 (13.4)	13 (12.9)	7 (14.3)	2	123 (13.8)
Northeast	3 (9.4)	17 (8.9)	33 (10.5)	11 (6.4)	9 (8.9)	2 (4.1)	3	78 (8.8)
South	19 (59.4)	126 (65.6)	211 (67.0)	120 (69.8)	68 (67.3)	33 (67.4)	21	598 (67.1)

Table 1 (continued)

Characteristics	Age Groups							
	< 20 Years *n* (%)[a]	20–29 Years *n* (%)[a]	30–39 Years *n* (%)[a]	40–49 Years *n* (%)[a]	50–59 Years *n* (%)[a]	> 59 Years *n* (%)[a]	Unknown *n*	Total *n* (%)[a]
West	3 (9.4)	24 (12.5)	25 (7.9)	18 (10.5)	11 (10.9)	7 (14.3)	4	92 (10.3)
Unknown	0	0	0	0	0	0	1	1
Total (Row %)[i]	32 (3.7)	192 (22.3)	315 (36.6)	172 (20.0)	101 (11.7)	49 (5.7)	31	892 (100.0)

Abbreviations: CCU - critical care unit, HCF - healthcare facility

[a]Column percentage may not sum to 100.0% because of rounding error

[b]Includes own residence and other residence

[c]Includes workplace, healthcare facility, school, public area, and other

[d]Includes unintentional - general, therapeutic error, unintentional – misuse, unintentional – unknown

[e]Includes contamination/tampering, malicious intent, adverse reaction (drug and other)

[f]Includes admission to a critical care unit or non-critical care unit

[g]Includes "not followed (minimal clinical effects possible)" and "not followed (judged as non-toxic exposure)"

[h]Includes "unable to follow (judged as a potentially toxic exposure)"

[i]Row percentages may not sum to 100.0% because of rounding error

CI: 0.68–0.93) but there was no evidence for an association with medical admission (RR: 0.78, 95% CI: 0.62–1.00).

Highest Level of Health Care Received and Medical Outcomes

More than half (51.5%) of tianeptine exposures resulted in moderate effects, followed by minor effects (24.7%) and major effects (12.0%) (Table 1). The proportion of individuals with major effects was greatest among 50–59-year-olds (18.1%) and > 59-year-olds (19.1%). Individuals 50 years and older were more likely to experience major effects than individuals younger than 50 years old (RR: 1.70, 95% CI: 1.13–2.56). No deaths were reported in this study. Most exposures (92.4%) received treatment in a healthcare facility, including 48.7% treated/evaluated and released, 40.1% requiring medical admission, and 3.6% admitted to a psychiatric facility. The proportion of medical admissions increased with increasing age group, ranging from 30.0% among individuals < 20 years old to 62.8% among individuals > 59 years old. Exposures among individuals 50 years and older were more likely to be associated with medical admission than those among individuals younger than 50 years old (RR: 1.43, 95% CI: 1.20–1.72).

Regional and State Comparisons

Reported tianeptine exposures predominated among states in the US South (67.1%), followed by the Midwest (13.8%), West (10.3%), and Northeast (8.8%) (Table 1). Alabama alone accounted for 23.8% ($n = 212$) of all exposures. State-specific average rates of tianeptine exposure during the study period were highest in Alabama (0.47 exposures per 100,000 state population), followed by Mississippi (0.20) (Appendix 1). The US region with the greatest proportion of exposures associated with moderate effects was the South (56.2%), while the Northeast had the greatest proportion of major effects (17.8%) as well as the lowest proportion of minor effects (15.1%) (Table 2). The proportion of exposures requiring medical admission to a healthcare facility was highest in the South (43.3%) and lowest in the West (29.8%). Abuse was the most frequent reason for exposure in all regions except for the West, where withdrawal was the leading reason (28.3%). Suspected suicide accounted for proportionally more exposures (11.2%) in the South compared with other regions.

Related Clinical Effects and Performed Therapies

Among the 701 tianeptine exposures associated with reasons for exposure other than withdrawal, agitation was the most frequent related clinical effect (33.5%), followed by tachycardia (24.7%), confusion (16.7%), hypertension (14.7%), and moderate central nervous system depression (12.3%); other less common, but important, related clinical effects included major central nervous system depression (6.4%), respiratory depression (6.1%), bradycardia (4.3%), acidosis (3.4%), hypotension (3.1%), seizure (single or multi/discrete, 2.4%), coma (1.3%), respiratory arrest (0.6%), and asystole (0.1%) (Table 3). Among the 191 reported tianeptine cases associated with withdrawal, agitation (54.5%) was the most frequent related clinical effect,

Table 2 Characteristics of Tianeptine Exposures Reported to the National Poison Data System by Region of the United States, 2015–2023

Characteristics	United States Region*			
	Midwest *n* (%)[a]	Northeast *n* (%)[a]	South *n* (%)[a]	West *n* (%)[a]
Sex				
Male	91 (74.6)	68 (87.2)	386 (64.5)	74 (80.4)
Female	31 (25.4)	10 (12.8)	212 (35.5)	18 (19.6)
Unknown	1	0	0	0
Exposure Site				
Residence[b]	115 (94.3)	71 (94.7)	548 (96.6)	87 (96.7)
Other[c]	7 (5.7)	4 (5.3)	19 (3.4)	3 (3.3)
Unknown	1	3	31	2
Reason for Exposure				
Unintentional[d]	4 (3.5)	5 (6.9)	28 (4.9)	4 (4.3)
Intentional	64 (55.7)	49 (68.1)	394 (69.0)	47 (51.1)
Suspected suicide	7 (6.1)	3 (4.2)	64 (11.2)	8 (8.7)
Intentional - Misuse	10 (8.7)	12 (16.7)	60 (10.5)	10 (10.9)
Abuse	44 (38.3)	30 (41.7)	243 (42.6)	24 (26.1)
Intentional - Unknown	3 (2.6)	4 (5.6)	27 (4.7)	5 (5.4)
Withdrawal	35 (30.4)	14 (19.4)	116 (20.3)	26 (28.3)
Other[e]	12 (10.4)	4 (5.6)	33 (5.8)	15 (16.3)
Unknown reason	8	6	27	0
Chronicity				
Acute	53 (47.3)	36 (51.4)	223 (44.2)	39 (44.3)
Acute-on-chronic	20 (17.9)	11 (15.7)	104 (20.6)	7 (8.0)
Chronic	39 (34.8)	23 (32.9)	178 (35.2)	42 (47.7)
Unknown	11	8	93	4
Highest Level of Health Care Received				
No HCF treatment received	9 (8.0)	5 (6.9)	20 (3.8)	9 (10.7)
Treated/evaluated and released	61 (54.0)	36 (50.0)	243 (45.9)	49 (58.3)
Medical admission[f]	41 (36.3)	25 (34.7)	229 (43.3)	25 (29.8)
Admitted to a CCU	23 (20.4)	13 (18.1)	134 (25.3)	13 (15.5)
Admitted to a non-CCU	18 (15.9)	12 (16.7)	95 (18.0)	12 (14.3)
Admitted to psychiatric facility	1 (0.9)	5 (6.9)	23 (4.3)	0 (0.0)
Patient refused referral/ did not arrive at HCF	1 (0.9)	1 (1.4)	14 (2.6)	1 (1.2)
Patient lost to follow-up/ left against medical advice/ unknown	10	6	69	8
Medical Outcome				
No effect	5 (4.2)	7 (9.6)	19 (3.6)	9 (10.3)
Minor effect	41 (34.2)	11 (15.1)	126 (23.8)	22 (25.3)
Moderate effect	48 (40.0)	34 (46.6)	298 (56.2)	38 (43.7)
Major effect	14 (11.7)	13 (17.8)	62 (11.7)	8 (9.2)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not followed[g]	12 (10.0)	8 (11.0)	25 (4.7)	10 (11.5)
Unable to follow[h]	3	5	68	5
Total (Row %)[i]	123 (13.8)	78 (8.8)	598 (67.1)	92 (10.3)

Abbreviations: CCU - critical care unit, HCF - healthcare facility

*State was unknown for one exposure

[a]Column percentage may not sum to 100.0% because of rounding error

[b]Includes own residence and other residence

[c]Includes workplace, healthcare facility, school, public area, and other

[d]Includes unintentional - general, therapeutic error, unintentional – misuse, unintentional – unknown

[e]Includes contamination/tampering, malicious intent, adverse reaction (drug and other)

[f]Includes admission to a critical care unit or non-critical care unit

[g]Includes "not followed (minimal clinical effects possible)" and "not followed (judged as non-toxic exposure)"

[h]Includes "unable to follow (judged as a potentially toxic exposure)"

[i]Row percentages may not sum to 100.0% because of rounding error

Table 3 Top 15 Related Clinical Effects Plus Additional Selected Important Related Clinical Effects Associated with Tianeptine Exposures Excluding Withdrawal and Tianeptine Exposures Associated with Withdrawal, National Poison Data System 2015–2023

Clinical Effects for Non-Withdrawal Exposures	*n* (%)[a]	Clinical Effects Associated with Withdrawal	*n* (%)[b]
Agitation	235 (33.5)	Agitation	104 (54.5)
Tachycardia	173 (24.7)	Nausea	61 (31.9)
Confusion	117 (16.7)	Tachycardia	45 (23.6)
Hypertension	103 (14.7)	Vomiting	38 (19.9)
CNS depression (Moderate)	86 (12.3)	Hypertension	33 (17.3)
Nausea	78 (11.1)	Tremor	30 (15.7)
Vomiting	75 (10.7)	Diaphoresis	28 (14.7)
Other - neurological	63 (9.0)	Other - neurological	24 (12.6)
CNS depression (Mild)	60 (8.6)	Diarrhea	22 (11.5)
Other - miscellaneous	49 (7.0)	Other - miscellaneous	21 (11.0)
Diaphoresis	47 (6.7)	Pain (not dermal, GI, ocular)	20 (10.5)
Tremor	47 (6.7)	Hallucinations/delusions	17 (8.9)
CNS depression (Major)	45 (6.4)	Confusion	15 (7.8)
Respiratory depression	43 (6.1)	Abdominal pain	11 (5.8)
Electrolyte abnormality	41 (5.9)	Headache	9 (4.7)
Additional Selected Important Clinical Effects			
Bradycardia	30 (4.3)	Acidosis	4 (2.1)
Acidosis	24 (3.4)	Bradycardia	4 (2.1)
Hypotension	22 (3.1)	Seizure (single or multiple/discrete)	1 (0.5)
Seizure (single or multiple/discrete)	17 (2.4)	Respiratory depression	1 (0.5)
Coma	9 (1.3)		
Respiratory arrest	4 (0.6)		
Asystole	1 (0.1)		

[a]Column percentages were calculated using total number of single-substance tianeptine exposures excluding withdrawal cases ($n=701$) as the denominator

[b]Column percentages were calculated using total number of single-substance tianeptine-related withdrawal cases ($n=191$) as the denominator

The percentage will not sum to 100.0% because (1) each exposure may result in 0, 1, or more clinical effects and (2) not all clinical effects are listed in this table

followed by nausea (31.9%), tachycardia (23.6%), vomiting (19.9%), and hypertension (17.3%); other less common, but important, related clinical effects included acidosis (2.1%), bradycardia (2.1%), seizure (single or multi/discrete (0.5%), and respiratory depression (0.5%). Of 97 exposures that resulted in a major effect, 95 of them had related clinical effects reported, of which, major central nervous system depression (45.4%) was most common, followed by agitation (38.1%).

Among the 701 tianeptine exposures associated with reasons for exposure other than withdrawal, intravenous fluids (42.5%) was the most common therapy performed, followed by benzodiazepines (29.2%), naloxone (17.6%), and oxygen (16.6%). Among the 191 tianeptine cases associated with withdrawal, the most frequent therapies performed were benzodiazepines (49.2%), intravenous fluids (37.2%), antiemetics (15.7%), and other sedation (excluding benzodiazepines and propofol) (8.9%). Other less common, but important, therapies performed among all 892 tianeptine exposures included mechanical ventilation (7.3%), vasopressors (1.5%), anticonvulsants (0.9%), cardiopulmonary resuscitation (0.4%), and non-invasive ventilation (CPAP, BiPAP, 0.2%).

Trends

The median rate of tianeptine exposures per 100,000 US population reported to US PCs increased by 200.0% from 0.01 during the first four years of the study period (2015–2018) to 0.03 during the last four years of the study period (2020–2023) (Mann-Whitney U test, $P<0.0001$). The number of tianeptine exposures increased 1,370.6% from 17 cases in 2015 to 250 cases in 2023, including a 541.0% increase from 39 cases in 2018 to 250 cases in 2023. The rate of tianeptine exposures per 100,000 US population increased non-linearly by 1,400.0% from 0.005 in 2015 to 0.075 in 2023, including a 525.0% increase from 0.012 in 2018 to 0.075 in 2023 (Fig. 1). Similar trend patterns were shown by males (with a 1,088.9% non-linear rate increase from 0.009 in 2015 to 0.107 in 2023) and

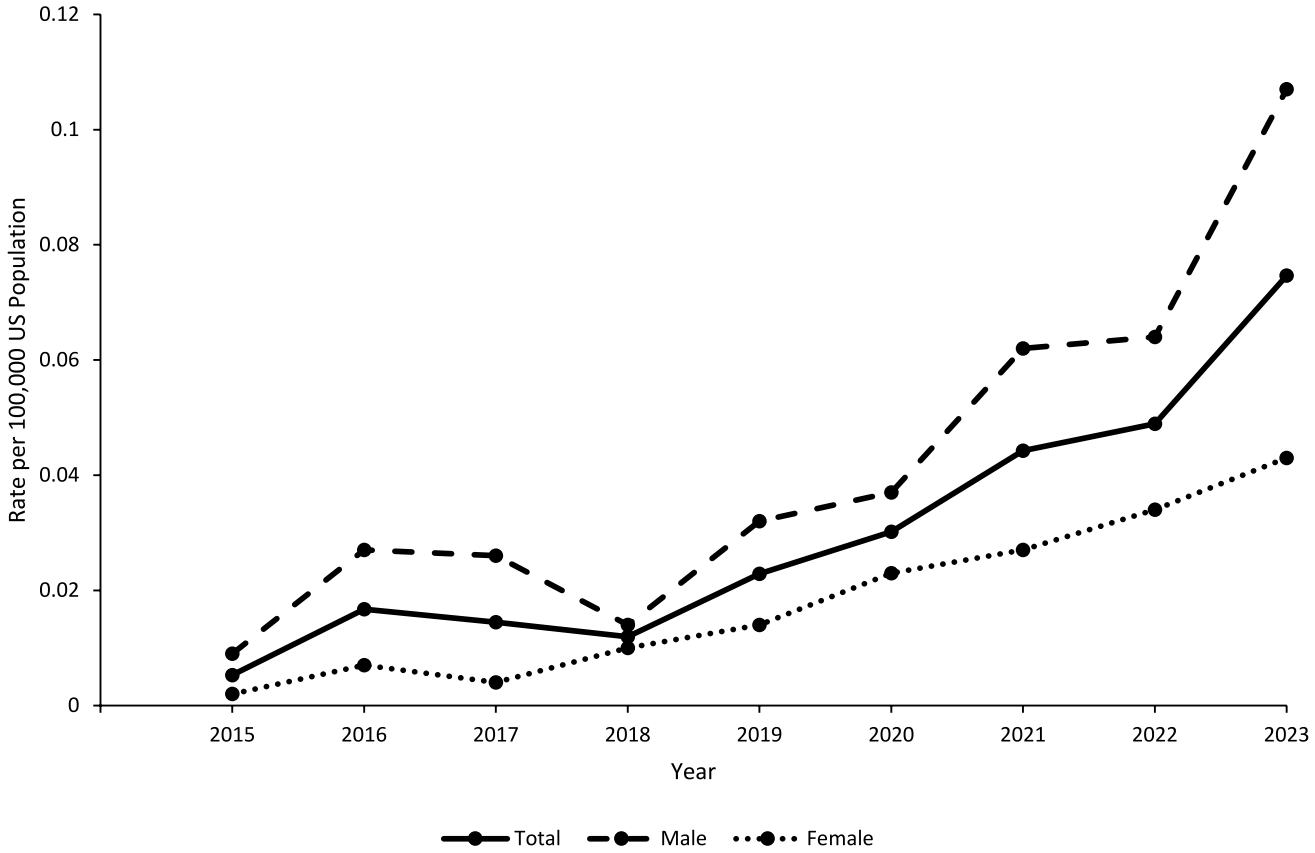

Fig. 1 Annual Rate of Tianeptine Exposures Reported to United States Poison Centers by Sex, National Poison Data System 2015–2023

females (with a 2,050.0% rate increase from 0.002 in 2015 to 0.043 in 2023). Males experienced higher tianeptine exposure rates than females throughout the study period.

Individuals 30–39 years old experienced the highest tianeptine exposure rate during the study period compared with other age groups (Appendix 2). The rate per 100,000 US population among this age group increased by 64.7% from 0.017 in 2015 to 0.025 in 2018, followed by an increase of 635.7% to 0.206 in 2023. Similar trend patterns were demonstrated by 20–29-year-olds and 40–49-year-olds.

The tianeptine exposure rate was highest in the South compared with the other US regions from 2018 to 2023 (Fig. 2). It increased by 240.0% from 0.005 in 2015 to 0.017 in 2018, followed by a 664.7% increase to 0.130 in 2023. When Alabama was excluded, the tianeptine exposure rate in the South increased by 280.0% from 0.005 in 2015 to 0.019 in 2020, followed by a 526.3% increase to 0.119 in 2023. The rate of tianeptine exposures in Alabama increased by 1,413.7% from 0.102 in 2018 to 1.544 in 2021, followed by a 74.6% decrease to 0.392 in 2023 (Appendix 3). The tianeptine exposure rate in the Northeast showed an increase of 120.0% from 0.005 in 2015 to 0.011 in 2022, followed by a rapid 472.7% increase to 0.063 in 2023.

The rate of tianeptine exposures per 100,000 US population associated with moderate effects demonstrated a non-linear increase of 1,700.0% from 0.002 in 2015 to 0.036 in 2023, including a rapid increase of 89.5% from 0.019 in 2022 to 0.036 in 2023 (Appendix 4). The rate of tianeptine exposures associated with major effects plateaued from 0.0003 in 2015 to 0.002 in 2020, followed by an increase of 500.0% to 0.012 in 2023. The rate of exposures associated with medical admissions followed a similar trend pattern as that seen for exposures associated with moderate effects, with a non-linear increase of 1,250.0% from 0.002 in 2015 to 0.027 in 2023.

The rate of tianeptine exposures per 100,000 US population associated with abuse increased non-linearly by 85.0% from 0.002 in 2015 to 0.0037 in 2018, followed by an 764.9% increase to 0.032 in 2023 (Appendix 5). The rate of suspected suicide-related exposures plateaued from 0.0003 in 2015 to 0.0006 in 2019, followed by a 1,233.3% non-linear increase to 0.008 in 2023. The rate of exposures associated with intentional-misuse showed a non-linear increase of 566.7% from 0.0009 in 2015 to 0.006 in 2023. The rate of withdrawal-related cases increased by 4,566.7% from 0.0003 in 2015 to 0.014 in 2023, including a more rapid 250.0% increase from 0.004 in 2018 to 0.014 in 2023.

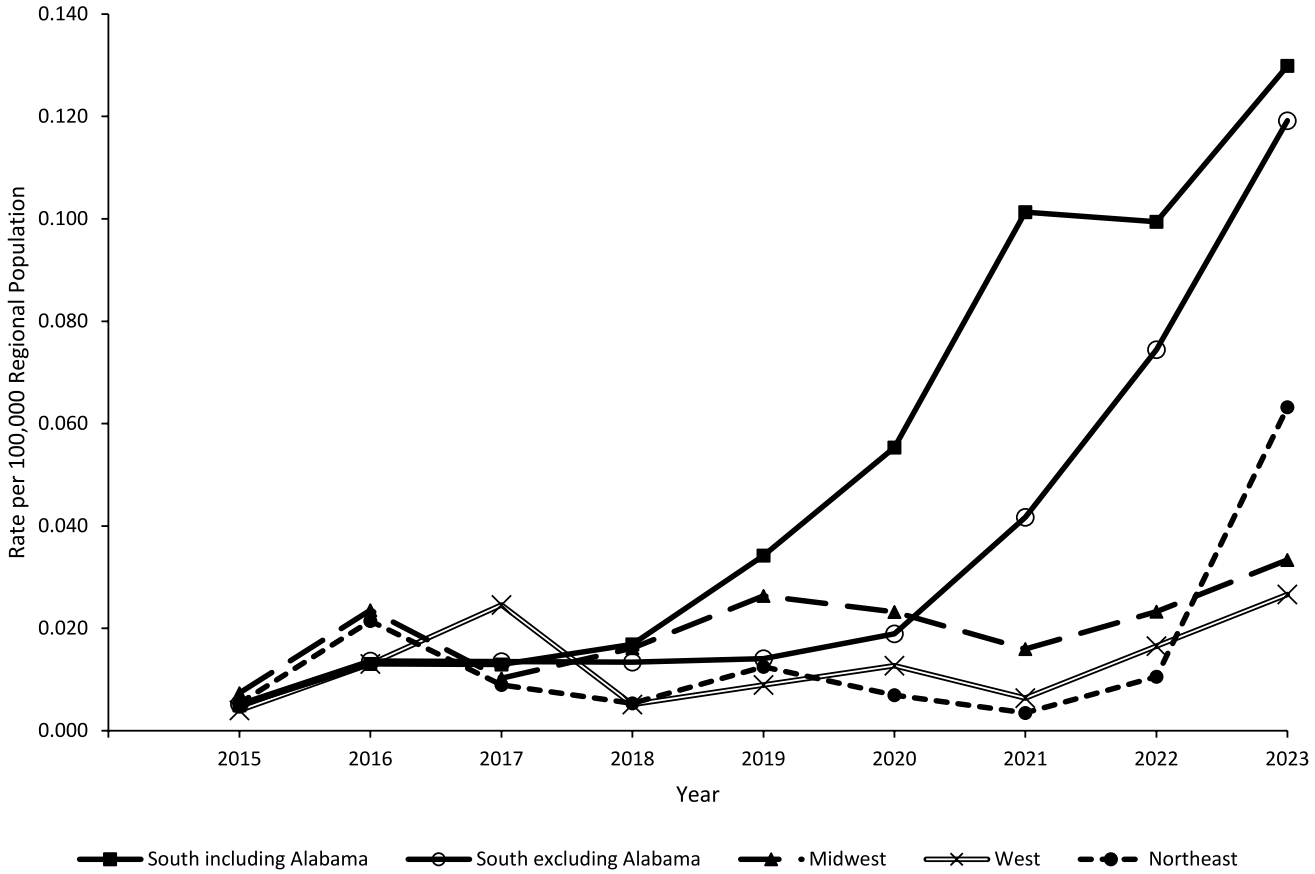

Fig. 2 Annual Rate of Tianeptine Exposures Reported to United States Poison Centers by Region with and without Alabama, National Poison Data System 2015–2023

The rates of unintentional exposures and exposures associated with other reasons did not change significantly during the study period.

Discussion

There were 892 single-substance tianeptine exposures reported to US PCs from 2015 to 2023, and the rate of exposures increased 1,400% during that period, including a 525% increase from 2018 to 2023. These findings show that the trend of increasing exposures from 2014 to 2017 identified by El Zahran, et al. has accelerated [8].

Tianeptine exposures commonly have serious medical outcomes. Almost two-thirds of reported tianeptine exposures were associated with moderate (52%) or major (12%) effects. 40% of exposures required medical admission, including 23% to a critical care unit. Therapies included mechanical ventilation (7%), vasopressors (2%), anticonvulsants (1%), and cardiopulmonary resuscitation (0.4%), which underscores the seriousness of these exposures. Although there were no fatalities in this study, tianeptine-related deaths have been reported [13, 34, 35]. More than three-fourths of tianeptine exposures involved individuals 20–49 years old, which is consistent with previous reports [8, 13, 14, 22, 36]. Although individuals 50 years and older were more likely to experience major effects and require medical admission, 30% of individuals < 20 years old were medically admitted, which emphasizes that all age groups experience serious effects associated with tianeptine. The reason for the increased severity among individuals 50 years and older in our study is unclear but may be related to factors such as comorbidities and drug dosage.

Tianeptine's potential for abuse has been previously recognized [34]. Abuse accounted for 40% of exposures in this study and was the most common reason for exposure in each age group. Abuse-related exposures were associated with moderate effects in more than half of cases and major effects in 15% of cases, and the association of abuse with these more serious medical outcomes was greater than that seen in association with other reasons for exposure.

Approximately 10% of tianeptine exposures in our study were related to exposures with suspected suicidal intent. Most of these suspected suicide exposures were associated

with moderate effects (57%) or major effects (20%); however, there were no suicide-related fatalities. This study was limited to single-substance exposures, and therefore underestimates the frequency and severity of tianeptine's involvement in self-harm exposures because suspected suicide often involves multiple-substances. El Zahran and colleagues [8] found that phenibut, ethanol, benzodiazepines, and opioids were the most common co-substances in multiple-substance tianeptine exposures, and that multiple-substance tianeptine exposures were significantly more likely to be associated with major effects than single-substance exposures.

Tianeptine exposures have been reported to have similar clinical effects and treatments as opioid exposures because of tianeptine's opioid receptor agonist properties [8, 23, 37, 38]. Although our study findings support the similarity of clinical effects associated with tianeptine and opioid withdrawal, we found that several of the most common clinical effects associated with non-withdrawal-related exposures to tianeptine were not typical for opioid exposures, such as agitation, tachycardia, and hypertension. The reasons for this are unclear, but our findings are consistent with those of El Zahran, et al. [8] Tianeptine's effects on receptors other than the mu receptor may play a role. It is possible that some cases are mis-categorized; for example, an individual who has longstanding tianeptine abuse or intentional-misuse presents in acute withdrawal and receives the code for their chronic condition, rather than withdrawal. It is possible that some cases are related to iatrogenic withdrawal following naloxone administration or presented with acute intoxication and developed withdrawal symptoms later during their clinical course, prompting a call to the PC. Consistent with other studies [3, 12], the presence of adulterants in tianeptine is another possible explanation.

Withdrawal accounted for more than one-fifth of reported tianeptine exposures, and the rate of tianeptine-related withdrawal increased > 4,500% during the study period, including a more rapid increase from 2018 to 2023. This is consistent with a previous study that analyzed social media posts about tianeptine from 2012 to 2020 and identified descriptions of tolerance, withdrawal, and addiction, including an increase in posts about withdrawal in 2017 to 2019 [10]. Although withdrawal cases were less likely to be associated with moderate or major effects than other tianeptine exposures in our study, more than half did experience such effects and almost one-third required medical admission. Neonatal abstinence syndrome has been reported; [36] however, there were none of these cases in our study.

The southern region of the US accounted for two-thirds of tianeptine exposures reported to US PCs. This is consistent with the findings of El Zahran, et al., [8] although their data only included exposures prior to 2018 and included multiple-substance exposures. For reasons that are unclear at the time of writing, Alabama alone accounted for almost one-fourth of all reported tianeptine exposures, and the exposure rate in Alabama increased by > 1,400% from 2018 to 2021. In April 2021, Alabama became the first southern state to enact legislation to regulate tianeptine as a controlled substance [39–41]. Subsequently, Alabama experienced a 75% decrease in the tianeptine exposure rate from 2021 to 2023, while the other states in the southern region continued to show an increase in the exposure rate. Despite the limitations of an observational study design, this suggests an association between Alabama's law and the observed decrease in tianeptine exposures and underscores the importance of policy in addressing public health problems. Although at least 12 US states have designated tianeptine as a controlled substance as of January 2024 [20], we were unable to assess the association of state regulation with changes in tianeptine exposure rates in other states because most restrictions were adopted in 2022 or 2023 or because of small numbers of reported exposures. There is a need for uniform regulation of tianeptine across all states.

Study Limitations

Not all tianeptine exposures are reported to PCs; therefore, NPDS data underestimate the true number of exposures. Only single-substance exposures involving tianeptine were included in this study. Reporting bias may also exist; for example, more severe exposures may be more likely to be reported to a PC. Unique personal identifiers are not used in the NPDS, which means the same person may be represented in the dataset more than once for different exposures. Because reports to PCs include self-reported data, the PCs and America's Poison Centers cannot completely verify all data. In addition, miscoding or mis-categorization may occur. Because tianeptine is not legally available in some states, non-healthcare personnel may intentionally not provide complete or correct data. The familiarity of healthcare personnel and PC staff with tianeptine products may vary by state. Because of inadequate quality control and product labeling, tianeptine dosage may vary and other adulterants may be present in tianeptine-containing products [3, 12]. Tianeptine dose was not accounted for in this study. Toxicological testing for tianeptine is not routinely done, and if done, was not reported in the NPDS database. Reported exposures do not necessarily represent a poisoning or overdose. Despite these limitations, the NPDS is a large, standardized national database commonly used for epidemiologic investigations of toxic exposures.

Conclusions

This study demonstrates the toxicity and rapid increase of tianeptine exposures reported to US poison centers. Uniform regulation of tianeptine across all states may offer

an important strategy to help mitigate this public health problem.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13181-024-01053-6.

Acknowledgements None.

Authors' Contributions **Mustafa Quadir** contributed to the conception and design of the study, conducted data analyses and contributed to interpretation of data; he drafted the article, approved the final version to be published, and agrees to be accountable for all aspects of the work.**Natalie Rine** contributed to the conception and design of the study, acquisition of data, and interpretation of data; she reviewed and revised the article critically for important intellectual content, approved the final version to be published, and agrees to be accountable for all aspects of the work.**Jaahnavi Badeti** conducted data analyses and contributed to interpretation of data; she reviewed and revised the article critically for important intellectual content, approved the final version to be published, and agrees to be accountable for all aspects of the work.**Hannah Hays, Nichole Michaels, and Jingzhen Yang** contributed to the interpretation of data; they reviewed and revised the article critically for important intellectual content, approved the final version to be published, and agree to be accountable for all aspects of the work.**Gary Smith** contributed to the conception and design of the study and interpretation of data; he assisted in drafting the article and reviewed and revised the article critically for important intellectual content, approved the final version to be published, and agrees to be accountable for all aspects of the work.

Funding First author, MQ, received a student scholar research stipend from the Child Injury Prevention Alliance while he worked on this study. The interpretations and conclusions in this article do not necessarily represent those of the funding organization. The funding organization was not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Availability Data analyzed in this study were from the National Poison Data System, which is owned and managed by America's Poison Centers. Data requests should be submitted to America's Poison Centers.

Declarations

Conflict of Interest The authors declare that they have no conflicts of interest nor financial disclosures relevant to this study.

Previous Presentation of Data Not applicable.

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