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Poison control center experience with tianeptine: an unregulated pharmaceutical product with potential for abuse

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ABSTRACT

Background: Interest in tianeptine as a potential drug of abuse is increasing in the United States. We performed a retrospective study of calls to the New York State Poison Control Centers (PCCs) designed to characterize one state's experience with tianeptine.

Methods: Data were gathered from existing records utilizing the poison center data collection system, Toxicall® entered between 1 January 2000 through 1 April 2017. Information regarding patient demographics, reported dose and formulation of tianeptine, reported coingestants, brief narrative description of the case, disposition, and case outcome was collected.

Results: There were nine reported cases of tianeptine exposure. Seven were male with a mean age of 27. Three reported therapeutic use of tianeptine and five reported intentional abuse. One case was an unintentional pediatric exposure. Doses were reported in three cases; 12.5 mg in a pediatric unintentional exposure, and 5 and 10g daily in the two reports of intentional abuse. Of note, five patients complained of symptoms consistent with opioid withdrawal. In one of two cases in which naloxone was administered, an improvement in mental status and the respiratory drive was noted. Outcomes reported in Toxicall® were minor in two cases, moderate in five cases, major in one case, and not reported in one case.

Conclusions: These cases, reported to the New York State PCCs should alert readers to the potential for tianeptine abuse, dependence, and withdrawal.

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Introduction

The United States is experiencing an epidemic of opioid addiction and overdose that has been steadily increasing over the past 15 years [1]. Initially precipitated by increased prescribing of opioid analgesics, the public health crisis of opioid addiction expanded to include heroin, fentanyl, and other novel opioid agonists [1,2]. Creative and often desperate Americans suffering from an Opioid Use Disorder are increasingly turning to "legal highs" such as over-the-counter (OTC) medications, plants and research chemicals to "get high," or to mitigate the symptoms of opioid withdrawal. Examples of substances exploited for their opioid agonism include the OTC anti-diarrheal loperamide [3,4], the traditional medicinal plant kratom [5], and an ever-expanding list of "research chemicals" such as acetylfentanyl, acryloylfentanyl, carfentanil, ocfentanil, AH-7921, MT-45, and U-47700 [6,7]. The opioid epidemic has brought drug-related deaths across the United States to unprecedented highs in recent years, in part due to increases in illicit fentanyl and fentanyl analogs in the drug supply [6–11]. In New York City, the prevalence of novel psychoactive substance (NPS) exposures reported to poison control centers (PCCs) increased from 7.1% in 2011 to 12.6% in 2014 [12]. Between 2010 and 2016,

New York City experienced a 143% increase in the rate of death due to unintentional overdose, and medical examiner data have determined that illicit fentanyl and fentanyl analogs contributed to the increase in deaths [9]. Although unpublished, these trends are consistent in all parts of New York State.

Tianeptine is an approved pharmaceutical in 66 countries throughout the world [13]. The potential for abuse as an NPS is likely due to its μ (OP1) receptor opioid agonist activity. Misuse of tianeptine reportedly causes euphoria similar with other opioid agonists. In France, Bahrain, and Singapore, tianeptine is controlled is a schedule 1 substance (or country equivalent) that is controlled due to its risk for abuse [13]. Tianeptine is currently not an approved drug in the United States. However, it is easily obtainable through the internet [14,15].

Objectives

The objective of this study is to characterize one state's experience with tianeptine through review of all reported cases of tianeptine toxicity reported to the state's PCCs.

Methods

PCCs provide free information on the evaluation, management, and treatment of suspected and known poisonings to the general public and health-care professionals. The 55 regional PCCs in the United States are staffed 24/7/365 by health-care professionals with specific training in managing poisoning exposures and information calls. Each poison center documents the details of each call received in a database and then these cases are uploaded in real-time to the National Poison Data System (NPDS). In conjunction with the American Association of PCCs, the Centers for Disease Control routinely monitor the NPDS database as a means of national surveillance for potential exposures and illness of public health concern. There are two PCCs in New York State, providing services for over 20 million people who live there. Together, they respond to over 130,000 calls annually and who together receive over 100,000 exposure calls.

This was a retrospective review of data describing all tianeptine-related exposure calls reported to PCCs in New York State from 1 January 2000 through 1 April 2017. After review and exemption by both the New York City Department of Health and Mental Hygiene and Upstate Medical University's, Institutional Review Boards (IRB), our electronic medical recording system (Toxicall®) was queried for calls regarding tianeptine exposure. A single reviewer from each PCC extracted the following data from Toxicall®: patient demographics, reported dose and formulation of tianeptine, reported coingestants, brief narrative description of the case, disposition, and case outcome. A single reviewer (JMM) then reviewed all cases to ensure there were no discrepancies in data collection.

Results

There were nine reported cases of tianeptine exposure during the examined time period. No discrepancies in data extraction were noted. The first tianeptine exposure was reported in 2009, with the remainder of the cases occurring in 2015 or later ($n=8$). Seven of the nine patients were male. Mean age was 27 years. There was one unintentional pediatric exposure. Three of the nine patients reported using tianeptine as a treatment for anxiety or depression. Five of the nine cases reported intentional abuse of tianeptine. Five of the nine cases complained of symptoms after discontinuing tianeptine. Three of the nine cases documented the dose of tianeptine: the unintentional pediatric exposure reported a dose of 12.5 mg; the other two cases reported abuse of 5 and 10 g daily. Discontinuation symptoms reported among the five withdrawal cases included anxiety, agitation, vomiting, diaphoresis, piloerection, lacrimation, and yawning. Two of the nine cases were originally believed to be opioid overdoses and were administered naloxone for central nervous system depression and/or respiratory depression. In one case, naloxone administration improved the mental status and respiratory drive. In the other case, no effect was observed after naloxone administration. None of the cases had seizures or electrocardiogram changes. Five of the nine cases were admitted to the hospital, and three of these cases were

admitted to an intensive care unit. Outcomes reported in Toxicall® were minor in two cases, moderate in five cases, major in one case, and not reported in one case. Cases are summarized in Table 1.

Discussion

Tianeptine is structurally similar with tricyclic antidepressants (TCAs) (Figure 1) and is used as an anxiolytic and antidepressant due to its ability to enhance serotonin concentrations in the synapse [16]. At higher doses, it is a μ (OP1) receptor opioid agonist [16]. There are several isolated reports of tianeptine abuse [17] including one reported fatality [18]. Examination of reimbursement patterns from the French health-care system suggests that patients prescribed tianeptine to treat depression engage in "doctor-shopping" to access multiple prescriptions and obtain higher-than-prescribed doses [19]. In the country of Georgia, abuse of tianeptine was noted to be a problem among heroin users, several years before the opioid agonist effects were described in the scientific literature [20]. There are numerous published reports of users crushing and injecting tianeptine to get high, particularly in Eastern Europe [20–22]. Our case series demonstrates that tianeptine abuse appears to be increasing in frequency in New York State and likely throughout the United States.

Despite its structural similarity with TCAs, our cases did not demonstrate any clinical findings consistent with TCA poisoning including seizure activity or cardiac conduction abnormalities. Similar with other μ (OP1) receptor opioid agonists, high doses of tianeptine cause respiratory depression that is reportedly reversed with naloxone [21–23].

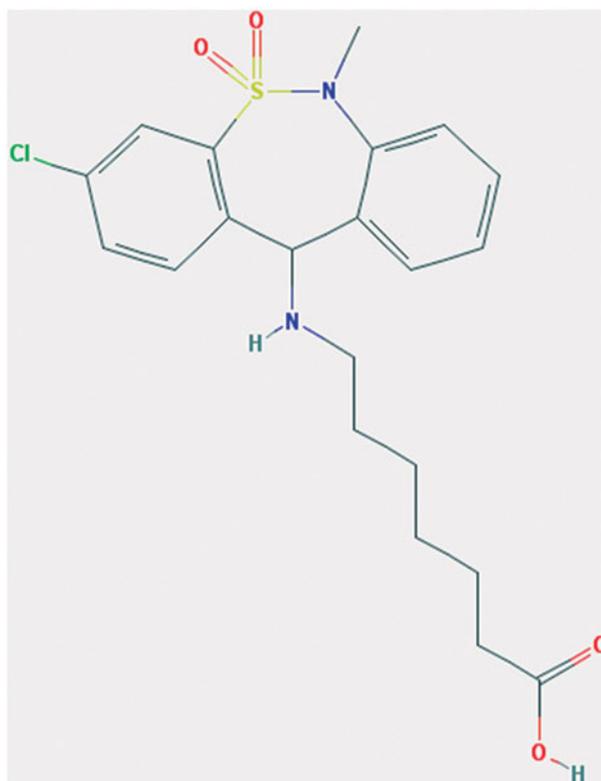


Figure 1: Chemical structure of tianeptine.

Table 1. Summary of tianeptine exposures reported to PCC.

Case no.	Age (years)	Gender	Dose	Narrative	Clinical scenario	Treatment and duration	Disposition
1	1	F	12.5 mg	Asymptomatic pediatric exposure.	Pediatric exposure	Observation only	Home from ED
2	27	M	NR	Ingested tianeptine mixed with alcohol to get high. Presented with depressed respiration, decreased level of consciousness, and pinpoint pupils.	Abuse	Naloxone was administered with marked improvement in respiration and mental status; redose of naloxone 2 hours after the initial.	ICU
3	51	F	NR	Presented with confusion and agitation after discontinuing tianeptine following 6 months of chronic use. Urine was positive for cocaine.	Withdrawal	Patient was sedated and intubated for 24 hours; required benzodiazepines for 48 hours for agitation	ICU for 48 hours
4	33	M	1 tab twice daily	Presented with diaphoresis and tachycardia after discontinuing tianeptine following 6 months of chronic use to treat depression.	Withdrawal	Observation only; discharged within 5 hours	Home from ED
5	19	M	NR	Ingested tianeptine powder with intent to get high. Patient presented to emergency department unresponsive but with adequate respirations. Other medications included sertraline, hydroxyzine, gabapentin, amphetamine/dextroamphetamine.	Abuse	Naloxone administration without improvement in mental status	ICU for 24 hours
6	31	M	5 g daily	Presented with malaise, yawning, piloerection, and GI distress after discontinuing tianeptine following 9 months of chronic use.	Withdrawal	Benzodiazepines and antiemetics given; discharged within 12 hours	Home from ED
7	24	M	NR	Presented with abdominal pain, back pain, and dysuria 12 hours after smoking tianeptine.	Abuse ^a	Observation only; discharged within 5 hours	Home from ED
8	36	M	NR	Presented with agitation, tremor, tachycardia after discontinuing tianeptine after chronic use three times daily. Patient also uses alcohol chronically (serum ethanol 182 mg/dL on presentation).	Withdrawal	Benzodiazepines for ~48 hours	Home from ED
9	23	M	10 g daily	Presented with anxiety, vomiting, shakiness, diaphoresis after discontinuing tianeptine following several weeks of chronic use.	Withdrawal	Benzodiazepines for ~48 hours	Psychiatric inpatient facility

NR: not reported; M: male; F: female.

^aUnclear if related.

The present case series includes two patients treated with naloxone. In one case, there was a clear reversal of mental status change and respiratory depression, in the other case no change in clinical status was noted in response

with naloxone. More research is needed to understand the role of naloxone in reversing tianeptine overdose.

Cessation of chronic tianeptine use, users precipitates a withdrawal syndrome that resembles the opioid withdrawal

syndrome [17,20]. Tianeptine use in pregnancy is even associated with neonatal abstinence syndrome [24]. More than half of the cases in this series sought medical attention related to withdrawal symptoms resulting from the cessation of chronic tianeptine use, further suggesting that tianeptine can produce physical dependence with chronic use and the development of withdrawal symptoms on cessation.

Limitations

This case series has several limitations that should be underscored. None of the cases that were reported as exposure to tianeptine had confirmatory diagnostic testing. In addition, definitive conclusions about the true incidence of tianeptine misuse/abuse are impossible while utilizing PCC data because of the passive reporting system. In all cases, other possible etiologies of symptoms or possible causes of withdrawal symptoms (e.g., opioids) could not be excluded. Finally, the role of naloxone in tianeptine toxicity remains unclear and further study is warranted.

Conclusions

Tianeptine is an antidepressant and a μ (OP1) receptor opioid agonist with risk for abuse, overdose, and physical dependence. Further research is necessary to describe the effects of tianeptine in overdose and responsiveness to naloxone. This product is inadequately regulated in the United States and poses a risk to public health. Future efforts should focus on improved regulation of this potentially dangerous substance in the United States.

Disclosure statement

No potential conflict of interest was reported by the authors.

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