HHS Public Access

Author manuscript

Am J Drug Alcohol Abuse. Author manuscript; available in PMC 2022 July 04.

Published in final edited form as:

Am J Drug Alcohol Abuse. 2021 July 04; 47(4): 455–466. doi:10.1080/00952990.2021.1904408.

When an obscurity becomes a trend: Social-media descriptions of tianeptine use and associated atypical drug use

Kirsten E. Smith[*,1], **Jeffery Rogers**[1], **Justin C. Strickland**[2], **David H. Epstein**[1]

[1]National Institute on Drug Abuse Intramural Research Program, 251 Bayview Blvd. Baltimore, Maryland 21224, USA.

[2]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224, USA

Abstract

Background: Originally believed to be an atypical antidepressant acting at serotonin transporters, tianeptine is now known to also be an atypical agonist at mu-opioid receptors. Its nonmedical use may be increasing amidst the broader context of novel drug and supplement use.

Objectives: To analyze social-media text from current, former, and prospective tianeptine users for better understanding of their conceptualizations of tianeptine, motives for and patterns of use, and reported benefits and harms.

Methods: Reddit posts were obtained and thematically coded; additional quantitative analyses were conducted.

Results: [1]—A total of 210 posts mentioning tianeptine were made between 2012–2020. Eighteen thematic categories were identified, 10 of which were consistent with expected themes. Two independent raters coded all text, generating 1,382 unique codes, of which 1,090 were concordant (78.9% interrater agreement). Tianeptine use was frequently associated with use of other drugs, particularly kratom, phenibut, and racetams. People conceptualized and variously used tianeptine as an opioid, antidepressant, and "nootropic" (cognitive enhancer). Between 2014–2020, mentions of positive effects decreased, while mentions of adverse effects and withdrawal increased. Motivations for use included: substitution or withdrawal mitigation for other drugs (especially opioids) and for kratom itself; self-treatment for psychiatric symptoms; and improvement of quality of life, mood, or performance. Descriptions of tolerance, withdrawal, and addiction were evident. Intravenous use was rare and strongly discouraged, with detrimental effects described.

Conclusion: Tianeptine is recognized as an opioid (though not only an opioid) in online communities. Posts describe benefits, acute risks, and patterns of co-use that warrant greater clinical attention.

[1]Please note that the gender/sex of participants could not be identified in many cases, meaning that we could not list in the abstract.

[*]**Address:** National Institute on Drug Abuse, Intramural Research Program, Translational Addiction Medicine Branch, 251 Bayview Blvd. Suite 200, Room 01B340, Baltimore, Maryland, 21224, USA, kirsten.smith@nih.gov.

Conflict of Interest: The authors report no conflict of interest.

Background

Tianeptine, a xenobiotic with a structure resembling those of tricyclic antidepressants, is currently prescribed in some Asian, European, and Latin American countries for the treatment of symptoms of depression and anxiety, though is not approved for those indications in the United States, United Kingdom, or Canada. A literature review in the 1980s concluded that tianeptine was effective for treating depression, especially depression with comorbid anxiety or associated with alcohol withdrawal [1]. Tianeptine's antidepressant and anxiolytic properties were variously attributed to monoamine reuptake inhibition, enhancement of serotonin reuptake, normalization of glutamatergic transmission, reversal of stress-associated neural changes, and neurogenesis, although more recent investigations have pointed to another possible mechanism: tianeptine is a full agonist at mu-opioid receptors (with some affinity for kappa-opioid receptors) [2, 3]. In animal models, mu-opioid receptor activation is necessary for many of tianeptine's behavioral effects, including antidepressant-like effects (assessed by forced-swim test), analgesia, hyperactivity, and reward (assessed by conditioned place preference) [4]. Mu activation may not account for the entirety of tianeptine's clinical efficacy. For instance, its anxiolytic properties may be mediated by reduction of glutamate release [5]. Still, the discovery of mu-activating properties is an important addition to its pharmacological profile. When prescribed, tianeptine is typically given at dosages of 12.5 to 50 mg/day; in clinical trials utilizing that therapeutic dose range, tianeptine gave little signal of abuse potential and was generally well tolerated and efficacious for treatment-resistant depression [1, 6, 7].

Nonmedical tianeptine use and misuse

Tianeptine has not been approved for any indication by the US Food and Drug Administration (FDA); reasons for this are unclear. Johnson & Johnson Pharmaceutical Research & Development completed a phase 1 clinical trial in 2009 [NCT0210398] but did not publish the results, nor pursue development. Gupta and colleagues, in 2017 [8], posited that tianeptine never underwent FDA approval process "simply because the cost of conducting a clinical trial for approval would exceed the expected profits." In 2020, enrollment began in a small clinical trial of tianeptine for treatment-resistant depression funded by the National Institutes of Health [NCT04249596].

Still, tianeptine remains unregulated in the US and many other countries, with web-based retailers proffering tianeptine products to consumers as a research chemical, nootropic (cognitive enhancer) [9], or dietary supplement [8]. Online, tianeptine is typically sold as either a sodium or sulfate salt. Vendors often claim that the sulfate salt is slower acting, longer lasting, and produces less intense effects. Typically, online products contain tianeptine in a proprietary blend with other substances, making dose determinations impractical (see supplementary materials, Figure S1). Case reports illustrate instances of problematic forms of consumption, such as intravenous injection and dose escalation exceeding 100x therapeutic recommendation [10]. Many of the reports of adverse events with tianeptine are characterized by initial adherence to clinical dosing recommendations followed by dose escalation for desired effects (e.g. antidepressant, anxiolytic, euphoric), eventually leading to tolerance and emergence of opioid-like withdrawal symptoms between

doses [11, 12]. Other adverse events from case reports and reports to poison-control agencies include dysphoria, anxiety, damage to peripheral venous tissue from injection, and hepatic toxicity [10, 13, 14].

These reports led us to suspect that tianeptine is emerging as a nonmedically used (or "self-prescribed") drug. We had also detected similar signals in recent analysis of social-media data pertaining to use of kratom during the Covid-19 pandemic (K.S. and J. R; findings currently unpublished.) that mentioned tianeptine use and during prior direct clinical interactions with substance use treatment clients who reported tianeptine use (K.S) in combination with other substances. We suspected that tianeptine may be co-used with many different substances. This includes prescribed and diverted prescription drugs (e.g., opioids, psychiatric medication, psychostimulants) as well as novel substances with the potential to have been purchased legally in many countries between the mid-2000s and 2020, even if some prohibitions have since been enacted (e.g., synthetic cannabinoids or cathinones, supplements, nootropics, such as phenibut) [15–19]. Additional factors considered before undertaking this project included the rise of "psychonaut" drug explorers who, among other substances, report use of cognitive-enhancing drugs or nootropics [18, 20–22]. We also considered the broader opioid epidemic, which may have inclined some to use diverted prescription opioids, nootropics, or dietary supplements in attempts to mitigate opioid misuse problems [23–27].

Aims

Given tianeptine's unique pharmacology, therapeutic and abuse potential, and preliminary reports indicating nonmedical misuse and co-use with other substances, one aim of this study was to learn more about nonmedical use and co-use of tianeptine. This included understanding how it is conceptualized and discussed among people who have used it and among people interested in trying it. We also sought to document motivations for use, patterns of co-use with other drugs, and effects associated with use. Although this study was exploratory, we anticipated that people would conceptualize tianeptine in one of three ways: (1) as an opioid (used for any or all of the purposes that can drive opioid use); (2) as an antidepressant; (3) as a cognitive-enhancing nootropic.

Methods

Data collection

Posts made to the popular social media platform Reddit were collected and thematically analyzed. We chose Reddit partly because other platforms that permit long-form text posts (e.g., Facebook and Instagram) impose considerable barriers to data collection. Notably, Facebook restricted access to their Application Programming Interfaces in 2018 alongside enactment of other privacy restrictions, requiring researchers to obtain consent from individual users prior to collecting their post text. Reddit data are accessible, contextualized, and often provide nuanced insights into drug-use experiences and related issues. Post data can be extracted using search terms within specific subreddit communities or for all subreddits.

We anticipated that mentions of tianeptine would appear on Reddit by approximately 2008, when many subreddits proliferated on the platform, and when physician prescribing practices for opioids began to be influenced by increased government monitoring systems and diversion concerns [28–30]. However, to ensure we did not omit earlier mentions, we imposed no date restrictions in our preliminary Reddit searches. We did not purposefully seek to use brand or street names in the search strategy for several reasons, one of which was the proprietary nature of Reddit's source code. However, the relevance search function likely displays content based on strength of correlations between related words and some other post-relevance function that accounts for recency, proportion of upvotes, number of upvotes, number of comments, and other metadata. At first pass, we generated a data set of over 15,000 posts with approximately 240,000 comments dating back to 2011. This was done by collecting post data from the top 30 individual subreddits that Reddit's search function returned after searching for "tianeptine" and "tia". From these posts and comments, we then: (1) created a document text corpus, (2) parsed the corpus into word tokens, (3) removed punctuation and stop words, (4) conducted searchers for misspellings of tianeptine as well as slang that included some derivative of tianeptine, including prescription brand names.

Using search queries from this list of tianeptine-related terms, we pulled data from Reddit regardless of subreddit. This resulted in our final sample of 210 posts from 31 unique subreddits. It is possible, but unlikely, that some posts referring to "tianeptine", but *only* using more obscure slang may not have been collected. However, by building search queries from both top tianeptine-related subreddits and by conducting a general Reddit-wide search, we believe we obtained nearly all the relevant material. Using *R*, we collected posts as individual datasets, then merged and exported using *R* packages {dplyr} and {writexl}, respectively. Because no personal identifiers were associated with the posts, this project was exempted from IRB review by the NIH IRB.

Social media text analysis

A list of themes that we expected to find in the Reddit posts was generated *a priori*—that is, prior to data collection—based on the background knowledge discussed in the Introduction. A total of 210 posts, dating back to no earlier than 2012, met search criteria. Two raters (K.S. and J.R.) read the compiled posts to identify appearances of the *a priori* themes and to document any additional themes. On group discussion after this first pass through the data, a codebook of 18 unique thematic categories was created and used for coding, 10 of which were consistent with expected themes. The same raters then independently coded posts using MAXQDA 2020 (VERBI Software, Berlin). Because Reddit posts can be lengthy, and because even one sentence could contain material relevant to more than one theme, raters applied unique codes to all text in order to calculate proportion of rater agreement for all items. Accordingly, no text that corresponded to a theme was left unlabeled, as multiple themes could be applied to the same segment of text.

Quantitative analysis

After coding was completed, codes were reviewed and used to generate three tianeptine-specific dichotomous measures: (1) mention of positive effects, (2) mention of adverse effects (except withdrawal symptoms), and (3) mention of withdrawal symptoms. These

were used as dependent variables in logistic regression analyses. First, we identified the reported daily dose in a subset of records (n=75). For these instances, the relationship between dose and outcomes was evaluated, with dose coded as mg/day and log-transformed to improve distributional qualities and interpretation. Second, we evaluated changes over time, treating time as a linear predictor. Data prior to 2014 were excluded because only one post was identified for 2012 and one for 2013 (≥20 posts/year were identified in 2014 onward). Finally, we evaluated associations among positive, adverse, and withdrawal variables and concomitant use of the three most frequently mentioned other substances: phenibut, kratom, and racetams. Quantitative analyses were conducted using *R*.

Results

Table 1 shows all coded themes, the interrater agreements versus disagreements, agreement percent, and the total number of posts coded (i.e., number of posts coded by at least one rater as constituting a given theme).[1] (See Table S1, in supplementary materials, for kappa coefficients.) A total of 1,382 unique codes were made, of which 1,090 were concordant and 292 were discordant, resulting in a 78.87% rate of interrater agreement. Corrected kappa for interrater agreement was 0.78, indicating moderate to substantial agreement. Given that total agreement was sufficient, and no discordance was lower than 50.0%, we did not conference and subsequently re-code text in order to achieve a higher agreement rate. Part of this is for the sake of transparency, but also because it underscores the complexity of how people wrote their posts and described highly detailed experiences.

Polydrug use

Across posts, a prominent theme was “polydrug use that included tianeptine” (n=210). This included polydrug use in which tianeptine was being used on the same occasions as other substances or as part of the same longer-term pattern of use (within weeks or months) with myriad licit and illicit substances. This also included research chemicals and supplements with varying degrees of legality. The breadth of substances discussed in posts was substantial and not all were psychoactive (see Table 2). Although there were mentions of substances we expected to find, there were also many we had not anticipated (e.g., memantine, Vortioxetine) or that were heretofore unknown to us (e.g., HRX-1074, GLYX-1). Substances frequently discussed as being co-used with tianeptine were typically referred to as “nootropics” (or “noots,” or “cognitive enhancers”). The most frequently mentioned nootropic drug was phenibut (n=35; 4-amino-3-phenul-butyric acid), a $GABA_B$ agonist with anxiolytic and putative cognitive-enhancing effects sold online as a dietary supplement, and clinically prescribed only in Russia [31–35]. The second most frequently mentioned nootropic drug (n=25) were racetams (e.g., piracetam, phenylpiracetam, levetiracetam), a drug class with a shared pyrrolidone nucleus that are also purported by vendors to have cognitive enhancing effects [36, 37].

The second most frequently mentioned substance (n=33) was kratom, which was almost always categorized as an opioid, not a nootropic. Also frequently mentioned were caffeine

[1]For transparency, all social media data collected and coded for this study are available upon request.

(n=19), L-theanine (n=15), cannabis (n=14), and alcohol (n=11). There were relatively few (n=19) mentions of heroin, fentanyl, U-47700, and prescription opioids such as buprenorphine and methadone. Psychostimulants other than caffeine and nicotine were mentioned 40 times.

The three most frequently mentioned other drugs (kratom, phenibut, and racetams) were often mentioned together. There were twenty instances (9.5% of all polydrug mentions) of co-use of tianeptine, kratom, and phenibut; there were 15 instances (7.1%) of tianeptine and phenibut without kratom; there were 13 instances (6.2%) of tianeptine and kratom without phenibut. These substances were often mentioned in posts that also described tolerance or withdrawal symptoms—sometimes as sources of those unwanted effects, and sometimes as remedies for withdrawal from (or tolerance to) other drugs, including opioids, tianeptine, and various “nootropics.” Column 1 of Table S2 displays some direct quotes to illustrate the complexity of patterns of co-use, particularly among kratom, phenibut, and tianeptine.

Many people, describing the effects of co-use (Table S2, columns 1 and 2), credited these drug combinations with either decreases in psychiatric symptoms or with improvements in mood, energy, and productivity irrespective of any stated pathology—a distinction with a difference. In both contexts, many people referred to their preferred combination of substances as their “stack.” Descriptions of “stacks” often gave the impression of being pragmatic, well-reasoned, and functionally adaptive, either alleviating a specific problem or increasing quality of life.

How tianeptine was conceptualized; effect profiles of different dosages

As noted above, tianeptine’s effects were described in ways that variously fell into the following categories: opioid (n=115), antidepressant (n=96), mood enhancer (n=48), or cognitive enhancer (n=45). Table 3 shows specific mentions corresponding to each of our three main categories of effects (positive effects, adverse effects besides withdrawal symptoms, and withdrawal symptoms). There was an unexpectedly high frequency of mentions of withdrawal (n=82), tolerance (n=41), and aspects of addiction (n=54), such as having a desire to quit using tianeptine (n=31) or having tried to quit (n=22). Tolerance was discussed in the context of its being rapid to develop, related to acute effects, and resulting in a need to dose frequently. Withdrawal was typically described as moderate to severe (Table S2, column 3).

Specific mentions of dosage occurred in 132 posts. Doses within a 24-hour period ranged from 12.5 mg to 7,500 mg. Figure 1 shows how those dose ranges were associated with each of our three main categories of effects. Higher doses were associated with greater odds of withdrawal symptoms, OR=4.42 [2.08,9.40], p<.001, and with greater odds of other adverse effects, OR=1.35 [1.01,1.79], p=.04, as well as lower odds of positive effects, OR=0.52 [0.38,0.72], p<.001. Analyses found that posts with any dosage information reported higher rates of all types of effects (positive, withdrawal, and adverse) than posts without dosage information, perhaps reflecting a richer overall narrative in the posts with dosing information.

Figure 2 further shows how mentions of effect categories changed by year. From 2014–2020, the percentage of posts describing positive effects steadily declined from 60% to just under 25.8%, linear OR=0.82[0.70,0.95], p=.008, while the percentage of posts describing withdrawal increased from 0% to a high of 27.3% before decreasing slightly in 2020 to just under 16.1%, linear OR=1.52 [1.18,1.97], p=.001. Frequencies of posts mentioning adverse effects fluctuated with no discernible temporal pattern, linear trend OR=0.98[0.80,1.19], p=.83.

Because tianeptine was so often co-used with kratom, phenibut, and racetams, we examined mentions of positive, adverse, and withdrawal effects in the context of co-use (Figure 3). People who used kratom were more likely to report positive effects from tianeptine, OR=2.72[1.27,5.82], p=.01, but also more likely to report withdrawal symptoms, OR=5.48[2.16,13.94], p<.001. Racetam use was also associated with a greater odds of positive effects from tianeptine, OR=3.74[1.53,9.13], p=.004, but not with withdrawal symptoms, OR=0.68[0.15,3.09], p=.62. Phenibut use was associated with neither. None of the three co-used drugs showed a statistically significant relationship with odds of non-withdrawal adverse effects of tianeptine.

It should be noted that while most posts were from people currently using tianeptine, a few people posted that they had stopped, whereas others were from people expressing curiosity. Specific advice was often sought (n=161) or given (n=68). Although every post we analyzed could be considered a form of information sharing, we applied the “information sharing” code only to posts in which the person was clearly intending to provide quality information of value to peers in their post (as opposed to a tangent, description of one’s emotional state, biographical sketch, etc.). One of the most salient of these pertained to tianeptine injection. Although not commonly discussed as a route of administration—oral being the most commonly noted or inferred—people who had injected tianeptine provided stern admonitions not to do it (see Table S2, column 3).

Discussion

Opioid, antidepressant, or cognitive enhancer?

In this exploratory study, we sought a better understanding of nonmedical tianeptine use by analyzing social-media posts made on Reddit between 2012 and 2020. Our findings suggest that among people using and misusing tianeptine, it is primarily conceptualized as an opioid, an antidepressant, or a nootropic. The categorization is complicated not just by the mixed properties of tianeptine itself, but by the likelihood that antidepressants improve cognition in depressed people [38] and the possibility that some mu opioids might function as antidepressants [39–41].

The consensus among people posting to Reddit was that tianeptine is an opioid. This was sometimes mentioned in terms of receptor pharmacology, sometimes in terms of subjective effects (e.g., euphoria, feelings of warmth or contentedness, “nodding off,” analgesia), and sometimes in terms of cross-tolerance (e.g., mentions of tianeptine’s ability to attenuate opioid withdrawal symptoms, and mentions of tianeptine withdrawal symptoms that could be attenuated by buprenorphine, methadone, or kratom). Still, alongside this consensus was

confusion, debate, and conjecture as to what tianeptine is or is not, and at what doses. Many people simply did not know how to characterize tianeptine. People's motivations for tianeptine use, however, often involved its antidepressant properties (some people used it after multiple failed attempts at treatment with traditional antidepressants) and, more often than not, additional beliefs in its potential to enhance cognition or to improve quality of life generally. Through these posts, people actively attempted to share experiential knowledge and academic information (e.g., links to published papers) to help each other navigate potential benefits of tianeptine in light of its potential of opioid-like risks.

Chasing the OK-ness

Although some people described using tianeptine for one reason (e.g., cognitive or performance enhancement, antidepressant effects, acute euphoria), this was not the majority. Many people expressed some *combination* of wanting to feel good, think clearly, and function to meet their everyday obligations and achieve basic goals. Indeed, many seemed to use tianeptine less to achieve a euphoric high and more to feel "less bad" or "more normal." Many mentioned using (or seeking to use) tianeptine to decrease general anxiety, irrespective of whether they met the diagnostic threshold for an anxiety disorder, or to achieve a state of what they perceived to be "equilibrium" or "feeling like one's true self." In short, posts did not consistently nor predominantly reflect attempts to "chase a high" so much as they reflected attempts to feel "OK" or to achieve a sense of being capable, healthy, and productive.

Use or misuse?

As noted above, some people described being primarily or solely interested in experiencing euphoric highs. For them, the development of tolerance sometimes led to large increases in dose, which, in turn, were associated with acute adverse effects and withdrawal symptoms. Especially striking were the deleterious effects of intravenous use. Still, if not all unprescribed use is relegated to the realm of *mis*use—if the possibility of successful instrumental use is acknowledged—then many people posting at least perceived their use that way. This is reflected in how people talked about their "stack" as if it were a daily regimen to be taken as directed and without deviation once they had established it, sometimes after months or years of experimentation.

Nonetheless, some mentioned problems, such as tolerance, withdrawal, or symptoms of addiction, that they had not anticipated at the outset of use. It is possible, but difficult to discern directly in these data, that this trajectory was more likely in people who began using tianeptine earlier, with less access to online advice from peers. Similar to other Internet fora, Reddit seems to have emerged as a hub for informal, but conscientious, information sharing [21, 42, 43].

Polydrug use

The frequent mentions of a "stack"—usually consisting of tianeptine plus at least one other substance—is one indication of the extent of polydrug use among those whose posts we analyzed. Mentions of tianeptine as a remedy for withdrawal from or substitute for other substances (e.g., phenibut, kratom) highlights one of several dark sides to tianeptine use in

our sample: it was but one substance in a long line of substances that eventually failed to have the desired benefit-harm ratio. Ongoing use of such substances, including tianeptine itself, was seen as a manifestation of dependence or addiction.

Although we anticipated mentions of phenibut, we had not expected them to be so frequent, given the differences in pharmacology between tianeptine and phenibut (even as both are proffered online as cognitive-enhancing dietary supplements or nootropics). As in prior studies [44–48], phenibut was described in both positive terms (e.g., “cognitive enhancement”, “mood improvement”, “decreased anxiety”) and negative terms (e.g., “addictive”). While we were surprised by how infrequently heroin and pharmaceutical opioids were mentioned, we were equally surprised by the frequency with which kratom was mentioned. Tianeptine had been noted only occasionally in other investigations related to kratom being undertaken by some authors, or in direct interactions with people reporting kratom and other substance use, which partially influenced us to undertake the present work. Kratom, a botanical that is legal in most US states and acts as a biased partial agonist at mu opioid receptors, is not commonly referred to as a “cognitive enhancer” or “nootropic” [49, 50]. In these and separate investigations, kratom was conceptualized by people as a “nootropic” only once. To the best of our knowledge, only one published paper refers to kratom as a “nootropic” [51]. The co-use of kratom and tianeptine, in hindsight, is perhaps unsurprising in that both appear to be used to self-treat anxiety, depression, fatigue, pain, and opioid withdrawal [25, 27, 52, 53]. Although the literature on kratom is growing, there are few documented cases of its co-use with tianeptine and/or phenibut [48, 54–56]. Our findings suggest that these patterns of co-use may be more common.

Other patterns of drugs co-used with tianeptine that merit further attention are the psychostimulant modafinil, commonly used to treat sleep disorders, and the NMDA antagonist memantine, which is a primarily used to treat symptoms of Alzheimer’s disease, both of which have been used or misused nonmedically [57–59]. These and other drugs co-used with tianeptine might all serve as starting points for additional work and greater awareness among medical professionals.

Limitations

This exploratory study has several important limitations. First, these social-media data come from only one platform, Reddit. Findings may therefore not be generalizable to people who use tianeptine but engage only with other social-media platforms or drug-use forums (e.g., Erowid, Bluelight), or none at all. People self-selecting to post tianeptine experiences may disproportionally include those who experienced particularly positive or negative effects. Another limitation is that in most cases posts did not distinguish between the sulfate and sodium salts of tianeptine, so we cannot address possible differences in the effects of those formulations. Similarly, there was likely variability among tianeptine products, both between vendors and across time. This includes the possibility that products advertised as tianeptine were adulterated or contained more than one substance. Due to the ambiguous and varied labeling of these products, dose information may be inaccurate, even when reported carefully by users. It is also possible that not every tianeptine-specific post was captured given that there may have been slang terms for tianeptine not utilized in our search

strategy. Dosage information was given in only a subset of posts, some of which could not be analyzed quantitatively due to insufficient temporal specificity or other ambiguities. Lastly, lack of demographic information, including country of origin, limits findings further, though, on the basis of content and style, many posts appeared to be from the US.

Conclusion

Findings here provide evidence of tianeptine use and misuse and conceptualization of the drug as an opioid and opioid substitute. Findings serve primarily as a starting point for future investigation into nonmedical tianeptine use, particularly among people co-using it with other substances, such as kratom, phenibut, and racetams. Systematic study among a wider and more diverse sample of people (not merely those self-reporting information on Reddit) is needed to help determine the prevalence, patterns, and demographic correlates of use. Until more research has been conducted, healthcare professionals should be aware of several factors, including the regularity with which tianeptine is co-used with other substances. This also includes the wide range of effects that tianeptine can produce. These should be taken into account when patients present with symptoms or toxicity associated with use of unspecified drugs or supplements, or when people present with opioid withdrawal symptoms unaccompanied by evidence of typical opioid use. A primary takeaway from this and similar work is that people who use, or come to misuse, unregulated psychoactive drugs are not always doing so with the primary intention of achieving a euphoric high. Many people in this sample reported using tianeptine and other substances in what they believed to be a pragmatic and rational manner. Moving forward, researchers and clinicians should be mindful of the motivations and intentions promoting tianeptine use and take such factors into account when seeking to understand it, treat it, or address underlying issues which may have motivated use to begin with.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Supported by National Institutes of Health T32 DA07209

References

1. Defrance R, Marey C, A. K.Antidepressant and anxiolytic activities of tianeptine: an overview of clinical trials, Clin Neuropharmacol1988: S74–S82. [PubMed: 2902922]
2. Kasper S, McEwen BSNeurobiological and clinical effects of the antidepressant tianeptine, CNS Drugs2008: 22: 15–26. [PubMed: 18072812]
3. Gassaway MM, Rives M-L, Kruegel AC, Javitch JA, Sames DThe atypical antidepressant and neurorestorative agent tianeptine is a μ-opioid receptor agonist, Translational Psychiatry2014: 4: e411. [PubMed: 25026323]
4. Samuels BA, Nautiyal KM, Kruegel AC, Levinstein MR, Magalong VM, Gassaway MMet al.The behavioral effects of the antidepressant tianeptine require the mu-opioid receptor, Neuropsychopharmacology2017: 42: 2052–2063. [PubMed: 28303899]

5. McEwen BS, Chattarji S, Diamond DM, Jay TM, Reagan LP, Svenningsson Pet al.The neurobiological properties of tianeptine (Stablon): From monoamine hypothesis to glutamatergic modulation, Molecular Psychiatry2010: 15: 237–249. [PubMed: 19704408]
6. Tobe EH, Rybakowski JKPossible usefulness of tianeptine in treatment-resistant depression, Int J Psychiatry Clin Pract2013: 17: 313–316. [PubMed: 23668804]
7. Woo YS, Bahk WM, Jeong JH, Lee SH, Sung HM, Pae CUet al.Tianeptine combination for partial or non-response to selective serotonin re-uptake inhibitor monotherapy, Psychiatry Clin Neurosci2013: 67: 219–227. [PubMed: 23683152]
8. Gupta S, Wallace R, Sloshower JOnline sales of unscheduled pharmaceutical agents: a case report of tianeptine use in the United States, Journal of Addiction Medicine2017: 11: 411–412. [PubMed: 28742625]
9. Giurgea C, Salama MNootropic drugs, Progress in Neuro-Psychopharmacology1977: 1: 235–247.
10. Vadachkoria D, Gabunia L, Gambashidze K, Pkhaladze N, Kuridze NAddictive potential of tianeptine—the threatening reality, Georgian Medical News2009: 174: 92–94.
11. Springer J, Cubała WJTianeptine abuse and dependence in psychiatric patients: a review of 18 case reports in the literature, Journal of Psychoactive Drugs2018: 50: 275–280. [PubMed: 29494783]
12. Bakota EL, Samms WC, Gray TR, Oleske DA, Hines MOCase reports of fatalities involving tianeptine in the United States, Journal of Analytical Toxicology2018: 42: 503–509. [PubMed: 29566235]
13. El Zahran T, Schier J, Glidden E, Kieszak S, Law R, Bottei Eet al.Characteristics of tianeptine exposures reported to the National Poison Data System—United States, 2000–2017, Morbidity and Mortality Weekly Report2018: 67: 815–818. [PubMed: 30070980]
14. Rushton W, Whitworth B, Brown J, Kurz M, Rivera JCharacteristics of tianeptine effects reported to a poison control center: a growing threat to public health, Clinical Toxicology2020: 1–6.
15. Ahuja T, Mgbako O, Katzman C, Grossman APhenibut (beta-phenyl-gamma-aminobutyric acid) dependence and management of withdrawal: emerging nootropics of abuse, Case Rep Psychiatry2018: 2018: 9864285. [PubMed: 29854531]
16. Baumann MH, Volkow NDAbuse of new psychoactive substances: threats and solutions, Neuropsychopharmacology2016: 41: 663–665. [PubMed: 26303285]
17. Jouney EAPhenibut (beta-phenyl-gamma-aminobutyric acid): an easily obtainable “dietary supplement” with propensities for physical dependence and addiction, Curr Psychiatry Rep2019: 21: 23. [PubMed: 30852710]
18. Napoletano F, Schifano F, Corkery JM, Guirguis A, Arillotta D, Zangani Cet al.The psychonauts’ world of cognitive enhancers, Front Psychiatry2020: 11: 546796. [PubMed: 33024436]
19. Schifano F, Orsolini L, Duccio Papanti G, Corkery JMNovel psychoactive substances of interest for psychiatry, World Psychiatry2015: 14: 15–26. [PubMed: 25655145]
20. Corazza O, Bersani FS, Brunoro R, Valeriani G, Martinotti G, Schifano FThe diffusion of performance and image-enhancing drugs (PIEDs) on the internet: the abuse of the cognitive enhancer piracetam, Subst Use Misuse2014: 49: 1849–1856. [PubMed: 24827869]
21. Deluca P, Davey Z, Corazza O, Di Furia L, Farre M, Flesland LHet al.Identifying emerging trends in recreational drug use; outcomes from the Psychonaut Web Mapping Project, Prog Neuropsychopharmacol Biol Psychiatry2012: 39: 221–226. [PubMed: 22841965]
22. O’Brien K, Chatwin C, Jenkins C, Measham FNew psychoactive substances and British drug policy: a view from the cyber-psychonauts, Drugs: Education, Prevention and Policy2015: 22: 217–233.
23. Chilcoat HD, Amick HR, Sherwood MR, Dunn KEBuprenorphine in the United States: Motives for abuse, misuse, and diversion, J Subst Abuse Treat2019: 104: 148–157. [PubMed: 31370979]
24. Cicero TJ, Ellis MS, Chilcoat HDUnderstanding the use of diverted buprenorphine, Drug Alcohol Depend2018: 193: 117–123. [PubMed: 30359928]
25. Garcia-Romeu A, Cox DJ, Smith KE, Dunn KE, Griffiths RRKratom (Mitragyna speciosa): User demographics, use patterns, and implications for the opioid epidemic, Drug Alcohol Depend2020: 208: 107849. [PubMed: 32029298]
26. Kavanaugh PR, McLean KMotivations for diverted buprenorphine use in a multisite qualitative study, Journal of Drug Issues2020: 50: 550–565.

27. Smith KE, Lawson TPrevalence and motivations for kratom use in a sample of substance users enrolled in a residential treatment program, Drug Alcohol Depend2017: 180: 340–348. [PubMed: 28950240]
28. Pauly NJ, Slavova S, Delcher C, Freeman PR, Talbert JFeatures of prescription drug monitoring programs associated with reduced rates of prescription opioid-related poisonings, Drug Alcohol Depend2018: 184: 26–32. [PubMed: 29402676]
29. Spiller H, Lorenz DJ, Bailey EJ, Dart RCEpidemiological trends in abuse and misuse of prescription opioids, J Addict Dis2009: 28: 130–136. [PubMed: 19340675]
30. Unick GJ, Rosenblum D, Mars S, Ciccarone DIntertwined epidemics: national demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993–2009, PLoS One2013: 8: e54496. [PubMed: 23405084]
31. Dambrova M, Zvejniece L, Liepinsh E, Cirule H, Zharkova O, Veinberg Get al.Comparative pharmacological activity of optical isomers of phenibut, Eur J Pharmacol2008: 583: 128–134. [PubMed: 18275958]
32. Downes MA, Berling IL, Mostafa A, Grice J, Roberts MS, Isbister GKAcute behavioural disturbance associated with phenibut purchased via an internet supplier, Clin Toxicol (Phila)2015: 53: 636–638. [PubMed: 26114346]
33. Kaupmann K, Huggel K, Heid J, Flor PJ, Bischoff S, Mickel SJet al.Expression cloning of GABA(B) receptors uncovers similarity to metabotropic glutamate receptors, Nature1997: 386: 239–246. [PubMed: 9069281]
34. Lapin IPhenibut (beta-phenyl-GABA): a tranquilizer and nootropic drug, CNS Drug Rev2001: 7: 471–481. [PubMed: 11830761]
35. Wong A, Little M, Caldicott D, Easton C, Andres D, Greene SLAnalytically confirmed recreational use of Phenibut (beta-phenyl-gamma-aminobutyric acid) bought over the internet, Clin Toxicol (Phila)2015: 53: 783–784. [PubMed: 26107626]
36. Cohen PA, Zakharevich I, Gerona RPresence of piracetam in cognitive enhancement dietary supplements, JAMA Intern Med2020: 180: 458–459. [PubMed: 31764936]
37. Loscher W, Richter APiracetam and levetiracetam, two pyrrolidone derivatives, exert antidystonic activity in a hamster model of paroxysmal dystonia, Eur J Pharmacol2000: 391: 251–254. [PubMed: 10729365]
38. Prado CE, Watt S, Crowe SFA meta-analysis of the effects of antidepressants on cognitive functioning in depressed and non-depressed samples, Neuropsychology Review2018: 28: 32–72. [PubMed: 29446012]
39. Robinson SA, Erickson RL, Browne CA, Lucki IA role for the mu opioid receptor in the antidepressant effects of buprenorphine, Behavioural Brain Research2017: 319: 96–103. [PubMed: 27818236]
40. Yovell Y, Bar G, Mashiah M, Baruch Y, Briskman I, Asherov Jet al.Ultra-low-dose buprenorphine as a time-limited treatment for severe suicidal ideation: a randomized controlled trial, American Journal of Psychiatry2016: 173: 491–498.
41. Lutz PE, Kieffer BLOpioid receptors: distinct roles in mood disorders, Trends in Neurosciences2013: 36: 195–206. [PubMed: 23219016]
42. Orsolini L, Papanti GD, Francesconi G, Schifano FMind navigators of chemicals' experimenters? A web-based description of e-psychonauts, Cyberpsychol Behav Soc Netw2015: 18: 296–300. [PubMed: 25965863]
43. Valeriani G, Corazza O, Bersani FS, Melcore C, Metastasio A, Bersani Get al.Olanzapine as the ideal "trip terminator"? Analysis of online reports relating to antipsychotics' use and misuse following occurrence of novel psychoactive substance-related psychotic symptoms, Hum Psychopharmacol2015: 30: 249–254. [PubMed: 26216558]
44. Hardman MI, Sprung J, Weingarten TNAcute phenibut withdrawal: A comprehensive literature review and illustrative case report, Bosn J Basic Med Sci2019: 19: 125–129. [PubMed: 30501608]
45. Magsalin RM, Khan AYWithdrawal symptoms after Internet purchase of phenibut (beta-phenyl-gamma-aminobutyric acid HCl), J Clin Psychopharmacol2010: 30: 648–649. [PubMed: 20841974]
46. O'Connell CW, Schneir AB, Hwang JQ, Cantrell FLPhenibut, the appearance of another potentially dangerous product in the United States, Am J Med2014: 127: e3–4.

47. Owen DR, Wood DM, Archer JR, Dargan PIPhenibut (4-amino-3-phenyl-butyric acid): Availability, prevalence of use, desired effects and acute toxicity, Drug Alcohol Rev2016: 35: 591–596. [PubMed: 26693960]

48. Samokhvalov AV, Paton-Gay CL, Balchand K, Rehm JPhenibut dependence, BMJ Case Rep2013: 2013.

49. Henningfield JE, Fant RV, Wang DWThe abuse potential of kratom according the 8 factors of the controlled substances act: implications for regulation and research, Psychopharmacology2018: 235: 573–589. [PubMed: 29273821]

50. Kruegel AC, Grundmann OThe medicinal chemistry and neuropharmacology of kratom: A preliminary discussion of a promising medicinal plant and analysis of its potential for abuse, Neuropharmacology2018: 134: 108–120. [PubMed: 28830758]

51. Mun M, Wong AKratom and phenibut: a concise review for psychiatric trainees, American Journal of Psychiatry Residents' Journal2020: 16: 6–8.

52. Bath R, Bucholz T, Buros AF, Singh D, Smith KE, Veltri CAet al.Self-reported health diagnoses and demographic correlates with kratom use: results from an online survey, J Addict Med2020: 14: 244–252. [PubMed: 31567595]

53. Coe MA, Pillitteri JL, Sembower MA, Gerlach KK, Henningfield JEKratom as a substitute for opioids: Results from an online survey, Drug Alcohol Depend2019: 202: 24–32. [PubMed: 31284119]

54. Högberg L, Szabó I, Ruusa JPsychotic symptoms during phenibut (beta-phenyl-gamma-aminobutyric acid) withdrawal, Journal of Substance Use2013: 18: 335–338.

55. McCabe DJ, Bangh SA, Arens AM, Cole JBPhenibut exposures and clinical effects reported to a regional poison center, Am J Emerg Med2019: 37: 2066–2071. [PubMed: 30878413]

56. Rod W, Kudryk A, Brunetti L, Sun N, Nguyen MPhenibut withdrawal management in the setting of concomitant kratom and alcohol dependence, Critical Care Medicine2018: 46: 451.

57. Hockenhull J, Wood DM, Dargan PIThe availability of modafinil and methylphenidate purchased from the internet in the United Kingdom without a prescription, Subst Use Misuse2020: 55: 56–65. [PubMed: 31431114]

58. Teodorini RD, Rycroft N, Smith-Spark JHThe off-prescription use of modafinil: An online survey of perceived risks and benefits, PLoS One2020: 15: e0227818. [PubMed: 32023288]

59. Mazanov J, Dunn M, Connor J, Fielding MLSubstance use to enhance academic performance among Australian university students, Performance Enhancement & Health2013: 2: 110–118.

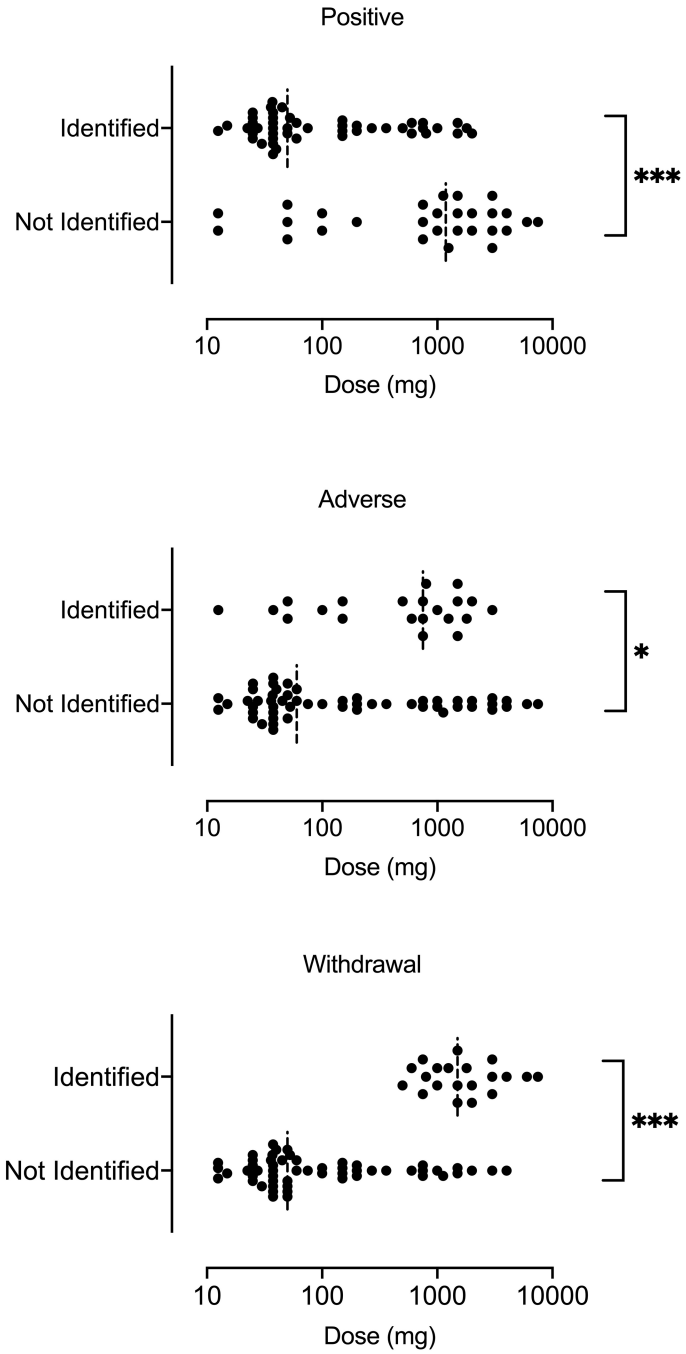

Figure 1.

Results from logistic regression showing coded subjective effects by daily dosing. This figure shows how tianeptine dose ranges, reported for a 24-h period, were associated with dichotomous variables for Identified (vs. Not Identified) “positive”, “adverse”, and “withdrawal” subjective effects attributed to tianeptine. Distributions of the dosing variable by coded variables of Identified positive effects (top panel), adverse effects (middle panel), and withdrawal effects (bottom panel). Vertical dashed lines are median dosing values. Dose is presented on a log scale. *$p < .05$; **$p < .01$; ***$p < .001$.

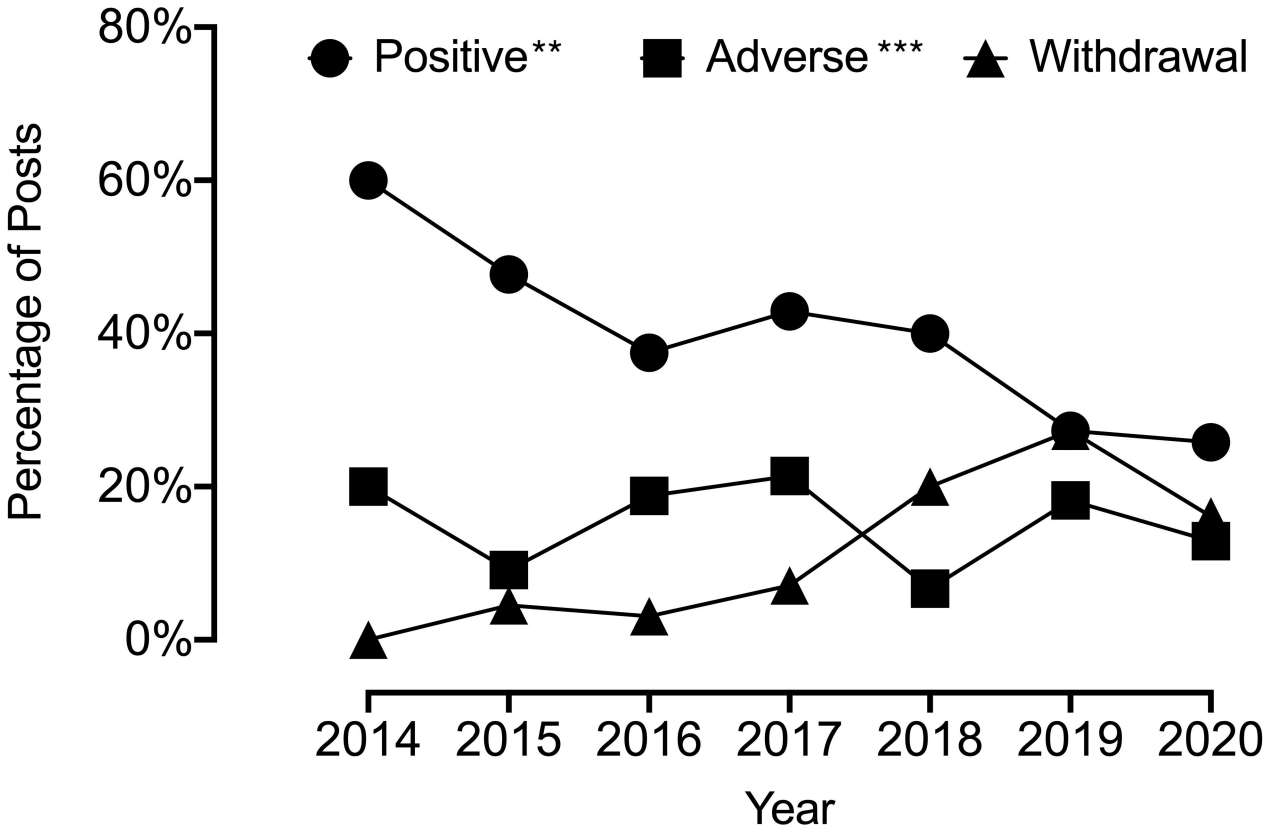

Figure 2.

Results from logistic regression showing proportion of posts with coded subjective effects by year. This figure shows how specific mentions of tianeptine subjective effects of "positive" (circles), "adverse" (squares), and "withdrawal" (triangles) changed between 2014 and 2020. *$p < .05$; **$p < .01$; ***$p < .001$.

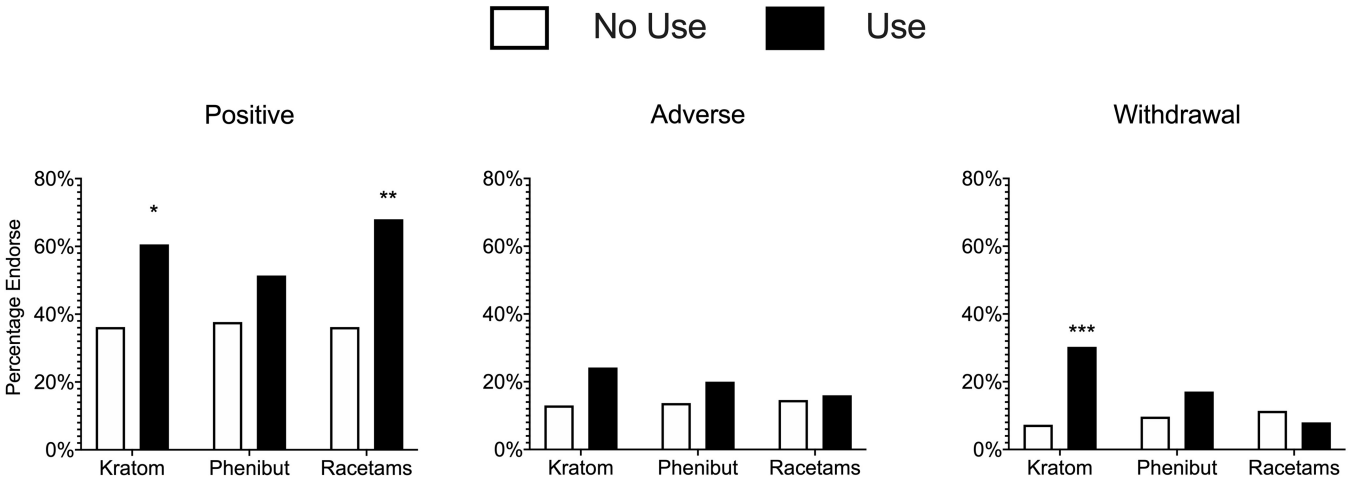

Figure 3.

Results from logistic regression showing percentage of coded subjective effects by the polydrug use variable. This figure shows the percentage of text coded for “positive” (left panel), “adverse” (middle panel), or “withdrawal” (right panel) effects from tianeptine as a function of use (black bars) or non-use (white parts) of the three drugs most commonly co-used with tianeptine: kratom, phenibut, and racetams. *$p < .05$; **$p < .01$; ***$p < .001$.

Table 1.0

All coded themes, the interrater agreements versus disagreements, agreement percent, and the total number of posts coded.

Thematic Code	Concordant	Discordant	Total	% Agreement
Tianeptine is a mood enhancer/has mood enhancing effects	26	22	48	54.17
Tianeptine tolerance	23	18	41	56.10
Tianeptine is an anti-depressant/has anti-depressant effects[±]	55	41	96	57.29
Plans for dealing with tianeptine withdrawal[±]	16	11	27	59.26
Tianeptine withdrawal[±]	58	24	82	70.73
Requesting advice from drug-using community	124	37	161	77.02
Tianeptine is an opioid/has opioid or opioid-like effects[±]	93	22	115	80.87
General peer-to-peer information sharing[±]	110	23	133	82.71
Polydrug use that includes tianeptine[±]	175	35	210	83.33
Professed or strongly inferred tianeptine addiction	45	9	54	83.33
Desire to discontinue use or quit tianeptine	26	5	31	83.87
Tianeptine is a cognitive enhancer/has cognitive-enhancing effects[±]	38	7	45	84.44
Tianeptine dosing range[±]	112	20	132	84.85
Desirable tianeptine effects[±]	97	14	111	87.39
Giving advice to drug-using community	64	4	68	94.12
Circumstances forcing discontinuation of tianeptine	4	0	4	100.0
Neurogenesis	2	0	2	100.0
Quitting tianeptine[±]	22	0	22	100.0
Total	**1,090**	**292**	**1,382**	**78.87**

[±]Denotes thematic codes which had been anticipated prior to reading the sample of social media posts collected for this study. All other themes were identified and used to create the codebook during and subsequent to the first reading of posts, but before independent coding began.

Table 2.0

Frequencies for unique drug terms appearing in Reddit posts made between 2011–2020 related to tianeptine use

Substance	*N*		*N*		*N*		*N*
Phenibut	35	Tramadol	6	Etifoxine	3	Moclobemide	1
Kratom	33	Kanna	6	Lexapro	3	Naltrexone	1
Racetams	25	Klonopin	5	Lyrica	3	Selegiline	1
Caffeine	19	Adderall	5	Diphenhydramine	3	U-47700	1
L-theanine	15	Celexa	5	Salvia	3	Cimitidine	1
Cannabis	14	Lyrica	5	Lions mane	3	HA-966	1
Semax	12	NSI-189	5	PRL-8-53	3	4-HO-MET	1
Benzodiazepam	11	MDMA	5	Morning glory seeds	3	Phenethylamine	1
Alcohol	11	Cocaine	5	Vyvanse	2	Atarax	1
Gabapentin	11	LSD	4	Ayahuasca	2	GLYX-13	1
Nooept	11	Abilify	4	Polygala	2	HRX-1074	1
Memantine	11	Ambien	4	Fentanyl	2	Agomelatine	1
Modafinil	10	Clonidine	4	Synthetic cannabinoids	2	Mebroqualone	1
Nicotine	10	Baclofen	4	DMT	2	Lithium	1
Kava	10	Heroin	4	Methadone	2	DMAA	1
Ashwagandha	10	Codeine	4	Nitrous	2	HGH	1
Amphetamine	9	Etizolam	4	IDRA-21	2		
Selank	8	Sertraline	4	Methylphenidate	2		
Agmatine	8	Sulbutiamine	4	Yopo seeds	1		
DXM	7	Amisulpride	4	Insulin	1		
Xanax	7	5-HTP	4	Propranolol	1		
Clonazolam	7	Bacopa	4	Epimedium	1		
BPC-157	7	Aolpidem	3	Inhalants	1		
Prescription Opioids	7	Suboxone	3	Emoxipine	1		
Melatonin	7	Wellbutrin	3	Phosphatidylserine	1		
Psilocybin	7	CBD	3	Vortioxitine	1		
Bromantane	7	Methamphetamine	3	Tranylcypromine	1		

Am J Drug Alcohol Abuse. Author manuscript; available in PMC 2022 July 04.

Substance	*N*		*N*		*N*		*N*
Ketamine	6	Picamilon	3	Reboxitine	1		

Note: Drug and supplement names in this table appear as they were written in the original Reddit posts so that future studies using social media data to investigate tianeptine, or any other substance on this list, will have these as potential search terms. The only alteration is that we capitalized each substance in cases where they were not otherwise capitalized.

Table 3.0

Positive effects, adverse effects, and withdrawal symptoms associated with tianeptine use that appeared at least once in Reddit posts made between 2011–2020

Positive effects	Adverse effects	General withdrawal symptoms	Specific withdrawal symptoms
Improved mood.	Tolerance.	Flu-like.	Tremors.
Increased energy.	Tolerance develops rapidly.	General withdrawal symptoms.	Muscle aches.
Increased productivity.	Physical dependence.	Severe opioid withdrawal.	Restless legs.
Mental focus, alertness, clarity, memory	Mild physical dependence.	Painful opioid withdrawal.	Restless Leg
Increased motivation.	Addiction.		Syndrome.
Feelings of contentedness.	Opioid effect is strong enough to precipitate relapse to harder opioids.		Sweating.
Stimulant.			Hot flashes.
Analgesic/pain relief.			Fever.
Anxiolytic.	Gut pain.		Nausea.
Anti-depressant.	Gnawing gut pain.		Vomiting.
Mood stabilizing.	Diarrhea.		Incontinence.
Mood enhancing.	Nausea.		Drowsiness.
Effective at mitigating general opioid withdrawal.	Vomiting.		Fatigue.
	Constipation.		Negative affect.
Substitutes well for buprenorphine.	Light-headedness.		Depression.
Effective at mitigating fentanyl withdrawal.	Nodding off.		Anxiety.
	Fatigue.		
Euphoria, intoxication.	Low motivation, sluggishness.		
Opioid-like effects.	Difficulty sleeping.		
Nodding off.	Makes kratom inert.		
Relaxation.	Unfavorable interaction with memantine.		
Anti-asthmatic.			
Good at potentiating effects from: cannabis, kratom, amphetamines.	Decreases effectiveness of other drugs; blunts their effectiveness.		
Increases socialization/decreases social anxiety.	Little to no positive effect.		

Positive effects	Adverse effects	General withdrawal symptoms	Specific withdrawal symptoms
	Tastes like nail polish.		
Increased otherwise depressed libido.			
	Tianeptine sulfate not as effective as tianeptine sodium.		
	Tianeptine sodium is shorter lasting than tianeptine sulfate.		
	Desired effect wears off too quickly; short-acting; need to dose frequently.		
	Anhedonia.		
	Negative affect at high doses.		
	Depressive symptoms.		
	Increased anxiety.		
	Severe vein damage from injecting.		
	Overdose.		
	Downsides unspecified.		