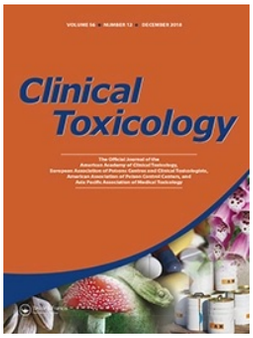

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BASIC RESEARCH

Quantity of phenibut in dietary supplements before and after FDA warnings

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ABSTRACT

Introduction: Phenibut is used to treat anxiety, insomnia, alcohol withdrawal and other conditions in Russia. The drug, however, has abuse potential and may cause lethargy, delirium, psychosis and coma. In the United States (US), the US Food and Drug Administration (FDA) has never approved the use of phenibut as a prescription medication, but the drug is available over-the-counter in dietary supplements. More than 80 cases of coma and death have been associated with phenibut consumption and withdrawal, and the FDA recently warned that the drug is not permitted in over-the-counter supplements. We designed our study to determine the presence and quantity of phenibut in over-the-counter supplements before and after the FDA warnings.

Methods: Phenibut products were included if they (a) listed phenibut or a synonym as an ingredient on the label, (b) were labeled as a dietary supplement, and (c) were available for sale both before and after the FDA warning. Supplements were analyzed by liquid chromatography time-of-flight mass spectrometry; quantification was performed by isotope dilution method.

Results: Four brands of dietary supplements labeled as containing phenibut met the inclusion criteria. Prior to the FDA warnings, two of the four brands contained phenibut, at dosages of 484 mg and 487 mg per serving. After the FDA warning, all four products contained phenibut, ranging in dosages from 21 mg to 1,164 mg per serving. Phenibut was first detected only after the FDA warnings in two brands, and the quantity of phenibut increased in three of four products after the FDA warnings. Quantities detected per dose were as much as 450% greater than a typical 250 mg pharmaceutical tablet manufactured in Russia.

Conclusion: Following FDA issuing an advisory that phenibut is not permitted in dietary supplements, the quantity of phenibut increased in 3 of 4 brands of over-the-counter phenibut supplements.

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Introduction

Phenibut (beta-phenyl-gamma-aminobutyric acid) is a gamma-aminobutyric acid-B (GABA-B) agonist, structurally similar to baclofen, and prescribed in Russia and elsewhere to treat anxiety, insomnia, alcohol withdrawal and other conditions [1]. The evidence to support these treatments is limited. However, the drug's risks have been well described. Phenibut has the potential to produce physical dependence, withdrawal and addiction [2]. In the United States, poison control centers have received more than 1,300 calls involving phenibut, the great majority since 2015 [3]. Lethargy, agitation, tachycardia and confusion are among the most commonly reported symptoms to poison control centers. Life-threatening adverse events from overdose and withdrawal include delirium, psychosis and coma [2,3]. In a recent study from the Centers for Disease Control and Prevention, life-threatening reactions or long-term disability occurred in 1 in 8 reported exposures to phenibut, including 80 cases of coma and three deaths [3].

In the United States (US), phenibut has never been approved by the US Food and Drug Administration (FDA) as a prescription drug but is available as an over-the-counter dietary supplement. The FDA does not approve dietary supplements prior to their entering the marketplace, but the agency is responsible for removing hazardous supplements after the product has been introduced for sale. In April 2019, the FDA issued an advisory and warning letters clarifying that phenibut is not a legal supplement ingredient [4]. The effect of these warnings on availability of phenibut in dietary supplements is not known. We designed our study to determine the presence and quantity of phenibut in dietary supplements before and after the FDA enforcement actions.

Materials and methods

Products were included if they (a) listed phenibut or a synonym as an ingredient on the label, (b) were labeled as a dietary supplement (i.e. included the words "dietary supplement" on the label), and (c) were available for sale online both before (February, 2017) and after (August, 2019) the FDA

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Supplemental data for this article can be accessed here.

warning (issued in in April 2019). All products were identified using the Google search engine. Supplements were excluded if, upon inspection of the bottle following purchase, the actual label did not list phenibut or one of its synonyms along with the words "dietary supplement".

Phenibut reference standard was obtained from Cayman Chemical Company, Ann Arbor, MI. Powder from dietary supplements were reconstituted in methanol, serially diluted and analyzed by liquid chromatography time-of-flight mass spectrometry; quantification was performed by isotope dilution method. (Complete methods provided in Supplemental Data).

Results

Nine brands of supplements listing phenibut as an ingredient and including the words "dietary supplement" on the label were purchased in February, 2017. Upon inspection of the bottle following purchase, the actual label of 1 brand did not include the words "dietary supplement" and was excluded. In August, 2019, six of the eight brands appeared to be available for sale; however, only 4 brands arrived following their online purchase. On inspection of the actual label of these 4 products, all listed the ingredient phenibut as well as the words "dietary supplement"; therefore, none were excluded. Four brands, with a total of eight samples (2 samples each of the four brands), were included in the analysis. The manufacturers of the four products analyzed were not specifically targeted by the FDA warning letters.

Two products declared specific quantities of phenibut on the label, 200 mg and 500 mg, and two products provided no quantities on the label. Two of the four samples purchased prior to the FDA warnings did not contain detectable quantities of phenibut. The two products purchased prior to the FDA warnings in which phenibut was detected contained 484 mg and 487 mg of phenibut per recommended serving size. After the FDA warning, phenibut was detected in all four products, and the quantity of phenibut ranged from 21 mg to 1,164 mg per serving. The quantity of phenibut increased in three of the four brands after the FDA warning. The product with the highest quantity of phenibut, both before and after the FDA warning, did not declare a quantity of phenibut per serving on the label (Table 1).

Discussion

In Russia and other Eastern European countries, phenibut is formulated in 250 mg tablets. We found phenibut dosages as high as 1,164 mg in dietary supplements sold over-the-counter in the United States with the quantity of the drug increasing in three of four supplement brands after the FDA issued an advisory that the drug is not a legal supplement ingredient.

The risks of phenibut have been well documented. More than 1,300 calls to US poison centers have involved phenibut ingestions with lethargy, agitation, tachycardia and confusion among the most commonly reported reactions with coma and death among the most serious adverse events [3]. In addition to adverse effects of acute consumption, consumers may seek medical care for symptoms due to phenibut withdrawal, and several pharmacological treatments, including phenobarbital and baclofen, have been used to manage phenibut withdrawal [2]. Case series have documented delirium, psychosis and respiratory arrest following phenibut consumption or withdrawal [1,2,5,6]. One recent case series, for example, included five adolescents all of whom were hospitalized and mechanically ventilated following acute phenibut intoxication [1].

While low dosages of phenibut, for example 250 mg and 500 mg, are prescribed in Russia for a wide variety of medical conditions, risks of acute toxicity typically occur with higher dosages. The quantity of phenibut that consumers are exposed to when using over-the-counter phenibut supplements is an important factor in understanding the risks of these products. Only three prior studies reported the quantity of phenibut in supplements available in the United States: In one analysis, investigators found each serving to contain 39 mg of phenibut and, following the recommendations on the label, consumers would be exposed to 116 mg of phenibut per day [7]. In the other two studies, supplements contained 15 mg and 79 mg of phenibut per serving, respectively [8,9]. We found dosages greater than 10-fold higher in the current analysis. We also found the quantity of phenibut in individual serving sizes were as much as 450% greater than a typical 250 mg pharmaceutical tablets.

In the United States, the FDA does not preapprove supplements prior to sale but is responsible for detecting and removing misbranded, adulterated and hazardous products from the market after they have been introduced. The agency, however, lacks adequate enforcement tools and often struggles to effectively remove hazardous products from the marketplace [10]. In the case of phenibut, the FDA issued warning letters to supplement manufacturers and a public advisory to all stakeholders that phenibut is not permitted in dietary supplements [4]. Prohibited ingredients, however, may not be removed from commerce after FDA warnings. A prior study found that several prohibited stimulants were still present in supplements after FDA warnings [11]. Our findings confirm this pattern: we found that an FDA advisory regarding phenibut did not lead to the removal of the prohibited drug from products produced by manufacturers not targeted by FDA warning letters. We found, to the contrary, that quantities of phenibut increased in three of four brands of supplements after the FDA warnings compared to the quantity of phenibut in the same brand before the FDA advisory.

Our study has several limitations: we analyzed only products that were marketed as dietary supplements, and our study is not a survey of all phenibut products on the market. Our results are not generalizable to all over-the-counter phenibut products, many of which are labeled "research chemicals" or "not for human consumption". In addition, we only included products that openly listed phenibut as an ingredient on the label. Phenibut has previously been found to be an undisclosed ingredient in supplements, [8] but

Table 1. Information provided on the label and corresponding measured quantities of phenibut in selected supplements.

Code for supplement product*	Declared ingredient on label meeting inclusion criteria	Number of other ingredients on label	Recommended serving size on label	Quantity declared on label of phenibut per serving size, mg	Maximum recommended daily dose per label	Measured Phenibut per serving size, mg (SD)	
						From purchase before FDA warning	From purchase after FDA warning
Product A	4-amino-3-phenylbutyric acid (phenibut)	13	1 scoop (14 g)	NP	NP	487 (33)	1164 (81)
Product B	phenibut	6	1 capsule (500 mg)	500[a]	4 capsules (2,000 mg)	484 (89)	425 (44)
Product C	phenibut	6	1 capsule	200[a]	NP	<LoD	21 (2)
Product D	phenibut	19	2 capsules	NP	2 capsules	<LoD	198 (29)

NP, not provided. LoD, Limit of Detection. Based on the concentrations of supplement extracts injected, this corresponds to <1.8 mg phenibut per serving of Product C and <35 mg phenibut per serving of Product D.
*FDA issued warnings letters to 3 manufacturers in April 2019. The 3 manufacturers who received FDA warning letters were not among the 4 manufacturers of the products included in the current analysis.
[a]The same quantity was declared on supplements purchased before and after the FDA warning.

supplements containing undeclared phenibut were not included in the current study.

Our findings provide further evidence that reforming the US law regulating dietary supplements, such as providing FDA with more effective enforcement tools, will be required to ensure that the FDA can efficiently and effectively remove hazardous supplements from the marketplace.

Conclusions

Phenibut, a drug with the potential to cause addiction, coma and death, was found in dietary supplements both before and after FDA warnings. The dosages of phenibut per serving increased in most products after the FDA warnings and were found to be as much as 450% greater than a typical 250 mg pharmaceutical tablet. Our findings are consistent with prior research that FDA advisories regarding supplement ingredients are not effective in removing prohibited ingredients from supplements. Clinicians should remain aware that, despite FDA warnings, phenibut remains available in high dosages in over-the-counter dietary supplement in the United States.

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Disclosure statement

Dr Gerona and Dr Cohen were subjects of a civil suit brought by Hi-Tech Pharmaceuticals, a supplement company, regarding β-methylphenylethylamine; Dr Gerona's case was dismissed and the jury found in Dr Cohen's favor. Dr Cohen has received research support from Consumers Union and PEW Charitable Trusts. Mr. Travis is an employee of NSF International, and some of NSF International's clients are dietary supplement manufacturers. No other disclosures were reported. Mr. Ellison and Dr. Gaufberg have no conflicts of interest to report.

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References

[1] Isoardi KZ, Kulawickrama S, Isbister GK. Severe phenibut poisoning: an adolescent case cluster. J Paediatr Child Health. 2020;56(2):330–331. Feb
[2] Jouney EA. Phenibut (β-phenyl-γ-aminobutyric acid): an easily obtainable "dietary supplement" with propensities for physical dependence and addiction. Curr Psych Rep. 2019;21:23.
[3] Graves JM, Dilley J, Kubsad S, et al. Notes from the field: Phenibut exposures reported to poison centers - United States, 2009-2019. MMWR Morb Mortal Wkly Rep. 2020;69(35):1227–1228.
[4] US Food and Drug Administration. Phenibut in dietary supplements. April 29, 2019. Available at: https://www.fda.gov/food/dietary-supplement-products-ingredients/phenibut-dietary-supplements. [accessed July 13, 2021]
[5] Downes MA, Berling IL, Mostafa A, et al. Acute behavioural disturbance associated with phenibut purchased via an internet supplier. Clin Toxicol (Phila)). 2015;53(7):636–638.
[6] McCabe DJ, Bangh SA, Arens AM, Cole JB. Phenibut exposures and clinical effects reported to a regional poison center. Am J Emerg Med. 2019;37(11):2066–2071.
[7] Avula B, Bae JY, Chittiboyina AG, et al. Liquid chromatography-quadrupole time of flight mass spectrometric method for targeted analysis of 111 nitrogen-based compounds in weight loss and ergogenic supplements. J Pharm Biomed Anal. 2019;174:305–323.
[8] Cohen PA, Avula B, Wang YH, et al. Five unapproved drugs found in cognitive enhancement supplements. Neurol Clin Pract. 2021;11(3):e303–e307.
[9] Cohen PA, Sharfstein J, Kamugisha A, et al. Analysis of ingredients of supplements in the National Institutes of Health supplement database marketed as containing a novel alternative to anabolic steroids. JAMA Netw Open. 2020;3(4):e202818.
[10] Cohen PA. The FDA and adulterated supplements-Dereliction of Duty. JAMA Netw Open. 2018;1(6):e183329.
[11] Cohen PA, Wen A, Gerona R. Prohibited stimulants in dietary supplements after enforcement action by the US Food and Drug Administration. JAMA Intern Med. 2018;178(12):1721–1723.