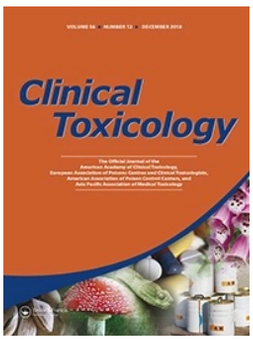

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Nine prohibited stimulants found in sports and weight loss supplements: deterenol, phenpromethamine (Vonedrine), oxilofrine, octodrine, beta-methylphenylethylamine (BMPEA), 1,3-dimethylamylamine (1,3-DMAA), 1,4-dimethylamylamine (1,4-DMAA), 1,3-dimethylbutylamine (1,3-DMBA) and higenamine

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BASIC RESEARCH

Nine prohibited stimulants found in sports and weight loss supplements: deterenol, phenpromethamine (Vonedrine), oxilofrine, octodrine, beta-methylphenylethylamine (BMPEA), 1,3-dimethylamylamine (1,3-DMAA), 1,4-dimethylamylamine (1,4-DMAA), 1,3-dimethylbutylamine (1,3-DMBA) and higenamine

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ABSTRACT

Background: Weight loss and sports supplements containing deterenol have been associated with serious adverse events including cardiac arrest.

Objective: To determine the presence and quantity of experimental stimulants in dietary supplements labeled as containing deterenol sold in the United States.

Methods: Dietary supplements available for sale in the US and labeled as containing deterenol or one of its synonyms (e.g., isopropylnorsynephrine and isopropyloctopamine) were purchased online. For each brand, one container or subsample was analyzed by NSF International (Ann Arbor, MI) and one container or subsample by the Netherland's National Institute for Public Health and the Environment (RIVM, Bilthoven, The Netherlands). When differences existed between the two containers or subsamples of the same brand, both products were reanalyzed by Sciensano (Brussels, Belgium). NSF International carried out qualitative and quantitative analyses using ultra-high-performance liquid chromatography (UHPLC) quadrupole-Orbitrap mass spectrometry. RIVM performed qualitative and quantitative analysis using UHPLC quadrupole time-of-flight mass spectrometry. Sciensano carried out qualitative analysis using UHPLC quadrupole-Orbitrap mass spectrometry.

Results: Seventeen brands of supplements were analyzed. Many brands included more than one prohibited stimulant in the same product: 4 brands (24%, 4/17) included 2 stimulants, 2 (12%, 2/17) combined 3 stimulants, and 2 (12%, 2/17) combined 4 stimulants. The range of quantities per recommended serving size of the 9 stimulants detected were 2.7 mg to 17 mg of deterenol; 1.3 mg to 20 mg of phenpromethamine (Vonedrine); 5.7 mg to 92 mg of beta-methylphenylethylamine (BMPEA); 18 mg to 73 mg of octodrine; 18 mg to 55 mg of oxilofrine; 48 mg of higenamine; 17 mg of 1,3-dimethylamylamine (1,3-DMAA); 1.8 mg to 6.6 mg of 1,3-dimethylbutylamine (1,3-DMBA); and 5.3 mg of 1,4-dimethylamylamine (1,4-DMAA).

Conclusion: Weight loss and sports supplements listing deterenol as an ingredient contained 9 prohibited stimulants and 8 different mixtures of stimulants, with as many as 4 experimental stimulants per product. These cocktails of stimulants have never been tested in humans and their safety is unknown.

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Cardiovascular; dietary supplements; adulteration

Introduction

Dietary supplements are estimated to be responsible for tens of thousands of emergency department visits each year in the United States (US) [1]. Weight loss and sports supplements contribute to a disproportionate number of these emergency department visits [1]. Serious adverse events including hemorrhagic stroke and sudden death have been attributed to these supplements [1–3]. However, the specific ingredients in these products responsible for the health risks are poorly understood. One possibility is that combinations of experimental stimulants pose health risks to consumers [4,5]. Investigators, for example, have linked one brand of sports supplements containing a mixture of stimulants to dozens of adverse events including nausea, vomiting, sweating, agitation, palpitations, chest pain and cardiac arrest [4]. The implicated product, Dexaprine (iForce Nutrition), was found to contain deterenol [4].

Deterenol is a pharmaceutical beta-agonist that has never been approved for use in humans in the US. In 2004, the US Food and Drug Administration (FDA) determined that

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Supplemental data for this article can be accessed here.

deterenol is not permitted as an ingredient in dietary supplements [6]. Nevertheless, since 2018, deterenol has been detected in several brands of dietary supplements sold in the US [7,8], and FDA chemists have confirmed the presence of deterenol in supplements [9]. The FDA, however, has not advised manufacturers to remove deterenol from products nor warned consumers to avoid supplements labeled as containing deterenol.

We designed our study to determine the presence and quantity of experimental stimulants in dietary supplements labeled as containing deterenol and available for sale in the US. For the purposes of this study, we refer to *experimental stimulants* as active pharmaceutical stimulants that have not been approved by the FDA for oral use as either prescription medications or dietary supplements, and we refer to *prohibited stimulants* as those that have been prohibited in dietary supplements by the FDA and/or prohibited in sport by the World Anti-Doping Agency.

Materials and methods

All dietary supplements listing deterenol or one of its synonyms (e.g., isopropyloctopamine or isopropylnorsynephrine) as an ingredient on the label were identified using the Google search engine. If the brand was sold in one flavor, we purchased 2 samples when available. In cases in which the brand was sold in multiple flavors, we purchased 2 samples of each flavor when available. Supplements were purchased online in April, 2018. Supplements were excluded if, upon inspection of the bottle following purchase, the actual label did not list deterenol or one of its synonyms.

For each brand, one container was analyzed by NSF International (Ann Arbor, MI), an independent not-for-profit organization that develops public health standards and certification programs, and one container by the Netherland's National Institute for Public Health and the Environment (RIVM, Bilthoven, The Netherlands). When a brand was available in more than one flavor, a container of each flavor was analyzed by each laboratory. In cases where only one container was available at the time of purchase, the content of the container was split and the sub-samples analyzed by each laboratory. If discrepancies were detected between the analyses of the same brand, samples or sub-samples were reanalyzed by Sciensano (Brussels, Belgium), an official medicines control laboratory, for an independent confirmation of identity. NSF International carried out qualitative and quantitative analysis using ultra-high-performance liquid chromatography (UHPLC) with quadrupole-Orbitrap mass spectrometry. RIVM performed qualitative and quantitative analysis using UHPLC quadrupole time-of-flight mass spectrometry. Sciensano carried out qualitative analysis using UHPLC with quadrupole-Orbitrap mass spectrometry. RIVM quantified deterenol, and NSF International quantified all other experimental stimulants. Experimental stimulants were reported as detected only if their presence was independently confirmed by two laboratories. See Supplemental data for details of analytical methods and their validation.

Results

Thirty-five samples of 17 brands of supplements were purchased (2 samples of 12 brands of supplements, 4 samples of 2 brands sold in 2 flavors each and 1 sample of 3 brands for which a second sample was not in stock at the time of purchase). When the purchased bottles were inspected, all products listed a synonym of deterenol on the actual label and, therefore, none were excluded.

The synonyms used for deterenol on the labels included isopropylnorsynephrine, isopropylnorsynephrine HCl, N-isopropylnorsynephrine HCl and isopropyloctopamine. The majority of supplements were marketed as either weight loss (8/17; 47%) or sports/energy supplements (6/17; 35%); 3 brands did not list an indication. Structures of the stimulants detected are illustrated in Figure 1. The identity and quantity of stimulants detected are provided in Table 1. The combination of detected stimulants did not vary between different flavors of individual brands, but there was modest variation in the quantities of each stimulant from flavor to flavor within a brand. For ease of analysis and interpretation, we calculated the average quantity of each stimulant across both flavors within a brand.

The quantity of deterenol ranged from 2.7 mg to 17 mg per serving. Consumers could be exposed to up to 69 mg of

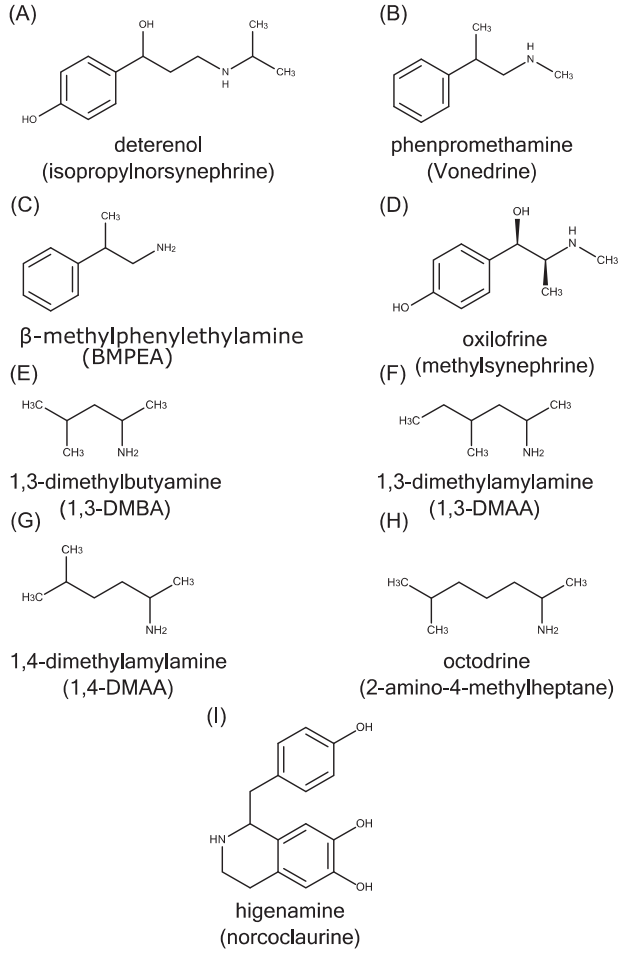

Figure 1. Chemical structures of (A) deterenol, (B) phenpromethamine, (C) β-methylphenylethylamine, (D) oxilofrine, (E) 1,3-dimethylbutylamine, (F) 1,3-dimethylamylamine, (G) 1,4-dimethylamylamine, (H) octodrine and (I) higenamine.

Table 1. Quantity of stimulants found in dietary supplements analyzed.

Supplement name (manufacturer)[a]	Labelled indication	Ingredient that met inclusion criteria	Recommended Serving size (grams)	Maximum daily intake (grams)	Stimulant(s)[b] detected	Stimulant(s) in mg per serving (±MU)[c]	Stimulant(s) in mg per maximum recommended daily intake (±MU)[c]
Thermal Black (Musclesport)	Fat burner	isopropylnorsynephrine	1 capsule	2 capsules	higenamine	48 ± 4.7	96 ± 9.3
N'Gorge NOS Extreme (ALR Industries)		isopropyloctopamine	1 scoop (9)	1 scoop (9)	deterenol BMPEA oxilofrine phenpromethamine	11 ± 0.88 92 ± 4.0 55 ± 8.3 11 ± 1.4	11 ± 0.88 92 ± 4.0 55 ± 8.3 11 ± 1.4
Fastin (Hi-Tech)	Weight loss	Isopropylnorsynephrine HCl	1 capsule	4 capsules	deterenol oxilofrine	17 ± 1.4 52 ± 7.8	69 ± 5.4 210 ± 31.2
Cannibal Ferox (Chaos and Pain)	Pre-workout	isopropylnorsynephrine	1 scoop (14.6)	1 scoop (14.6)	deterenol	10. ± 0.80	10. ± 0.80
Cannibal Riot (Chaos and Pain)	Pre-workout	isopropylnorsynephrine	1 scoop (10)	1 scoop (10)	deterenol	16 ± 1.3	16 ± 1.3
Oxy Lean Elite (GenOne Laboratories)	Fat burner	isopropylnorsynephrine	1 capsule	2 capsules	deterenol	13 ± 1.0	27 ± 2.1
Shredded-AF (Steel)		isopropylnorsynephrine	2 capsules	2 capsules	deterenol phenpromethamine	15 ± 1.2 1.3 ± 0.17	15 ± 1.2 1.3 ± 0.17
Old Jack Extreme multiple flavors (GenOne Laboratories)*	Pre-workout	isopropylnorsynephrine	1 scoop (17)	1 scoop (17)	deterenol phenpromethamine	14 ± 1.1 20. ± 2.6	14 ± 1.1 20. ± 2.6
Thermo Shock (SciLabs Nutrition)	Fat burner	N-isopropylnorsynephrine HCl	1 capsule	2 capsules	1,3-DMAA octodrine 1,3-DMBA	17 ± 0.75 18 ± 0.85 1.8 ± 0.085	35 ± 1.5 35 ± 1.7 3.6 ± 0.17
OxyXtreme (6 Rings)	Thermogenic	N-isoproplynorsynephrine [sic]	1 capsule	2 capsules	deterenol	11 ± 0.88	22 ± 1.8
TURNITUP multiple flavors (EPG)*	Pre-workout	N-isopropylnorsynephrine	1 scoop (10)	1 scoop (10)	deterenol	16 ± 1.3	16 ± 1.3
Edge of Insanity (Psycho Pharma)	Pre-workout	isopropylnorsynephrine	1 scoop (10)	1 scoop (10)	deterenol	10. ± 0.80	10. ± 0.80
Optilean Plus (Kewlify)	Fat burner	isopropylnorsynephrine	3 capsules	3 capsules	deterenol	14 ± 1.1	14 ± 1.1
10 Seconds to Launch (Avenger Performance Nutrition)	Pre-workout	N-isopropyloctopamine HCl	1 scoop (10)	1 scoop (10)	octodrine 1,4-DMAA oxilofrine	24 ± 1.1 5.3 ± 0.19 18 ± 2.7	24 ± 1.1 5.3 ± 0.19 18 ± 2.7
LipoTherm (ALR Industries)	Weight loss	N-isopropylnorsynephrine HCl	1 caplet	3 caplets	deterenol oxilofrine phenpromethamine BMPEA	2.7 ± 0.22 21 ± 3.2 3.1 ± 0.40 5.7 ± 0.25	8.1 ± 0.22 63 ± 9.4 9.3 ± 1.2 17 ± 0.74
Blue Ice (EPG)	Weight loss	N-isopropylnosynephrine [sic]	1 capsule	2 capsules	deterenol	15 ± 1.2	30. ± 2.4
Deep 6 Pro (Avenger Performance Nutrition)		N-isopropylnorsynephrine HCl	1 capsule	2 capsules	octodrine 1,3-DMBA	73 ± 3.4 6.6 ± 0.31	150 ± 6.9 13 ± 0.62

[a]All products were analyzed in duplicate except*, which were 2 flavors both analyzed in duplicate.
[b]BMPEA – beta-methylphenylethylamine. 1,3-DMAA – 1,3-dimethylamylamine. 1,3-DMBA – 1,3-dimethylbutylamine. 1,4-DMAA – 1,4-dimethylamylamine.
[c]The MU = measurement uncertainty and is expressed as a two sided 95% confidence interval, based on the standard deviation of the results obtained in a series of replicate quantification assays.

deterenol per day when following recommended serving sizes provided on the label. Deterenol was the only stimulant present in 47% (8/17) of the brands, and in 4 brands (24%), deterenol was not detected.

Phenpromethamine was the next most commonly detected stimulant. Four of the 17 brands (24%) contained the drug which ranged in quantity from 1.3 mg to 20 mg per serving. Only 1 of the 4 products found to contain phenpromethamine listed a synonym of the drug, n-methyl-beta-methylphenylethylamine, on the label.

Eight brands contained more than one prohibited stimulant: one brand, for example, contained 92 mg of BMPEA, 55 mg of oxilofrine, 11 mg of deterenol and 11 mg of phenpromethamine per serving. Four brands (24%) combined 2 stimulants, 2 brands (12%) combined 3 stimulants, and 2 brands (12%) combined 4 stimulants.

The range of quantities per recommended serving size of the 9 stimulants detected were 2.7 mg to 17 mg of deterenol; 1.3 mg to 20 mg of phenpromethamine (Vonedrine); 5.7 mg to 92 mg of beta-methylphenylethylamine (BMPEA); 18 mg to 73 mg of octodrine; 18 mg to 55 mg of oxilofrine; 48 mg of higenamine; 17 mg of 1,3-dimethylamylamine (1,3-DMAA); 1.8 mg to 6.6 of 1,3-dimethylbutylamine (1,3-DMBA); and 5.3 mg of 1,4-dimethylamylamine (1,4-DMAA).

Within both categories of supplements, sports and weight loss, individual products were found to contain a single stimulant and other products contained a complex mixture of stimulants.

Discussion

We identified 9 experimental stimulants and 8 different combinations of prohibited stimulants in weight loss and sports supplements in 17 brands of supplements labeled as containing deterenol. In less than half of the brands, deterenol was the only stimulant present, deterenol was not present in a quarter of the brands, and the majority of brands contained multiple different prohibited stimulants including individual brands with combinations of 4 experimental stimulants.

Seven stimulants (i.e., 1,3-DMAA, 1,4-DMAA 1,3-DMBA, BMPEA, higenamine, oxilofrine and octodrine) have previously been subject to FDA regulatory actions including product seizures, warning letters and public notices. To our knowledge, 2 of the stimulants detected, deterenol and phenpromethamine, have not been subject to any FDA enforcement actions or consumer warnings. To better understand the potential health consequences of oral consumption of deterenol and phenpromethamine, we reviewed all relevant animal and human studies in the published literature. We also considered why prohibited experimental stimulants may remain present in dietary supplements after FDA enforcement action.

Deterenol (isopropyloctopamine)

Several studies have been published that examine deterenol's effects in animals and humans. Dozens of studies have demonstrated deterenol's beta-agonists effects *in vitro* and *in vivo*. An *in vitro* study of deterenol on guinea pig atria and trachea, for example, found the drug to be a highly selective beta-agonist with no alpha-adrenergic activity [10]. The beta-agonist effects of deterenol in humans has been documented in a study of intravenously administered deterenol to 6 human subjects [11]. To our knowledge, the effects of orally administered deterenol has only been examined in a single study with 16 human subjects [12]. The study, published in 1949, examined the effects of three oral dosages of deterenol: at 1 mg/kg the drug was found to have vasodepressor effects; at 2–3 mg/kg the drug led to flushing, tingling of extremities and face, anxiety, decreased diastolic blood pressure and increased heart rate; and at 5 mg/kg deterenol induced vomiting, hypotension, inability to sit up, blurred vision, palpitations, weakness and respiratory distress [12]. In addition to these 2 human studies, the only other studies of deterenol in humans are one study examining ophthalmic administration and one study in which deterenol was administered subcutaneously – neither study provides evidence of safety of orally administered deterenol [13,14]. Furthermore, we are not aware of any study in animals or humans of the safety of combining deterenol with any of the other experimental stimulants detected in the current study.

Deterenol has never been approved by the FDA. Between 1975 and 1982, the drug was marketed in Europe as an ophthalmological preparation for the treatment of glaucoma [15]. In the US, following the prohibition of ephedra alkaloids in supplements in 2004, a manufacturer submitted an application to the FDA to introduce deterenol into supplements [16]. The FDA responded that deterenol, which has never been identified as a constituent of botanicals, is not permitted as a supplement ingredient [6].

Despite deterenol's legal status, 4 prior studies have detected deterenol in over-the-counter supplements. Dutch investigators in 2013 identified 19 mg to 39 mg deterenol combined with other stimulants in Dexaprine (iForce Nutrition) and found this product to be associated with a series of serious adverse events including nausea, vomiting, agitation, palpitations, chest pain and cardiac arrest [4]. Since 2018, three investigations have confirmed the presence of deterenol in supplements available in the US ranging in doses from 20 to 76 mg per serving [7–9]. One of these studies was performed by the FDA's analytic chemists [9]; nevertheless, we are not aware of any enforcement action by the agency to eliminate deterenol from dietary supplements or warn consumers of the stimulant's presence in supplements.

Phenpromethamine (Vonedrine)

In the early 1940s, Merrell Co. developed Vonedrine, a phenpromethamine nasal inhaler to compete with Smith, Kline & French's Benzedrine, an amphetamine nasal inhaler [17]. The FDA approved Vonedrine as a nasal inhaler in 1943 and it remained available until Merrell Co. withdrew the inhaler in 1960 (see Supplementary Fig 2 for c.1940s advertisement of

Vonedrine) [18]. The FDA formally withdrew the approval for Vonedrine in 1971 [19].

The introduction of phenpromethamine in supplements parallels the history of 1,3-DMAA as a supplement ingredient [20,21]. In 1948, Eli Lilly & Co marketed 1,3-DMAA in the Forthane nasal inhaler but withdrew the drug from the market by the 1970s. After ephedra alkaloids were banned in supplements, 1,3-DMAA was introduced into hundreds of products. While the FDA has taken multiple enforcement actions to eliminate 1,3-DMAA from supplements, the stimulant remains widely available, including in a product analyzed in the current study.

Phenpromethamine has never been approved for oral use in the US or elsewhere. There exists very limited clinical data regarding phenpromethamine's efficacy and safety. Anecdotal experiences with the Vonedrine nasal inhaler have been described in 2 reports from the 1940s [22,23], and 1 study found the Vonedrine nasal inhaler to be comparable to an amphetamine nasal inhaler for its decongesting effects [24]. Subcutaneous phenpromethamine has been found to cause skin blanching [25] and, to our knowledge, oral use of phenpromethamine has only been described in a single report [26]. The report published in 1944 involved 10 patients and is notable in that it was sponsored by the drug's manufacturer and authored by a pediatric resident; the author claimed that in 6 of 10 patients with asthma, oral deterenol improved symptoms of asthma without changes in blood pressure or pulse [26].

Prior studies have provided preliminary evidence that phenpromethamine might be present in supplements. A study from Brazil of several US products found preliminary evidence of phenpromethamine in 4 brands of supplements [27], and an Australian study found preliminary evidence of phenpromethamine in 1 brand of supplements [28]. Both studies used library matches to identify the drug but the presence of the stimulant was not confirmed using a reference standard nor was the quantity of phenpromethamine determined. To our knowledge, our study is the first to confirm and quantify the presence phenpromethamine in supplements.

Given the very limited data available in the scientific literature, the dose at which oral phenpromethamine poses risks to humans is not known. To our knowledge, no published study of animals or humans has investigated the safety of consuming phenpromethamine combined with the other experimental stimulants identified in the current study.

FDA enforcement of the supplement law

In the US, the FDA is responsible for removing adulterated supplements from the marketplace. The agency, however, does not always act accordingly [29]. The FDA, for example, failed to recall more than half of 746 brands of supplements found to be adulterated with drugs [30]. In another case, the FDA did not warn consumers after the agency's scientists discovered a novel stimulant in sports and weight loss supplements [31]. Our study provides further evidence that the FDA may fail to act even when the agency's own scientists identify adulterated supplements, as appears to be the case for deterenol.

We also detected many stimulants which the FDA has attempted to remove from supplements. Previously, when the FDA has taken action to remove prohibited stimulants from the marketplace, their enforcement actions have not always been successful. For example, an analysis of 27 brands of supplements subject to FDA recalls found that two-thirds of the products, up to 4 years after the FDA recalls, still contained prohibited drugs [32]. Another analysis found that FDA public notifications regarding specific prohibited stimulants did not lead to their removal from the products [33]. In fact, one brand of supplements introduced a prohibited stimulant *only after* the FDA's public notice regarding the stimulant [33]. This pattern was again evident in the current study in which the FDA has taken enforcement action regarding several of the experimental stimulants detected (i.e., 1,3-DMAA, 1,3-DMBA and oxilofrine), but the prohibited stimulants remain present in supplements despite FDA warnings.

The present study raises an additional concern regarding FDA enforcement of the laws regulating supplements in the US. A legal route to introduce a new ingredient as a dietary supplement ingredient is to submit a 'new dietary ingredient' application to the FDA. If the FDA acknowledges receipt of the application without expressing concerns, the ingredient can be introduced in dietary supplements. The agency declined to acknowledge the application for deterenol in 2004 arguing that it is not a permitted dietary ingredient [6]. Our study is not the first to document the introduction of a drug in supplements after the FDA rejected an application to market the drug as a supplement, as was also the case for the nootropic piracetam [34]. In the case of deterenol, the lack of enforcement is particularly concerning given that supplements containing deterenol have been linked in Europe to a series of serious adverse effects including sudden death [4].

Limitations

Our study has several limitations. The sample size is small and therefore the quantitative findings are not necessarily representative of all deterenol-containing products. The quantitative data, however, do provide initial estimates of the amounts of stimulants to which consumers might be exposed per serving. In addition, we analyzed only supplements that listed deterenol or one of its synonyms on the label. It is possible that supplements not listing one of these synonyms as an ingredient might also contain deterenol with or without the other experimental stimulants. Therefore, our study should not be considered a survey of all supplements available in the US that contain deterenol. Finally, we sampled the products at only one time point and prior studies have demonstrated that stimulants in individual brands may change over time [33]. Therefore, our results might not be representative of stimulants present in these products sampled at a different time point.

Conclusions

In a study of dietary supplements available for sale in the US, we found 9 prohibited stimulants formulated into 8 different combinations – none of which have been studied in humans. We detected two stimulants for which the FDA has not issued warnings to manufacturers or consumers: deterenol, a beta-agonist with potentially serious adverse effects when consumed orally in humans, and phenpromethamine which was marketed as a pharmaceutical stimulant in the Vonedrine nasal inhaler in the 1940s and 1950s. Neither deterenol nor phenpromethamine have been approved for oral use in the US or elsewhere. In addition to deterenol and phenpromethamine, 7 additional experimental stimulants were identified including oxilofrine, octodrine, BMPEA, 1,3-DMAA, 1,4-DMAA, 1,3-DMBA and higenamine. The risks of consuming these combinations of stimulants is unknown. The FDA should warn consumers about the presence of cocktails of experimental stimulants in weight loss and sports supplements and take immediate effective action to remove these stimulants from the market. Clinicians should remain alert to the possibility that patients may be inadvertently exposed to experimental and prohibited stimulants when consuming weight loss and sports supplements.

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Disclosure statement

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