Conflict of Interest Disclosures: None reported.

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Editor's Note

The Persistent Problem of Overuse of Diagnostic Testing Among House Staff—Time to Move Forward

I was a second-year medical student at the University of Pennsylvania, Philadelphia, in 1978, and I had the immense good fortune to work with Sankey Williams, MD, and John Eisenberg, MD. They were performing a trial to evaluate the influence of education on reducing house staff use of unnecessary inpatient laboratory testing.[1] The educational intervention had no benefit on house staff ordering behavior, but it had resounding effects on how I came to view routine use of many different types of testing and treatments that I had previously assumed were evidence based. That early research experience led me to carefully question the evidence base for many commonly used tests and procedures: How will the information from this test help me to take better care of my patient? Will it lead to better outcomes? Could I have gotten there without the use of this test?

The Research Letter by Geleris et al[2] in this issue of *JAMA Internal Medicine* brought back my 40-year-old memories of research on the overuse of diagnostic testing by house staff. Clearly, the problem has not gone away. In their study, Geleris et al[2] found that there is tremendous variation in inpatient laboratory test and radiology test ordering among the house staff, an indicator (particularly when outcomes do not differ) of questionable or unnecessary care, and we publish studies like this one to keep the conversation moving forward. Medicine remains largely an apprenticeship. The practice patterns that residents develop are likely to persist throughout their careers. Residency is the perfect time to think clearly and deeply what can be learned from each potential test and to order only those tests that will affect the care of the patient.

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Prohibited Stimulants in Dietary Supplements After Enforcement Action by the US Food and Drug Administration

The US Food and Drug Administration (FDA) is responsible for eliminating adulterated and potentially hazardous dietary supplements from the marketplace. The FDA uses a variety of enforcement actions, including public notices, to remove potentially hazardous ingredients. However, it is not known whether public notices are effective. We explored the effectiveness of the FDA's public notices issued between 2013 and 2016 targeting prohibited sympathomimetic stimulants in supplements. We analyzed supplements purchased in 2014 and the same brands purchased again in 2017 to determine the presence of prohibited stimulants before and after the FDA issued public notices.

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Methods | From January 1, 2013, to December 31, 2016, the FDA issued notices regarding 4 prohibited sympathomimetic stimulants: 1,3-dimethylamylamine (1,3-DMAA), 1,3-dimethylbutylamine (DMBA), β-methylphenylethylamine (BMPEA), and methylsynephrine (oxilofrine).[1-4] The FDA notices regarding ingredients in supplements not categorized as sympathomimetic stimulants, such as picamilon, were excluded from the current analysis. We previously analyzed all supplements on sale in 2014 listing *Acacia rigidula* as an ingredient for the presence of 1 stimulant, BMPEA.[1] For the current study, we purchased the same brands of supplements in 2017. Supplements purchased in 2014 were reanalyzed for 1,3-DMAA, DMBA, and oxilofrine, and supplements purchased in 2017 were analyzed for all 4 prohibited stimulants subject to FDA enforcement action. As previously described,[1] liquid chromatography–quadrupole time-of-flight mass spectrometry was used to analyze the supplements, and the presence of each stimulant was confirmed by accurate mass, retention time, isotope pattern, and at least 1 fragment ion in the mass spectra.

Results | Of the 21 brands of supplements analyzed in 2014, a total of 12 brands (57%) were still available for purchase in 2017. The 12 brands that were available in both 2014 and 2017 were included in the current analysis (**Table**). In 2013, the FDA issued a public notice about the use of 1,3-DMAA. Of the 12 supplements purchased in 2014, 1,3-DMAA was present in 6 (50%). The FDA issued notices about the use of DMBA and BMPEA in 2015 and oxilofrine in 2016. Of the 12 supplements purchased in 2017, a total of 9 (75%) contained at least 1 of the 4 stimulants subject to FDA notices, and 6 (50%) contained 2 or more. One stimulant, DMBA, was not detected in any supplement purchased in 2014. After the FDA issued a public notice about DMBA in 2015, DMBA was detected in 4 of the 12 supplements (33%) purchased in 2017.

Table. Quantities of 4 Experimental Stimulants Subject to FDA Public Notices in Supplements Purchased in 2014 and 2017

Product[a]	Claim on Label or Website	BMPEA,[b] Mean (SD), mg per Pill or Capsule	1,3-DMAA,[c] Mean (SD), mg per Pill or Capsule	DMBA,[d] Mean (SD), mg per Pill or Capsule	Oxilofrine,[e] Mean (SD), mg per Pill or Capsule
Supplements Purchased in 2014					
A	Cognitive function	ND	ND	ND	0.07 (0.04)
B	Weight loss	ND	ND	ND	54.31 (0.82)
C	Weight loss	18.71 (2.16)	36.70 (11.91)[f]	ND	34.07 (10.06)
D	Weight loss	5.74 (1.15)	ND	ND	26.48 (2.56)
E	Weight loss	27.35 (5.87)	34.68 (0.89)[f]	ND	34.31 (2.06)
F	Weight loss	ND	ND	ND	0.31 (0.04)
G	Sports supplement	3.22 (0.67)	ND	ND	7.78 (0.49)
H	Sports supplement	31.23 (5.72)	ND	ND	31.07 (1.94)
I	Weight loss	9.89 (1.26)	12.17 (1.23)[f]	ND	25.62 (1.53)
J	Weight loss	3.35 (0.74)	12.03 (1.31)[f]	ND	37.45 (1.21)
K	Weight loss	0.97 (0.31)	11.39 (1.74)[f]	ND	40.75 (5.31)
L	Weight loss	23.05 (2.79)	26.89 (6.05)[f]	ND	37.44 (7.43)
Supplements Purchased in 2017					
A	Cognitive function	ND	ND	ND	0.05 (0.01)[f]
B	Weight loss	ND	ND	ND	40.84 (6.48)[f]
C	Weight loss	ND	ND	30.43 (3.26)[f]	7.09 (0.91)[f]
D	Weight loss	ND	ND	ND	28.38 (0.82)[f]
E[g]	Weight loss	17.23 (1.47)[f]	36.12 (5.45)[f]	ND	27.43 (1.06)[f]
F	Weight loss	ND	ND	ND	ND
G	Sports supplement	ND	ND	ND	ND
H	Sports supplement	ND	ND	ND	ND
I	Weight loss	ND	ND	10.98 (3.09)[f]	5.59 (0.85)[f]
J	Weight loss	ND	27.99 (1.37)[f]	ND	8.77 (0.47)[f]
K	Weight loss	ND	ND	17.05 (1.63)[f]	8.44 (0.51)[f]
L	Weight loss	ND	ND	39.53 (4.39)[f]	8.85 (0.81)[f]

Abbreviations: BMPEA, indicates β-methylphenylethylamine; DMBA, 1,3-dimethylbutylamine; 1,3-DMAA, 1,3-dimethylamylamine; FDA, US Food and Drug Administration; ND, not detectable.

[a] Coded indicator of the product.

[b] β-Methylphenylethylamine is not approved for use in humans. Quantities of BMPEA in products purchased in 2014 were previously reported.[1]

[c] 1,3-Dimethylamylamine is a 1940s to 1960s nasal decongestant (Eli Lilly & Co) that was withdrawn from the market in the 1970s. It was never approved for oral use.

[d] 1,3-Dimethylbutylamine is not approved for use in humans.

[e] Oxilofrine was previously available in several European countries. It increased blood pressure and cardiac output and was available in 16- to 40-mg capsules. It was never approved for use in the United States.

[f] Quantities represent stimulants in supplements after the FDA issued a public notice about the stimulant. The date of the FDA warning for 1,3-DMAA was July 2013; DMBA, April 2015; BMPEA, April 2015; and oxilofrine (referred to as methylsynephrine), April 2016.

[g] Manufacturer of product E also received an FDA warning letter in 2015 that BMPEA was a prohibited ingredient listed on the label of product E.

Discussion | To eliminate potentially hazardous supplements from the marketplace, the FDA recalls individual products and issues public notices regarding individual ingredients. The effectiveness of FDA recalls of individual products has been previously studied.[5,6] One analysis[6] found that 67% of brands subject to FDA recalls still on sale contained adulterants. Our current study explores the use of public notices targeting individual ingredients in supplements rather than individual products. Two findings are notable. First, the number of products that contained 1,3-DMAA, BMPEA, and oxilofrine decreased, but most supplements tested contained 1 or more prohibited stimulant, some up to 4 years after FDA action. Second, 1 stimulant was introduced only after FDA enforcement action. Future studies will be necessary to determine whether the FDA's public notices may, on occasion, inadvertently lead to the introduction of prohibited stimulants in supplements.

Our study has several limitations. It was small; we analyzed 12 brands of supplements at 2 time points during a 3-year period. Larger studies will be necessary to confirm our findings. Furthermore, we analyzed only 1 sample of each supplement, and stimulants might vary from batch to batch.

Despite these limitations, our study provides further evidence that a regulatory system that relies on postmarket enforcement activities is insufficient to ensure the safety of dietary supplements. Practitioners should advise patients that dietary supplements may contain prohibited stimulants.

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Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Wen, Gerona.
Drafting of the manuscript: Cohen.
Critical revision of the manuscript for important intellectual content: Wen, Gerona.
Statistical analysis: Wen, Gerona.
Administrative, technical, or material support: Wen, Gerona.
Supervision: Cohen, Gerona.

Conflict of Interest Disclosures: 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 collaborated in research with NSF International and received research support from Consumers Union. No other disclosures were reported.

Additional Information: While the study was being conducted, Ms Wen was affiliated with the Clinical Toxicology and Environmental Biomonitoring Laboratory, University of California, San Francisco.

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Editor's Note

Regulating the Dietary Supplement Industry: The Taming of the Slew

The iconic image of the snake oil salesman, hawking his panaceas and elixirs, reminds us that the sale of unregulated medicinal products has been debated for more than a century. Interestingly, the origin of the term dates back to a decision rendered by the predecessor of the US Food and Drug Administration (FDA)—the Bureau of Chemistry—on Clark "the Rattlesnake King" Stanley in 1916. Through chemical analysis, the bureau found that Stanley's snake oil, in fact, contained no snake oil at all but rather capsaicin, camphor, and turpentine. Hoping to make an example of him, federal prosecutors took Stanley to court for misbranding his product under the newly enacted Pure Food and Drug Act, ultimately fining him the lofty sum of $20.[1] It is unclear what influence this had at the time, but 100 years later snake oil remains available as just one of a vast number of nutritional supplements marketed and sold without routine oversight.

Dietary supplements are ubiquitous; in 2013, more than half of Americans reported taking one. There are approximately 90 000 products currently on the market, representing a $30 billion industry in the United States alone.[2] Although the FDA is charged with regulating vitamins and supplements under the Dietary Supplement Health and Education Act of 1994, the impediments in place make this a Sisyphean task. The sheer number of supplements on the market, underreporting of adverse events that could trigger an investigation, difficulty successfully prosecuting cases against offenders, and the ease with which suppliers can rebrand products removed from the shelves have led to a largely unregulated environment.[3] In addition, the Dietary Supplement Health and Education Act of 1994 assumes supplements are safe without any testing and puts the onus on the FDA to demonstrate harm; however, under existing law, the FDA is not permitted to investigate a supplement before it is marketed to the public.[4] In this issue of *JAMA Internal Medicine*, Cohen et al[5] report that public notices, another FDA regulatory measure, had little effect in changing the behavior of companies discovered to be in clear violation of the law by placing undisclosed stimulants into their products.

High out-of-pocket costs and regulatory concerns raise the question of why so many people take supplements at all. In clinical trials, they have rarely provided benefit compared with a healthful diet (with the possible exception of specific groups, such as pregnant women or those with nutritional deficiencies). In the real world, there is little guarantee that a supplement will even contain what is advertised on the packaging and not contain unlisted ingredients, potentially leading to significant harms—an estimated 23 000 emergency department visits annually are attributable to supplements.[6] It is hard to imagine how, without many more resources, the FDA could regulate such a large and amorphous entity as the dietary supplement industry. Thus, as in the era of the original snake oil salesmen, the rule remains, "Buyer beware." Given the existing safety concerns, high costs, and lack of benefit for most people, health care professionals should routinely ask about supplement use and encourage discontinued use when there is no evidence-based indication.

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COMMENT & RESPONSE

The Alleged Health-Protective Effects of Coffee

To the Editor Using UK Biobank data from more than 400 000 people, Loftfield and colleagues[1] examined associations between