Presence of Banned Drugs in Dietary Supplements Following FDA Recalls

Letters

RESEARCH LETTER

Presence of Banned Drugs in Dietary Supplements Following FDA Recalls

The US Food and Drug Administration (FDA) initiates class I drug recalls when products have the reasonable possibility of causing serious adverse health consequences or death.[1] Recently, the FDA has used class I drug recalls in an effort to remove dietary supplements adulterated with pharmaceutical ingredients from US markets. Approximately half of all FDA class I drug recalls since 2004 have involved dietary supplements adulterated with banned pharmaceutical ingredients.[2,3]

Prior research has found that even after FDA recalls, dietary supplements remain available on store shelves.[4] However, it is not known if the supplements on sale after FDA recalls are free of the adulterants. In the present study, dietary supplements purchased at least 6 months after FDA recalls were analyzed to determine if banned drugs were still present.

Methods | Dietary supplements were analyzed if they met the following inclusion criteria: (1) recalled due to adulteration with pharmaceutical ingredients between January 1, 2009, and December 31, 2012[3,5]; (2) available for purchase in July or August 2013 directly from websites of supplement manufacturers or retailers (as opposed to general e-commerce sites such as Amazon.com, eBay Inc, or Alibaba Group); and (3) the supplement name, manufacturer, and distributor listed on the purchased supplement was identical to the information provided in the FDA recall.

Dietary supplements were analyzed by Flora Research Laboratories (J.N-K.). Samples were labeled with the marketing claim on the supplement label (eg, weight loss, sexual enhancement, or sports enhancement), but did not include the supplement name, manufacturer, and prior FDA findings.

Analyses were performed using the same methods that the FDA's field laboratories use to screen for clandestine adulteration. In short, dietary supplements were analyzed using either gas chromatography mass spectrometry or liquid chromatography tandem mass spectrometry in data-triggered mode. Adulterants, except for anabolic steroids, were confirmed against a standard using retention time, mass spectrum, and UV spectrum.

Results | The FDA recalled 274 dietary supplements between January 1, 2009, and December 31, 2012. Twenty-seven of the 274 recalled supplements (9.9%) met our inclusion criteria and were analyzed. Supplements were purchased a mean (SD) of 34.3 (11.5) months after the FDA recall (range, 8-52 months). Seventy-four percent of supplements (20/27) were produced by US manufacturers.

One or more pharmaceutical adulterant was identified in 66.7% of recalled supplements still available for purchase (18/27; **Table**). Supplements remained adulterated in 85% (11/13) of those for sports enhancement, 67% (6/9) for weight loss, and 20% (1/5) for sexual enhancement. Of the subset of supplements produced by US manufacturers, 65% (13/20) remained adulterated with banned ingredients.

Sixty-three percent of analyzed supplements (17/27) contained the same adulterant identified by the FDA. Six of the 27 (22.2%) supplements contained 1 or more additional banned ingredients not identified by the FDA (Table). Some supplements contained both the previously identified adulterant as well as additional pharmaceutical ingredients. Banned substances identified in recalled supplements included sibutramine, sibutramine analogs, sildenafil, fluoxetine, phenolphthalein, aromatase inhibitor, and various anabolic steroids. One novel adulterant, benzyl sibutramine, was first described as recently as 2013.[6]

Discussion | To our knowledge, this is the first study to determine if adulterants remain in supplements sold after FDA recalls. We found that 66.7% of recalled supplements still available for purchase at least 6 months after FDA recalls remained adulterated with banned ingredients.

Our study has several limitations. First, we limited testing to common adulterants expected based on marketing claims (eg, weight loss supplements were tested for adulterants commonly found in weight loss products). Second, our analyses may have failed to detect recently introduced drug analogs. Third, although every effort was made to purchase recently manufactured supplements, it is not known if all supplements were manufactured after the FDA recall.

Action by the FDA has not been completely effective in eliminating all potentially dangerous adulterated supplements from the US marketplace. More aggressive enforcement of the law, changes to the law to increase the FDA's enforcement powers, or both will be required if sales of these products are to be prevented in the future.

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Author Contributions: Dr Cohen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Cohen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Cohen.

Table. Pharmaceutical Adulterants Identified in Recalled Dietary Supplements Purchased at Least 8 Months After US Food and Drug Administration (FDA) Recalls

Recalled Supplement	Date of FDA Recall[a,b]	Date Purchased	Expiration Date on Purchased Supplement	Adulterant Found by FDA[a,c]	Adulterant Found After FDA Recall[c]
2a, 17a Methastadrol	November 3, 2009	August 2013	January 2014	Steroid or steroid-like compound or analog	Anabolic steroid
4-ad	September 16, 2010	July 2013	March 2015	Aromatase inhibitor	None identified
Açai-Man Mangosteen	February 3, 2012	July 2013	Not available	Tadalafil	None identified
Botanical Slimming 100% Natural Softgel	September 2, 2011	August 2013	Not available	Sibutramine	Sibutramine
E-pol: Inslinsified	November 3, 2009	August 2013	Not available	Steroid or steroid-like compound or analog	Two anabolic steroids
Everlax capsules	February 3 and 22, 2012	July 2013	Not available	Sibutramine	None identified
EverSlim	February 3, 2012	July 2013	January 2018	Sibutramine	Fluoxetine, sibutramine
Finaflex 550-XD	November 3, 2009	August 2013	June 2014	Steroid or steroid-like compound or analog	Two anabolic steroids
Forged Extreme Mass	November 3, 2009	August 2013	November 2011	Steroid or steroid-like compound or analog	Anabolic steroid
Joyful Slim	July 22, 2010	July 2013	December 2013	Desmethylsibutramine (an analog of sibutramine)	None identified
M-Drol	November 3, 2009	August 2013	Not available	Steroid or steroid-like compound or analog	Anabolic steroid
Magic Power Coffee	June 25, 2010	August 2013	February 2015	Hydroxythiohomosildenafil (an analog of sildenafil)	Sildenafil
Massdrol	November 3, 2009	August 2013	Not available	Steroid or steroid-like compound or analog	Anabolic steroid
Mince Belle	February 3, 2012	July 2013	Not available	Sibutramine	Fluoxetine, N-didesmethyl sibutramine (an analog of sibutramine)
Novedex XT	January 15 and October 7, 2010	July 2013	July 2013	Aromatase inhibitor and steroid or steroid-like compound or analog	Aromatase inhibitor and an anabolic steroid
On Cycle II Hardcore	November 3, 2009	August 2013	Not available	Steroid or steroid-like compound or analog	Two anabolic steroids
P-Plex	November 3, 2009, and January 15, 2010	August 2013	October 2012	Steroid or steroid-like compound or analog	Anabolic steroid impurities
Pandora: Sexual Enhancer for Women	December 23, 2010	July 2013	October 2013	Analog of sildenafil	None identified
RockHard Weekend	November 9, 2009, and December 22, 2010	July 2013	March 2014	Sulfoaildenafil (an analog of sildenafil)	None identified
Testra-flex	January 15, 2010	July 2013	May 2014	Steroid or steroid-like compound or analog	Anabolic steroid
Slim-30	July 16 and August 18, 2010	July 2013	December 2015	Desmethyl sibutramine (an analog of sibutramine)	None identified
Slim Forte Slimming Capsule	July 27, 2011	July 2013	April 2018	Sibutramine	Sibutramine, phenolphthalein
Slim Xtreme Herbal Slimming Capsule	May 11, 2011	July 2013	January 2015	Sibutramine	Sibutramine, phenolphthalein, benzyl sibutramine (an analog of sibutramine)
Stamina-RX	June 15, 2009	August 2013	September 2014	Benzamidenafil (an analog of sildenafil)	None identified
Trenadrol	November 3, 2009	August 2013	Not available	Steroid or steroid-like compound or analog	Anabolic steroid
X-TREN	November 3, 2009, and January 15, 2010	August 2013	September 2014	Steroid or steroid-like compound or analog	None identified
Zi Xiu Tang Bee Pollen Capsule	October 24, 2012	July 2013	July 2015	Sibutramine	Sibutramine, phenolphthalein

[a] Information available at http://www.fda.gov/ForConsumers/ProtectYourself/HealthFraud/ucm255499.htm.

[b] May have been recalled more than once.

[c] May have included more than 1 adulterant.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Mr Maller reported receiving personal fees from NY State Senator Jeffrey Klein and SSP Nutrition outside of the submitted work. Mr Neal-Kababick reported being the vice chair of the US Pharmacopeia expert panel on Adulteration of Dietary

Supplements with Drugs and Drug Analogues; reported being a co-owner of Flora Research Laboratories (some of the clients are dietary supplement manufacturers); and reported serving as an expert witness in cases involving the investigation of quality issues in the production of dietary supplements. No other disclosures were reported.

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COMMENT & RESPONSE

Insulin vs Sulfonylureas for Second-Line Diabetes Treatment

To the Editor Dr Roumie and colleagues[1] reported that compared with sulfonylureas the addition of insulin to metformin to improve glycemic control was associated with an increased risk of a composite of nonfatal cardiovascular outcomes and all-cause mortality in patients with diabetes mellitus. Although the results presented require verification in carefully designed clinical trials, we have some concerns about the current analyses.

Roumie et al[1] stated that subgroup analyses stratifying by age were consistent with the primary analysis. However, eFigure 3 showed that the hazard ratio (HR) for cardiovascular events or death was 1.14 (95% CI, 0.82-1.59) for patients younger than 65 years, whereas for those aged 65 years or older, the HR was 1.51 (95% CI, 1.19-1.92). For the composite death outcome, the HR was 1.28 (95% CI, 0.85-1.97) for patients younger than 65 years, whereas for those aged 65 years or older, the HR was 1.66 (95% CI, 1.29-2.14). Contrary to the conclusion made by the authors, the results suggest that insulin added to metformin is safe among patients younger than 65 years but appears to be hazardous in older patients with diabetes.

Part of the explanation may be differences in types of insulin used and hypoglycemia by age group. Of the patients in the metformin plus insulin group, 47% used long-acting agents only; 22%, both long- and short-acting agents; 17%, premixed insulin; and 11%, short-acting agents only. Although premixed insulin use in older adults can increase the risk of hypoglycemia compared with long-acting analogs,[2] even the choice of regular or analog insulin can influence the frequency of hypoglycemic episodes when multiple injections are used.[3] Thus, the type of insulin chosen for older patients with diabetes should be taken into consideration in such database analyses.

In addition, below a hemoglobin A_{1c} level of 8%, the risk of treatment-induced hypoglycemia increases.[4] Because mean achieved hemoglobin A_{1c} levels were 7% among sulfonylurea users and 6.9% among insulin users in this study, missing hypoglycemia data are of concern. Even though Roumie et al[1] used an extensive database, they were unable to obtain data on hypoglycemia frequency, especially the number of severe events requiring hospital admission.

Such information is essential for appropriate interpretation of the study. Although sulfonylurea drugs can also increase the risk hypoglycemia of among older patients, comparative data are still required.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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In Reply We agree with Drs Tasci and Safer that the risk of metformin and insulin compared with metformin plus sulfonylurea as a second-line diabetes treatment after failure of metformin monotherapy may differ in certain populations. They point to eFigure 3 that shows a statistically significant increased risk in persons aged 65 years or older and no statistically significant increase in younger persons.

However, the confidence intervals for the HRs in the 2 age groups have considerable overlap and a formal test for interaction between metformin plus insulin and age is not significant (P = .22). Thus, we have not proven significant differences in risk by age. The numerical differences observed could represent real differences or simply chance variation in the estimated associations.