8-2020

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Andrew R. Jagim

Patrick S. Harty

Karen M. Fischer

Chad M. Kerksick

Jacob L. Erickson

MAYO CLINIC

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Andrew R. Jagim, PhD; Patrick S. Harty, MS; Karen M. Fischer, MPH; Chad M. Kerksick, PhD; and Jacob L. Erickson, DO

Abstract

Objective: To examine differences in the frequency and severity of federally reported adverse events between caffeine-containing and non–caffeine-containing products while also identifying the category of caffeine-containing products associated with the highest frequency and severity of adverse events.

Patients and Methods: All adverse event reports that met specified eligibility criteria and were submitted to the Center for Food Safety and Applied Nutrition Adverse Event Reporting System between January 1, 2014, and June 29, 2018, were extracted. In this retrospective observational study, the most severe adverse event experienced, an ordinal variable, was categorized into death, life-threatening, hospitalization/disability, and emergency department visit. A nonproportional odds model was used to compare the odds of caffeine-containing products being associated with more severe adverse events relative to a noncaffeine group. The analysis is of data only from those reporting adverse events and may or may not be representative of the entire population exposed to these products, which is not known from the examined data.

Results: Energy and preworkout products saw a significant increase in the odds of the adverse event experienced being death rather than the other less severe outcomes relative to the noncaffeinated group. Those products, along with weight loss products, had greater odds of the adverse event being death or life-threatening vs the less severe outcomes relative to the noncaffeinated group.

Conclusion: Caffeine-containing products have a greater association with severe adverse events compared with non–caffeine-containing products. Exposure to preworkout and weight loss products had greater odds of being associated with a more serious adverse event relative to noncaffeinated products. Health care practitioners should use these outcomes to better inform and educate patients about the many factors related to caffeine intake and adverse outcomes.

 ■ Mayo Clin Proc. 2020;95(8):1594-1603

For editorial comment, see page 1562

From the Department of Sports Medicine, Mayo Clinic Health System, Onalaska, WI (A.R.J., J.L.E.); Department of Kinesiology & Sport Management, Texas Tech University, Lubbock, TX (P.S.H.); Division of Biomedical Statistics and Informatics, Department of

Affiliations continued at the end of this article.

The US Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition (CFSAN) is responsible for monitoring the safety of all food-based products and dietary supplements, which also includes responsibility over adverse event (AE) reports (AERs).[1] In 2003, the FDA created the CFSAN Adverse Event Reporting System (CAERS) to serve as a self-initiated postmarket centralized reporting system for any AERs associated with food, dietary supplement, or cosmetic products. In the context of this reporting system, serious AEs are defined as (A): (1) death; (2) a life-threatening experience; (3) inpatient hospitalization; (4) a persistent or significant disability or incapacity; (5) a congenital anomaly, birth defects, or other serious outcomes; or (B) requires, based on a reasonable medical judgment, a medical or surgical intervention to prevent an outcome described under (A).[1] The purpose of this system is to encourage greater transparency regarding health concerns related to dietary supplement use and encourage more reporting by health care professionals. The reporting of AEs is voluntary for consumers and health professionals,

whereas dietary supplement manufacturers are mandated by law to report serious AERs upon notification.[2]

Recently, this system has been used to identify dietary supplement products, resulting in a higher number of AERs and how the AERs differ across age groups or between sexes.[3,4] Or et al[4] indicated that dietary supplements marketed for muscle building, energy, and weight loss were more likely to result in a severe AE compared with vitamins in children, adolescents, and young adults using a similar database. Similarly, Markon et al[3] compared call data from CAERS with the US National Poison Data System for caffeinated energy drinks and identified 40 unique energy drink products within CAERS, with the top 6 most frequently specified products accounting for 89% of all reports. Additionally, they noted that those between the ages of 20 and 50 years had a higher number of cases reported and more females were identified within CAERS for being associated with multiple product reports compared with males.

These studies help highlight certain product categories that may be associated with a higher number of AERs. From this information, health care practitioners can be more vigilant about educating and counseling their patients that certain populations should exercise greater caution before consuming such products and may also better understand the importance of reporting AEs to the FDA.

Caffeine-containing products such as multi-ingredient preworkout supplements (MIPS), energy products, and weight loss products are growing in popularity and are common sources of caffeine in peoples' diets.[5-7] Collectively, these products tend to promote benefits including increased energy, metabolic activity, and alertness while reducing sensations of fatigue or hunger. These product ingredient labels generally state caffeine concentrations ranging from 60 to 400 mg per serving.[8,9] However, previous studies have found discrepancies between caffeine content of the label vs the actual caffeine amount in certain product lots that were assessed.[10-12]

Although similar, each product class tends to have a distinct ingredient profile with differing purported benefits and reasons for use. For example, MIPS are a specialized class of dietary supplements intended to be ingested before exercise and often include a blend of ingredients such as caffeine, creatine, β-alanine, betaine, and L-citrulline, all of which have varying degrees of efficacy to enhance exercise performance.[8,13] Conversely, energy drinks and "shots" tend to primarily contain caffeine, vitamins, herbs, and amino acids, all of which have varying degrees of stimulatory and energy-enhancing benefits.[9] Weight loss products generally contain caffeine coupled with various herbal extracts purported to enhance metabolism, lipolysis, and fat oxidation.[14,15] Because of their convenience, purported benefits, and high concentration of caffeine, these products may be more susceptible to misuse in that consumers may consume more than the recommended serving size.[6] As a result of the combination of multiple ingredients and concentrated amounts of caffeine, excessive consumption of these products may increase the likelihood of adverse effects.

To date, it is unknown whether AEs are more likely to be associated with caffeine-containing products compared with the global average of food and dietary supplement—related AERs or the most common health outcomes. Such estimations would require knowledge of not only how many AEs were reported but also of how many individuals were exposed. Further, it is not known which category of caffeine-containing products is associated with the highest frequency of AERs submitted to CFSAN.

Therefore, the objective of this study was to examine differences in the number and severity of AERs in CFSAN between caffeine-containing products and non—caffeine-containing products. A secondary aim was to identify the category of caffeine-containing products associated with the

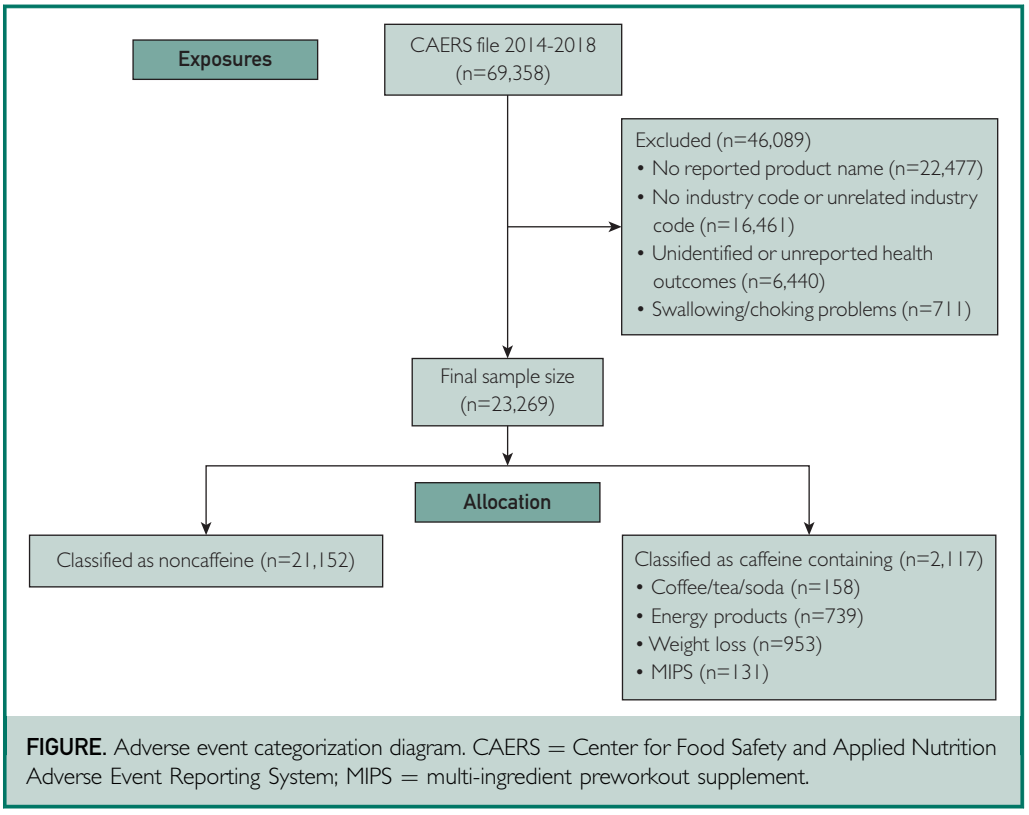

FIGURE. Adverse event categorization diagram. CAERS = Center for Food Safety and Applied Nutrition Adverse Event Reporting System; MIPS = multi-ingredient preworkout supplement.

highest number and severity of AERs in the CFSAN database from 2014 to 2018.

PATIENTS AND METHODS

We extracted the entire CAERS data file from 2014 to 2018, including all AE submissions by consumers, food and dietary supplement companies, and health care professionals directly from the FDA website.[16] All AERs that were not associated with a dietary supplement or food product category that could potentially encompass caffeine-containing products were subsequently removed from the analysis, that is, any products other than those with an FDA-assigned industry code of 54 (vitamin/mineral/protein/unconventional diet), 41 (dietary conventional foods/meal replacements), 31 (coffee/tea), and 29 (soft drink/water) were excluded from the data set. All AERs with an unspecified health outcome were also excluded from analysis.

All AEs associated with the consumption of identified dietary supplement categories using previously published definitions for MIPS, energy products, weight loss products, and common caffeine-containing beverages (coffee, tea, and soda)[8,9,15] were identified, coded, and categorized by 2 independent researchers based on previously established criteria for AERs.[1,4] The categorization and exclusion process for all AEs is outlined in the Figure (the AE categorization diagram). The classification of products associated with the AERs into the respective categories based on product ingredients and marketing descriptions was verified using the US Department of Agriculture National Nutrient Database (https://ndb.nal.usda.gov/ndb/search/list?home=true) and the National Institutes of Health/Office of Dietary Supplements Dietary Supplement Label Database (https://www.dsld.nlm.nih.gov/dsld/index.jsp). If a search of these resources did not yield sufficient product information, the researchers accessed the information on relevant manufacturer websites.

Mayo Clin Proc. ■ August 2020;95(8):1594-1603 ■ https://doi.org/10.1016/j.mayocp.2020.02.033
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TABLE 1. AE Descriptive Characteristics for Total AEs

	Total (N=23,269)	Caffeine (N=2117)	No Caffeine (N=21,152)
Most severe AE experienced, no. (%)			
Death	329 (1.4%)	45 (2.1%)	284 (1.3%)
Life-threatening	2021 (8.7%)	287 (13.6%)	1734 (8.2%)
Disability or hospitalization	7373 (31.7%)	831 (39.3%)	6542 (30.9%)
ED visit	13,546 (58.2%)	954 (45.1%)	12,592 (59.5%)
Product role, no. (%)			
Suspect	15,261 (65.6%)	1981 (93.6%)	13,280 (62.8%)
Concomitant	8008 (34.4%)	136 (6.4%)	7872 (37.2%)
Industry, no. (%)			
Vitamin/mineral/protein/ unconventional diet	22,401 (96.3%)	1873 (88.5%)	20,528 (97.1%)
Dietary conventional foods/ meal replacements	419 (1.8%)	12 (0.6%)	407 (1.9%)
Coffee/tea	145 (0.6%)	124 (5.9%)	21 (0.1%)
Soft drink/water	304 (1.3%)	108 (5.1%)	196 (0.9%)

Sorted by Subgroups, Age, and Sex

	Energy Products (N=546)	Preworkout (N=103)	Coffee, Tea, or Soda (N=79)	Weight Loss Products (N=643)	Noncaffeinated Products (N=8803)
Age (y)					
Mean ± SD	43.2±16.6	31.0±10.0	41.3±19.0	40.6±15.0	58.4±20.6
Minimum, maximum	0.11, 91	16, 66	1, 90	0.02, 104	0, 104
Sex, no. (%)					
Female	391 (71.6)	13 (12.6)	47 (59.5)	464 (72.2)	5687 (64.6)
Male	155 (28.4)	90 (87.4)	32 (40.5)	179 (27.8)	3116 (35.4)
Severe AE outcome, no. (%)					
Death	11 (2.0)	9 (8.7)	1 (1.3)	15 (2.3)	160 (1.8)
Life-threatening	60 (11.0)	32 (31.1)	12 (15.2)	109 (17.0)	815 (9.3)
Disability or hospitalization	171 (31.3)	31 (30.1)	30 (38.0)	257 (40.0)	4891 (55.6)
ED visit	304 (55.7)	31 (30.1)	36 (45.6)	262 (40.8)	4891 (55.6)

AE = adverse event; ED = emergency department.

Applicable data extracted from each AER included the date of the AE, suspected product name, sex, AE outcomes, and symptoms associated with the AE. In accordance with the methods of Timbo et al,[1] if a single AER contained more than one category of caffeine-containing product, it was counted multiple times. Occurrences with a concomitant product role are included in Table 1, but were excluded from any further analysis. Caffeinated products were further divided into subgroups based on the type of product: energy products; preworkout; coffee, tea, or soda; and weight loss products. Observations that had both age and sex reported were analyzed using additional models and categorized into subgroups. Choking and choking sensation AEs were removed, unless it was due to an allergic reaction or other symptoms were involved (this excluded 711 observations). Dysphagia symptoms were retained in the data set. Because this study used only publicly available data, it was exempt from institutional review board approval.

The following analysis is based solely on the AERs reported to the CAERS database. Baseline characteristics were calculated using mean ± SD, minimum, and maximum for continuous variables and frequency percentages for categorical variables. The primary outcome of interest was the most

TABLE 2. Most Severe AE Outcome by Caffeine Subgroup

	Energy Products (N=739)	Preworkout (N=131)	Coffee, Tea, or Soda (N=158)	Weight Loss Products (N=953)	No Caffeine (N=13,280)
Severe AE outcome, no. (%)					
Death	15 (2.0%)	9 (6.9%)	1 (0.6%)	15 (1.6%)	250 (1.9%)
Life-threatening	76 (10.3%)	40 (30.5%)	17 (10.8%)	137 (14.4%)	1122 (8.5%)
Disability or hospitalization	235 (31.8%)	45 (34.4%)	41 (26.0%)	450 (47.2%)	4263 (32.1%)
Emergency department visit	413 (55.9%)	37 (28.2%)	99 (62.7%)	351 (36.8%)	7645 (57.6%)

AE = adverse event.

severe AE experienced, which was an ordinal variable that was categorized and ranked by the following outcomes: death, life-threatening, hospitalization/disability, and emergency department (ED) visit. The main explanatory variable of interest was the effect of the different caffeine groups.

An ordered logistic model using all observations that met the inclusion criteria was fit. Due to the caffeine group variable not meeting the proportional odds assumption needed for the model, a nonproportional odds model was fit. For some of the AE records, the age and sex of the case were reported. Another ordered logistic model was fit using these observations, with age and sex included as covariates. After examining graphs of each covariate and testing the parallelism assumption, it was determined that a nonproportional odds model should be fit for both the unadjusted and covariate-adjusted models. The reference group for the caffeine variable in all models was the noncaffeinated group. $P=.05$ was considered significant in all cases and 95% CIs are reported with all odds ratios (ORs). The statistical software used was SAS (version 9.4; SAS Institute Inc).

RESULTS

A total of 23,269 AEs were reported from the designated categories during 2014 to 2018, with a higher frequency of reports associated with noncaffeinated products (21,152 vs 2117) compared with caffeine products. Characteristics for the observations are presented in Table 1 and are divided between any product that contained caffeine and products that did not. Of the reports included in this data set, 96.3% (22,401 of 23,269) were in the vitamin/mineral/protein/unconventional diet industry code. Table 1 also summarizes the descriptive characteristics of the subset AERs by subgroup, age, and sex. More reports for females were recorded in all groups except for the preworkout caffeine group. Table 2 summarizes the most severe AEs by subgroup.

Table 3 reports results from the nonproportional odds model comparing the different caffeine groups. The reference group for the caffeine group variable was the noncaffeinated group. Energy products (OR, 1.83; 95% CI, 1.16 to 2.89; $P=.01$) and preworkout products (OR, 4.90; 95% CI, 2.47 to 9.72; $P<.001$) saw a significant increase in the odds of the AE experience being death rather than the other less severe outcomes compared with the noncaffeinated group. Those products, along with weight loss products, had greater odds of the AE being death or life-threatening vs the less severe outcomes compared with the noncaffeinated group. Energy products had 1.46 times the odds of having the 2 most serious outcomes compared with noncaffeinated products. Weight loss products had 1.26 times the odds and preworkout products had 1.75 times the odds of the AE being death or life-threatening vs the less severe outcomes compared with the noncaffeinated group.

Mayo Clin Proc. ■ August 2020;95(8):1594-1603 ■ https://doi.org/10.1016/j.mayocp.2020.02.033
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TABLE 3. Ordered Logistic Regression; Nonproportional Odds Model (N=15,261)[a]

	Severe AE	Odds Ratio (95% CI)	*P*
Energy products[b]	Death vs < death	1.83 (1.16-2.89)	.01
	Death, life-threatening vs hospitalization/disability, ED visit	1.46 (1.19-1.80)	<.001
	> ED visit vs ED visit	1.28 (1.12-1.48)	.001
Preworkout[b]	Death vs < death	4.90 (2.47-9.72)	<.001
	Death, life-threatening vs hospitalization/disability, ED visit	4.89 (3.45-6.92)	<.001
	> ED visit vs ED visit	3.13 (2.21-4.45)	<.001
Coffee, tea, or soda[b]	Death vs < death	0.44 (0.06-3.12)	.41
	Death, life-threatening vs hospitalization/disability, ED visit	1.26 (0.79-2.02)	.33
	> ED visit vs ED visit	0.84 (0.62-1.16)	.29
Weight loss products[b]	Death vs < death	1.14 (0.68-1.93)	.92
	Death, life-threatening vs hospitalization/disability, ED visit	1.75 (1.47-2.10)	<.001
	> ED visit vs ED visit	2.52 (2.21-2.88)	<.001

[a]< = health outcome regarded as less severe than; > = health outcome regarded as more severe than; AE = adverse event; ED = emergency department.
[b]Reference group is noncaffeinated group.

Both the unadjusted and adjusted nonproportional odds models that included age and sex as covariates are reported in Table 4. The unadjusted model with sex as the independent variable shows significantly decreased odds of the more severe AEs in females compared with males, with 0.24 times the odds for death vs all other outcomes, 0.54 times the odds for death and life-threatening vs all other outcomes, and 0.69 times the odds for more severe AEs vs AEs that required only an ED visit.

In the unadjusted model with age, for every 1-year increase in age, the odds of experiencing a more severe AE that ended in death or was life-threatening compared with less severe AEs was significantly lower. This was also seen for age when comparing the outcome of any AE more severe than an ED visit, but no significant difference when comparing death vs all other AEs. The unadjusted model containing the group variable had similar results to the model in Table 3, which used all reports regardless of whether age and sex were recorded. For every ordinal outcome, the preworkout group had significantly higher odds of having a more severe AE than the noncaffeinated group (OR, 5.17; OR, 5.21; and OR, 2.90). Weight loss products had significantly higher odds than the noncaffeinated group when the outcome was death or life-threatening AE vs all others (OR, 1.92) or more severe AEs vs an ED visit (OR, 1.82).

Table 4 also includes the full model in which all covariates are adjusted for. Females had consistently significantly lower odds of having a more severe AE than males. The age category was significant when comparing death vs other outcomes and also when comparing death and life-threatening vs other outcomes, but the odds were in different directions. When the outcomes of death and life-threatening were combined and compared with the disability, hospitalization, and ED visit groups, for every unit increase in age, the odds of being in the more severe groups decreased (OR, 0.99; 95% CI, 0.98 to 0.99; $P<.001$). Preworkout and weight loss products had greater odds of having a more serious AE than the noncaffeinated group. For the ordinal outcome of death vs a less serious AE, the preworkout subgroup was

TABLE 4. Ordered Logistic Regression With Age and Sex Included as Covariates: Nonproportional Odds Models (N=10,174)[a]

		Unadjusted Models[b]		Adjusted Model[c]	
	Severe AE	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Female vs male	Death vs < death	0.24 (0.18-0.32)	<.001	0.23 (0.17-0.32)	<.001
	Death, life-threatening vs hospitalization/disability, ED visit	0.54 (0.48-0.61)	<.001	0.57 (0.50-0.64)	<.001
	> ED visit vs ED visit	0.69 (0.63-0.74)	<.001	0.70 (0.64-0.76)	<.001
Age	Death vs < death	1.00 (0.99-1.01)	.80	1.00 (1.00-1.01)	.23
	Death, life-threatening vs hospitalization/disability, ED visit	0.98 (0.98-0.99)	<.001	0.99 (0.98-0.99)	<.001
	> ED visit vs ED visit	0.99 (0.99-1.00)	<.001	1.00 (0.99-1.00)	<.001
Energy products[d]	Death vs < death	1.11 (0.60-2.06)	.74	1.03 (0.56-1.91)	.92
	Death, life-threatening vs hospitalization/disability, ED visit	1.20 (0.93-1.55)	.17	1.04 (0.80-1.35)	.77
	> ED visit vs ED visit	1.00 (0.84-1.18)	.96	0.96 (0.80-1.14)	.61
Preworkout[d]	Death vs < death	5.17 (2.56-10.43)	<.001	3.05 (1.47-6.31)	.003
	Death, life-threatening vs hospitalization/disability, ED visit	5.21 (3.56-7.92)	<.001	2.76 (1.83-4.16)	<.001
	> ED visit vs ED visit	2.90 (1.90-4.43)	<.001	2.12 (1.38-3.25)	.001
Coffee, tea, or soda[d]	Death vs < death	0.69 (0.10-5.01)	.72	0.71 (0.10-5.14)	.74
	Death, life-threatening vs hospitalization/disability, ED visit	1.58 (0.87-2.88)	.13	1.25 (0.69-2.29)	.47
	> ED visit vs ED visit	1.49 (0.96-2.33)	.08	1.36 (0.87-2.12)	.18
Weight loss products[d]	Death vs < death	1.29 (0.76-2.20)	.35	1.60 (0.93-2.76)	.09
	Death, life-threatening vs hospitalization/disability, ED visit	1.92 (1.56-2.36)	<.001	1.66 (1.34-2.05)	<.001
	> ED visit vs ED visit	1.82 (1.55-2.14)	<.001	1.72 (1.46-2.04)	<.001

[a]< = health outcome regarded as less severe than; > = health outcome regarded as more severe than; AE = adverse event; ED = emergency department.
[b]Univariate unadjusted models for each covariate.
[c]Adjusted model that includes all covariates.
[d]Reference group is noncaffeinated group.

associated with 3.05 times the odds of death vs a less serious AE compared with the noncaffeinated group. The odds of having a more severe AE that was death or life-threatening was 2.76 times the odds for preworkout compared with the noncaffeinated group. Preworkout also had significantly higher odds of having an AE more severe than an ED visit compared with the noncaffeinated group (OR, 2.12). Weight loss products had 1.66 times the odds of a severe AE than the noncaffeinated group when the outcome was death or life-threatening vs a less severe AE and 1.72 times the odds of an AE more severe than an ED visit.

DISCUSSION

Results of the current study indicate that during 2014 to 2018, AERs associated with noncaffeine product represented a greater number of total AEs (91%; 21,152 of 23,269) compared with caffeine-containing products, regardless of industry code. However, there was a higher relative frequency for the most severe 2 categories of AEs (death and life-threatening) associated with exposure to caffeine-containing products. The AEs associated with products marketed as "energy enhancing" and "weight loss" represented the highest percentage of AEs from the caffeine-containing subgroups.

Mayo Clin Proc. ■ August 2020;95(8):1594-1603 ■ https://doi.org/10.1016/j.mayocp.2020.02.033
www.mayoclinicproceedings.org

Previous studies have reported a nearly 2-fold increase in ED visits as a result of energy drink exposure from 2007 to 2011, with 1 in 10 visits resulting in hospitalization.[17] Similarly, a recent study found an average of 1943 to 2071 (15% to 16%) calls per year to the National Poison Data System associated with exposure to caffeinated energy drinks.[3] These AERs relating to caffeine and energy drinks are not limited to adult populations as a previous investigation using a similar AE database reported that products marketed for energy and weight loss, which commonly include caffeine, were associated with 2.6 times the odds for severe medical events compared with vitamins in individuals between the ages of 11 and 25 years.[4] When adolescent and young adult ED patients were surveyed regarding their energy drink and caffeine use, coffee and sodas represented the most common source of caffeine among these populations, with prevalence of use ranging from 46% to 84% of patients reporting consumption of these items within the previous 30 days.[5] In addition, the prevalence of energy drink consumption was also within this range, with 35% of adolescents and nearly 58% of young adults reporting consumption of energy drinks within the previous 30 days. Currently there is a lack of sufficient information regarding the safety of long-term consumption of these products, but these types of analyses highlight that "energy" products of this nature may be susceptible to misuse or potentially be dangerous, ultimately resulting in a higher rate of AERs.

An interesting observation from the current study was that MIPS represented a greater relative frequency of AERs resulting in death and life-threatening health outcomes. The odds of the AE being death rather than a less severe outcome were approximately 5 times higher in the preworkout subgroup relative to the noncaffeinated group using the total sample and approximately 3.1 times higher after adjusting for age and sex. It is not possible to determine causality using such a database, but MIPS are known to contain varying amounts of caffeine, herbs, and performance-enhancing amino acids,[8] which may increase the risk for AERs if consumed in high amounts or when mixed with other dietary supplements or prescription medications. Moreover, a higher frequency of preworkout-related AERs was experienced by younger males when compared with females. It is worth noting that there is also the possibility of these types of products being more frequently contaminated with prescription drugs or off-label ingredients that may be contraindicated for consumption, as indicated in previous studies.[18-22] For example, there have been published cases of illegal stimulants and methamphetamine analogues being present in weight loss and preworkout supplements.[18,19] The inadvertent consumption of such ingredients could lead to severe AEs if a person had an underlying medical condition or consumed excess amounts of the product. For these reasons and others, health care practitioners should use information from this analysis to better inform and educate their patients on the potential harms, particularly if these patients exhibit any previous health history that may be exacerbated by using such products.

Although a higher relative risk exists for severe AEs associated with caffeine-containing products, the high total frequency of AEs from noncaffeinated products should not be dismissed. Kantor et al[23] estimated that more than 50% of adults reported regularly using a dietary supplement in 2012. When taking into consideration the outcomes from this analysis and recent trends in the sales of dietary supplements, future research should focus on the safety of dietary supplement use and identifying specific categories of supplements that may be classified as higher risk. Also worth noting is the average age of individuals reporting AEs from non–caffeine-containing products that again may warrant health care professionals having future discussions about dietary supplement use with older adult patients because individuals 55 years or older represent the age group associated with the highest percentage of US adults who experience AEs.[1] Additionally, older adults may be more likely to be taking

medications that have contraindications for combining with certain dietary supplements.

This analysis is not without limitations as CAERS serves as a self-initiated postmarket reporting system for medical professionals, consumers, and dietary supplement companies. It is important to note that there is insufficient medical information available in the publicly available data sets to directly link the AERs or specific products themselves to deaths. Therefore, these results do not imply any cause-and-effect relationship between caffeine-containing product use and subsequent safety concerns or health outcomes.

Another limitation of self-reported AEs is that little information is available regarding details of serving size, preexisting medical conditions, current prescription or over-the-counter drug use, or patient medical background, which most certainly operates as a key confounding variable for our reported outcomes. As mentioned with previous reports of this nature,[4] there is the risk for selection bias toward more severe AEs being reported because consumers may ignore less severe AEs. Further, the population in this study is only patients who at least seek some level of medical treatment or self-report their AE and symptoms; therefore, there are no patients included in this sample without an AE. Supplement companies are mandated to report AERs upon notification; however, FDA researchers have asserted that only 2% of all supplement-related AEs are reported in a database such as CAERS (likely attributable to a lack of awareness of such reporting systems). Therefore, it is possible that this database is a gross underestimation of the true number of AEs.[1] Additionally, although the regression modeling used in the current study may provide an estimation of the odds of certain AE outcomes being reported based on the respective supplement category, these results may not be representative of the entire population because the number of exposures is unknown. Also, an inherent bias toward the more severe AERs and underreporting are present.

CONCLUSION

Results of this study indicate that although AERs for noncaffeinated products are much greater in number than AERs from caffeine-containing products, AERs associated with caffeine-containing products are more likely to be classified as severe AERs relative to non—caffeine-containing products based on reported data. Furthermore, exposure to preworkout and weight loss products had greater odds of having a more serious AE than the noncaffeinated products. More reports for females were recorded in all caffeine subgroups except for the preworkout caffeine group; however, females appear to have lower odds of having a more severe AE than males. Additionally, young adult males represent a higher percentage of AEs associated with preworkout supplement ingestion. Therefore, consumers may want to exercise caution when consuming multiple caffeine-containing products with overlapping ingredients to avoid "poly-supplementation" and reduce the likelihood of AEs or negative interactions and are particularly warned against doing so if they have any current medical history or medication use (prescription or over the counter) that could be complicated by their ingestion.

This investigation is not to be misconstrued as a condemnation of all dietary supplements or caffeine-containing products but is intended to act as a warning to consumers to promote safe consumption practices. If a person is insistent on consuming a given product similar to what was examined in this report, he or she should be made aware of the categories of dietary supplements (ie, energy products, weight loss supplements, and MIPS) associated with a higher relative risk for AEs. Additionally, consumers should seek out companies that follow good manufacturing practices and subscribe to third -party testing for determination of product quality and to ensure the absence of any off-label ingredients or contaminants. This strategy is increasingly important for athletes who may be routinely drug tested for ingredients banned for use by sporting organizations. Last, health care professionals

Mayo Clin Proc. ■ August 2020;95(8):1594-1603 ■ https://doi.org/10.1016/j.mayocp.2020.02.033
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should be made more aware of this reporting system and are encouraged to use its submission process.

Abbreviations and Acronyms: **AE** = adverse event; **AER** = adverse event report; **CAERS** = Center for Food Safety and Applied Nutrition Adverse Event Reporting System; **CFSAN** = Center for Food Safety and Applied Nutrition; **ED** = emergency department; **FDA** = US Food and Drug Administration; **MIPS** = Multi-ingredient preworkout supplement; **OR** = odds ratio

Affiliations (Continued from the first page of this article.): Health Sciences Research, Mayo Clinic, Rochester, MN (K.M.F.); and Exercise & Performance Nutrition Laboratory, Lindenwood University, St. Charles, MO (C.M.K.).

Potential Competing Interests: Authors of this manuscript have not received any financial remuneration for preparing or reviewing this paper from outside sources. Drs Jagim and Kerksick have consulted with and received external funding from companies that sell certain dietary ingredients; have received remuneration from companies for delivering scientific presentations at conferences.; and also write for online and other media outlets on topics related to exercise and nutrition.

Correspondence: Address to Andrew R. Jagim, PhD, Department of Sports Medicine, Mayo Clinic Health System, Onalaska, WI 54601 (jagim.andrew@mayo.edu; Twitter: @Ajagim).

ORCID

Andrew R. Jagim: https://orcid.org/0000-0002-6651-5096

REFERENCES

1. Timbo BB, Chirtel SJ, Ihrie J, et al. Dietary supplement adverse event report data from the FDA Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS), 2004-2013. *Ann Pharmacother*. 2018;52(5):431-438.
2. Dietary Supplements and Nonprescription Consumer Protection Act of 2006, 109th Cong 109-462 (2006).
3. Markon AO, Jones OE, Punzalan CM, Lurie P, Wolpert B. Caffeinated energy drinks: adverse event reports to the US Food and Drug Administration and the National Poison Data System, 2008 to 2015. *Public Health Nutr*. 2019;22(14):2531-2542.
4. Or F, Kim Y, Simms J, Austin B. Taking stock of dietary supplements' harmful effects on children, adolescents, and young adults. *J Adolesc Health*. 2019;65(4):455-461.
5. Cotter BV, Jackson DA, Merchant RC, et al. Energy drink and other substance use among adolescent and young adult emergency department patients. *Pediatr Emerg Care*. 2013;29(10):1091-1097.
6. Jagim AR, Camic CL, Harty PS. Common habits, adverse events, and opinions regarding pre-workout supplement use among regular consumers. *Nutrients*. 2019;11(4).
7. Vercammen KA, Koma JW, Bleich SN. Trends in energy drink consumption among U.S. adolescents and adults, 2003-2016. *Am J Prev Med*. 2019;56(6):827-833.
8. Jagim AR, Harty PS, Camic CL. Common ingredient profiles of multi-ingredient pre-workout supplements. *Nutrients*. 2019;11(2).
9. Campbell B, Wilborn C, La Bounty P, et al. International Society of Sports Nutrition position stand: energy drinks. *J Int Soc Sports Nutr*. 2013;10(1):1.
10. Desbrow B, Hall S, O'Connor H, Slater G, Barnes K, Grant G. Caffeine content of pre-workout supplements commonly used by Australian consumers. *Drug Test Anal*. 2019;11(3):523-529.
11. Haller CA, Duan M, Benowitz NL, Jacob P 3rd. Concentrations of ephedra alkaloids and caffeine in commercial dietary supplements. *J Anal Toxicol*. 2004;28(3):145-151.
12. Cohen PA, Attipoe S, Travis J, Stevens M, Deuster P. Caffeine content of dietary supplements consumed on military bases. *JAMA Intern Med*. 2013;173(7):592-594.
13. Harty PS, Zabriskie HA, Erickson JL, Molling PE, Kerksick CM, Jagim AR. Multi-ingredient pre-workout supplements, safety implications, and performance outcomes: a brief review. *J Int Soc Sports Nutr*. 2018;15(1):41.
14. Saper RB, Eisenberg DM, Phillips RS. Common dietary supplements for weight loss. *Am Fam Physician*. 2004;70(9):1731-1738.
15. Jeukendrup AE, Randell R. Fat burners: nutrition supplements that increase fat metabolism. *Obes Rev*. 2011;12(10):841-851.
16. US Food and Drug Administration. CFSAN Adverse Event Reporting System (CAERS). 2019. https://www.fda.gov/food/compliance-enforcement-food/cfsan-adverse-event-reporting-system-caers. Accessed January 20, 2020.
17. Substance Abuse and Mental Health Services Administration (SAMHSA). The DAWN Report: 1 in 10 Energy Drink-Related Emergency Department Visists Results in Hospitalization. 2014. https://www.samhsa.gov/data/sites/default/files/spot124-energy-drinks-2014.pdf. Accessed January 20, 2020.
18. Cohen PA, Travis JC, Keizers PHJ, Boyer FE, Venhuis BJ. The stimulant higenamine in weight loss and sports supplements. *Clin Toxicol (Phila)*. 2019;57(2):125-130.
19. Cohen PA, Travis JC, Venhuis BJ. A methamphetamine analog (N,alpha-diethyl-phenylethylamine) identified in a mainstream dietary supplement. *Drug Test Anal*. 2014;6(7-8):805-807.
20. Eichner S, Maguire M, Shea LA, Fete MG. Banned and discouraged-use ingredients found in weight loss supplements. *J Am Pharm Assoc (2003)*. 2016;56(5):538-543.
21. Martinez-Sanz JM, Sospedra I, Ortiz CM, Baladia E, Gil-Izquierdo A, Ortiz-Moncada R. Intended or unintended doping? A review of the presence of doping substances in dietary supplements used in sports. *Nutrients*. 2017;9(10).
22. Maughan RJ. Contamination of dietary supplements and positive drug tests in sport. *J Sports Sci*. 2005;23(9):883-889.
23. Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in dietary supplement use among US adults from 1999-2012. *JAMA*. 2016;316(14):1464-1474.