

## An Ongoing Series

### Be in the Know

#### Dietary Supplements for Cognitive Performance

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#### ABSTRACT

Dietary supplements promoted for brain health and enhanced cognitive performance are becoming increasingly popular. Special Operations Forces (SOF) is likely a prime target for this market as they strive to continually optimize and then sustain their high level of performance at all times. When a dietary supplement hits the market, it is considered safe until it is proven otherwise; yet the majority have not been analyzed for quality or tested for safety. The authors describe issues related to products marketed for brain health and cognitive enhancement and focus on products brought to our attention by the operational communities. The overwhelming majority of product labels were found to be misbranded and some were found to contain prohibited ingredients and drugs. The problematic ingredients in these products are introduced. The Operation Supplement Safety scorecard algorithm is demonstrated as a tool to quickly screen a product for potential safety; it can be used in real-time when considering the use of any dietary supplement product. These resources are available to help SOF medical assets evaluate whether a product's claims may be deceiving and potentially harmful to the health or career of Operators.

**KEYWORDS:** *consumer product safety; decision aid; dietary supplements; education; mental processes*

#### Introduction

Military Servicemembers are showing great interest in dietary supplements marketed for enhanced cognitive performance and brain health as indicated by the many questions that come in through the Operation Supplement Safety website—Ask The Expert (ATE) function. Operation Supplement Safety (OPSS) is the Department of Defense's resource for Servicemembers and healthcare providers and is overseen by the Consortium for Health and Military Performance (CHAMP) at the Uniformed

Services University of the Health Sciences. OPSS (OPSS.org) was established to provide evidence-based information related to dietary supplements, increase awareness within the community about potential health risks, and educate personnel on how to choose safe dietary supplements. The OPSS ATE function allows us to hear from medical providers and Servicemembers what is going on in the field and while at home.<sup>1</sup> They tell us why dietary supplements for cognitive performance or brain health are of interest and ask questions related to specific products.

#### *Why Are Brain Health Dietary Supplements of Interest?*

Many of the brain health/cognitive enhancement products (sometimes also referred to as “nootropic” supplements) have claims for improving memory, focus, enhancing cognitive performance, energy, and motivation; they are widely available across the Internet and in stores both in and outside of military bases. In fact, brain health supplements generated \$3 billion in sales globally in 2016 and are projected to reach \$5.8 billion by 2023.<sup>2</sup> This massive market is now targeting healthy individuals who want to optimize their performance and not just the elderly who may be experiencing cognitive decline. SOF communities are a prime target for this market because SOF strive to continually optimize and then sustain a high level of performance at all times. Thus, it is important that healthcare providers, trainers, and leaders who work with SOF to have the information they need to help make appropriate and safe dietary supplement decisions.

#### *Brain Health Supplements vs Nootropics: What Are They?*

Brain health supplements are often referred to as “nootropics” or “cognitive enhancers” and claim to improve mental performance. By law, dietary supplements contain dietary ingredients defined as “vitamins, minerals, amino acids, and herbs or botanicals, as well as other substances that can be used to supplement the diet.”<sup>3</sup> Some common ingredients meeting

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this definition and found in “brain health” products include B-complex vitamins, magnesium, omega 3 fatty acids, L-citrulline, green tea extracts, Bacopa, Ginseng, and *Ginkgo biloba*.

Nootropics are not exclusive to dietary supplements. In fact, some nootropics are prescription drugs intended to treat (or manage) specific medical conditions, like attention-deficit/hyperactivity disorder or Alzheimer disease<sup>4,5</sup>; others are approved, over-the-counter drugs (e.g., NoDoz) and yet some are drugs in other countries but have not gone through the US FDA drug approval process (unapproved drug). Neither prescription, over-the-counter, nor unapproved drugs are allowed in dietary supplements. Also, some nootropic ingredients found in dietary supplements have not gone through the regulatory framework to be considered a dietary ingredient.<sup>6,7</sup> These ingredients fall into a *gray zone*: are they a drug or *potentially* a new dietary ingredient? Unknowingly ingesting these ingredients might not only jeopardize a career by popping positive on a drug test; they might pose a serious health risk to Operators.

### Do We Have to Question Supplements Already on the Market?

Dietary supplements are regulated by the FDA but not in the same way as prescription and over-the-counter drugs. The various regulatory issues related to dietary supplements were described in detail in the 2018 Winter JSOM issue, but this was before nootropics became so popular.<sup>8</sup> Importantly, dietary supplements cannot claim to “treat” any medical condition, yet we see this regularly: products for concussions, pain, arthritis, Alzheimer disease, and the like are being marketed. As the brain health market booms exponentially, reports are uncovering unfounded claims and some unsafe products.<sup>9-11</sup> Given the emerging interest in brain health and cognitive performance coupled with the surge in nootropic dietary supplements, it is important to answer the questions – *are dietary supplements promoted for cognitive enhancement safe? And, what does the SOF community need to know?* To that end, we analyzed the content and label claims of various products Servicemembers had asked about and then we applied the OPSS scorecard algorithm to identify the various potential red flags and ascertain the relative safety of the various products.

### How We Addressed the Questions

A scoping review was performed to identify dietary supplement products marketed for brain health and cognitive performance in otherwise healthy adults. The authors searched the Dietary

Supplement Label Database, Natural Medicines, and popular websites selling such products. Full details are reported elsewhere.<sup>9</sup> Overall, 650 unique products were identified as marketed with claims for enhancing cognitive performance. We selected 24 products that had been asked about in an ATE query submitted to OPSS by Military Servicemembers in 2019.

Each product was purchased and sent to National Center for Natural Products Research, University of Mississippi, MS, for analysis to verify whether the ingredients listed on the labels were accurate. The specific methods for analysis are reported on elsewhere.<sup>9,10</sup> All products analyzed were also screened for relative safety according to the OPSS scorecard, a tool designed for consumers to identify potential red flags when reading the product label.<sup>12</sup>

### What We Found

#### Scientific Product Analysis: Label Claim Verification

Of the 24 products analyzed, 17 (71%) had at least one ingredient (and up to six ingredients total) claimed on the Supplement Facts label that was not detected through analysis. When one reviewed the ingredients on the labels, nine (38%) products listed ingredients not meeting current regulations for being in a dietary supplement according to the FDA. Table 1 presents these ingredients, some of which are on the OPSS prohibited list<sup>13</sup> and thus not allowed for use by any Servicemember; these include DMHA (octodrine), DMAA, piracetams (Noopept), and vinpocetine. DMHA and DMAA are not allowed by the FDA in any dietary supplement. Vinpocetine is a drug in other countries and FDA tentatively concluded in September 2016 that vinpocetine does not meet the definition of a dietary ingredient; the FDA has also issued warnings that it could cause “a miscarriage or harm fetal development.”<sup>14</sup> Higenamine, hordenine, and sulbutiamine are currently on the FDA advisory list, which means they are being looked at by the FDA and likely not dietary supplement ingredients.<sup>15</sup> Despite clear issues, these ingredients remain in many dietary supplement products marketed to the military community for performance and cognitive enhancement.

Other ingredients of concern, but commonly found on supplements labels of products we tested, include *Mucuna pruriens* extract “standardized for L-Dopa,” which is a drug used to treat Parkinson disease.<sup>16</sup> To “standardize” means to make them all exactly the same, but it is unclear what “standardization” process the extract went through or how this was determined. In addition, another common ingredient being tracked

**TABLE 1** Products Where Red Flag Ingredients Are Found Listed on Supplement Facts Labels and Being Sold to US Consumers

Ingredient Found in Dietary Supplement Product	Safety Concern	Products Found and Marketed, n
DMAA (1,3-dimethylamylamine)	Stimulant drug, FDA notice, OPSS Prohibited list, World Anti-Doping Agency list	268
DMHA (1,5-dimethylhexylamine) or Octodrine	Stimulant drug, FDA notice, OPSS Prohibited list	71
Noopept (Omberacetam)	Stimulant drug, OPSS Prohibited list	9
Vinpocetine	Stimulant drug, OPSS Prohibited list	678
Higenamine	Stimulant, FDA advisory list, World Anti-Doping Agency list	139
Hordenine (N,N-dimethyltyramine)	Stimulant, FDA advisory list	317
Sulbutiamine	Stimulant drug, FDA advisory list	44
Halostachine (N-methylphenylethanolamine)	Stimulant	44
β-Phenylethylamine (β-PEA)	Stimulant	422

by OPSS is *Rauwolfia yomitoria* root bark extract (yohimbine) or “standardized for yohimbine” or yohimbine HCl.<sup>17</sup> Reports suggest this ingredient is being synthetically produced in some products, and ingesting it could result in severe side-effects or interact with other ingredients.<sup>18</sup> Some countries outside the United States have banned this ingredient due to potential serious health effects.

Finally, we found multiple hidden compounds in the products analyzed. Eighteen (75%) products had compounds detected that were not present on the labels, with an average of 3.1 unlisted ingredients per product. These consisted of amino acids or other acids typical of flavoring agents or preservatives; adenosine or an adenosine-derivative; the stimulants/drugs 1,5-DMHA and 1,3-DMAA (not dietary ingredients according to the FDA); and various phenethylamines (PEA) such as  $\beta$ -PEA, hordenine (on FDA advisory list), demelverine (a synthetic drug) and halostachine. PEAs are stimulant, psychoactive, and hallucinogenic substances with structures similar to amphetamine, catecholamines, and other substances: none of them should be in dietary supplements.<sup>19,20</sup> Finally, caffeine was detected in a product that explicitly claimed to be decaffeinated. For any of these products, it is unclear whether (and how much of) these ingredients were added and what the source was: synthetic or a plant extract?

#### How Many Products on the Market Contain These Red Flag Ingredients Identified?

We analyzed only 24 of at least 650 products on the market; the fact that other brain health products might also contain red flag ingredients was considered. We searched Natural Medicines to quantify how many products, regardless of claimed use, were being marketed as dietary supplements and contained red flag ingredients listed above. As shown in Table 1 (right column), over 600 products are currently on the market containing the ingredient ‘vinpocetine’ alone, an ingredient the FDA has tentatively concluded does not meet the definition of a dietary ingredient. The more recent safety risks of dietary supplements containing vinpocetine for women of child-bearing age support the conclusion it should not be in dietary supplements.<sup>21</sup> Yet we still see it on Supplement Fact labels. Also, at least 268 products contained DMAA, which the FDA declared did not meet the definition of a dietary supplement over 5 years ago.

#### OPSS Scorecard: Identification of Red Flags With Operation Supplement Safety

On the Operation Supplement Safety [OPSS.org] website, an interactive scorecard is available to screen for red flags when reading the Supplement Facts labels before considering a dietary supplement. It is an educational tool and resource to help consumers within the Department of Defense community make informed decisions: you need to read the label and answer seven simple questions to make an informed go/no go determination about a specific product. Table 2 presents the seven yes/no questions providing a quick screening for risk stratification. Figure 1 shows the percentage of the 24 products scoring a 1 for each question, and the total score. Overall, only one product had a score of 4 or greater and would be considered “Likely Safe.” This product contained only one ingredient listed on the label and was also verified to contain only that one ingredient. Remember more does not mean better; quality is better than quantity. It is important to note that the scoring algorithm has no relevance to effectiveness.

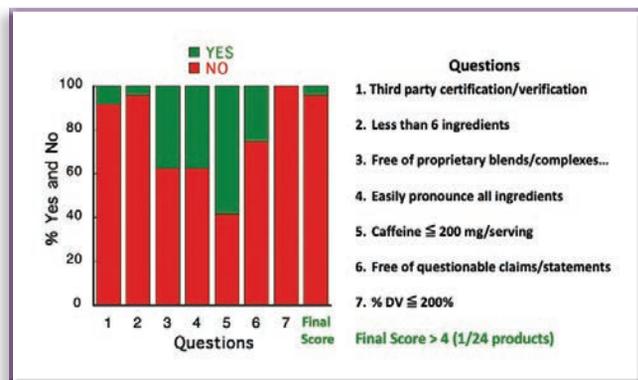
TABLE 2 OPSS Questions to Risk Stratify Supplements as Likely Safe vs Likely Unsafe

Questions	Yes = 1	No = 0
1. Is any one of these third-party certification seals on the product label? (i.e., BSCG, Informed Sport, NSF Certified Sport, USP)		
2. Are there less than six ingredients on the Supplement Facts label?		
3. Is the label free of the words proprietary, blend, matrix or complex?		
4. Can you easily pronounce the names of each ingredient on the Supplement Facts label?		
5. Is the amount of caffeine listed on the label 200mg or less per serving? (If caffeine is not listed mark “Yes”)		
6. Is the label free of questionable claims or statements?		
7. Are all the % Daily Values (%DV) on the Supplement Facts label less than 200% (If % DV is not listed, mark “No”)		

Read the label on your supplement and mark 1 for “yes” and 0 for “no”.

Total: Add up the “1’s”. 4 or more is okay. Less than 4 is a “no-go”.

FIGURE 1 Dietary supplements screened according to Operation Supplement Safety Scorecard for Relative Safety.



#### Take-Home Messages

- Evidence indicates that many dietary supplement products marketed for brain health or cognitive enhancement contain ingredients (either present on or hidden from the label) that are ‘red flag’ ingredients or unapproved drugs. Check with OPSS to find the names to watch out for.
- OPSS.org is an important resource for SOF community and provides updated and trusted, evidence-based information.
  - Use the *Ask The Expert* feature when you have questions about dietary supplements.
  - Become familiar with the Prohibited List of Ingredients.
  - Check the High Risk List of Products that OPSS has available, when considering dietary supplements.
  - Use the OPSS scorecard algorithm to screen a product for relative safety.

#### Summary

The dietary supplement market is booming with nootropic and cognitive enhancement products as brain health and cognitive performance becomes a public focus. It is likely SOF communities will be a prime target for advertisements, which could be deceptive and promoting potentially unsafe products.

Importantly, there is evidence that some ingredients present or hidden from the labels of products currently on the market do not meet the regulatory framework for being a dietary supplement ingredient, some considered as unapproved drugs. Just because a product is on the market does not mean it has been shown to be safe. Becoming familiar with red flag and prohibited ingredients, avoiding high-risk products, and using educational tools such as OPSS scorecard are important. Together, these resources can help users make informed decisions in real-time about dietary supplements and reduce the potential risks to their health and careers.

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### Authorship Contributions

CC and PD were responsible for the concept, design, analysis, and interpretation of the data. CC wrote the first draft and PD revised it critically; both authors approve the final version.

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### Conflict of Interest

The authors have no financial interests or relationships to disclose.

### References

1. **Operation Supplement Safety.** Ask the Expert. <https://www.opss.org/ask-the-expert>. Accessed on March 30, 2020.
2. **Global Counsel on Brain Health.** *The Real Deal on Brain Health Supplements: Global Counsel on Brain Health Recommendations on Vitamins, Minerals, and Other Dietary Supplements*. Available at [www.GlobalCouncilOnBrainHealth.org](http://www.GlobalCouncilOnBrainHealth.org) DOI: [https://www.aarp.org/content/dam/aarp/health/brain\\_health/2019/06/gcbh-supplements-report-english.doi.10.26419-2Fpia.00094.001.pdf](https://www.aarp.org/content/dam/aarp/health/brain_health/2019/06/gcbh-supplements-report-english.doi.10.26419-2Fpia.00094.001.pdf).
3. **United States Congress.** Dietary supplement health and education act of 1994. *PubL103-417*. 1994; [www.congress.gov](http://www.congress.gov). Accessed on March 30, 2020.
4. **Cui CC, Sun Y, Wang XY, et al.** The effect of anti-dementia drugs on Alzheimer disease-induced cognitive impairment: a network meta-analysis. *Medicine*. 2019;98(27):e16091. doi:10.1097/md.000000000016091
5. **Wilms W, Wozniak-Karczewska M, et al.** Nootropic drugs: methylphenidate, modafinil and piracetam—population use trends, occurrence in the environment, ecotoxicity and removal methods: a review. *Chemosphere*. 2019;233:771–785.
6. **Binns CW, Lee MK, Lee AH.** Problems and prospects: public health regulation of dietary supplements. *Annu Rev Public Health*. 2018;39:403–420.
7. **FDA.** New dietary ingredients in dietary supplements—background for industry. <https://www.fda.gov/food/new-dietary-ingredients-ndi-notification-process/new-dietary-ingredients-dietary-supplements-background-industry>. 2019. Accessed on March 30, 2020.
8. **Deuster PA.** What the SOF community needs to know about dietary supplements. *J Spec Oper Med*. 2018;18(4):131–136.
9. **Crawford C, Boyd C, Avula B, et al.** A public health issue: dietary supplements promoted for brain health and cognitive performance. *J Altern Complement Med*. 2020. Mar 2. doi:10.1089/acm.2019.0447
10. **Crawford C, Wang YH, Avula B, et al.** The scoop on brain health dietary supplement products containing huperzine A. *Clin Toxicol (Philadelphia, Pa)*. 2020:1–6.
11. **D’Cunha NM, Georgousopoulou EN, Dadigamuwage L, et al.** Effect of long-term nutraceutical and dietary supplement use on cognition in the elderly: a 10-year systematic review of randomised controlled trials. *Br J Nutr*. 2018;119(3):280–298.
12. **Operation Supplement Safety.** Screen your supplement for safety. <https://www.opss.org/screen-your-supplement-safety-read-label-your-supplement-and-answer-these-questions>. Accessed on March 30, 2020.
13. **Operation Supplement Safety.** Dietary supplement ingredients prohibited by the Department of Defense. <https://www.opss.org/dietary-supplement-ingredients-prohibited-department-defense>. Accessed on March 30, 2020.
14. **FDA.** Statement on warning for women of childbearing age about possible safety risks of dietary supplements containing vinpocetine. <https://www.fda.gov/news-events/press-announcements/statement-warning-women-childbearing-age-about-possible-safety-risks-dietary-supplements-containing>. 2019; Accessed on March 30, 2020.
15. **FDA.** Dietary supplement ingredient advisory list. <https://www.fda.gov/food/dietary-supplement-products-ingredients/dietary-supplement-ingredient-advisory-list>. 2020; Accessed on March 30, 2020.
16. **Hornykiewicz O.** How L-DOPA was discovered as a drug for Parkinson’s disease 40 years ago. *Wiener klinische Wochenschrift*. 2001;113(22):855–862.
17. **Mukherjee E, Gantait S, Kundu S, et al.** Biotechnological interventions on the genus *Rauvolfia*: recent trends and imminent prospects. *Appl Microbiol and Biotechnol*. 2019;103(18):7325–7354.
18. **Cohen PA, Wang YH, Maller G, et al.** Pharmaceutical quantities of yohimbine found in dietary supplements in the USA. *Drug Test Anal*. 2016;8(3–4):357–369.
19. **Dean BV, Stellflug SJ, Burnett AM, Engebretsen KM.** 2C or not 2C: phenethylamine designer drug review. *J Med Toxicol*. 2013;9(2):172–178.
20. **King LA.** New phenethylamines in Europe. *Drug Test Anal*. 2014;6(7–8):808–818.
21. **FDA.** Vinpocetine in dietary supplements. <https://www.fda.gov/food/dietary-supplement-products-ingredients/vinpocetine-dietary-supplements>. 2019; Accessed on March 30, 2020.