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Challenges in Reporting Adverse Events from Dietary Supplements

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Abstract

In 2008, the Institute of Medicine (IOM) Committee on Dietary Supplement Use by Military Personnel recommended the development of service wide military policies (e.g., education or regulations) to guide commanders in management practices for safe use of dietary supplements (DS). This review summarizes the activities the military has undertaken to advance the safe use of DS by Service Members and develop best practices on reporting adverse events across the Department of Defense (DoD). In March 2022, the Department of Defense issued a DoD Instruction (DoDI) regarding the use of DS by members of the U S. military. This DoDI provides guidelines to establish an official list of prohibited substances. The DoDI also identifies Operation Supplement Safety (OPSS) at CHAMP as DoD's "go to" program for DS use and information about DS and ingredients. Noted are a number of gaps in the reporting of adverse events from DS that need to be addressed by multiple constituencies.

Background

In 2008, the Institute of Medicine (IOM) Committee on Dietary Supplement Use by Military Personnel recommended the development of service wide military policies (e.g., education or regulations) to guide commanders in management practices for safe use of dietary supplements (DS).[1] The lack of consistent policies for the safe use of DS has raised concerns owing to the vulnerabilities of some military subpopulations. However, this is not a problem unique to the military as many young, physically active and/or weight conscious individuals strive on a daily basis to have a competitive edge in sports or improve their physical looks and well-being. This review summarizes the activities the military has undertaken to advance the safe us of DS by Service Members and develop best practices on reporting adverse events (AEs) across the Department of Defense (DoD).

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It is recognized that Service Members are under pressure to meet body composition and physical fitness standards, and these factors may contribute to use of dietary supplements by Service Members. Based on the 2015 DoD Survey of Health-Related Behaviors, 32% of Service Members report using at least one DS daily, and 13% of males report using body-building supplements each day. Women use body-building supplements less frequently (4.5% daily) but are more likely to use weight-loss supplements (8.6%) than men (6.3%).[2] Although Service Members are concerned about weight status or "popping positive" on a routine military drug test, their family members may also use DS for health-related reasons. It is clear that multi-ingredient, adulterated (e.g., steroids, stimulants, prescription drugs, heavy metals),[3] and contaminated DS pose a significant risk to our military population and compromise military readiness.[4–7] A recent review of the US Food and Drug Administration (FDA) Tainted Dietary Supplement Database for the years 2007 through 2021 revealed 1,068 unique DS products adulterated with active pharmaceutical ingredients.[8] Although this is a mere fraction of the more than 100,000 DS currently on the market, only a small fraction of DS were even tested. The majority of the identified products were for sexual enhancement and weight loss.[8] Other investigators have also published papers on dietary supplement adulteration with various controlled substances and pharmaceuticals.[4, 5, 9–11] The potential to scan and pair problematic DS ingredients with likely and known adverse events by using the FDA CFSAN Adverse Event Reporting System (CAERS) database with signal detection methodology was recently demonstrated.[12] The database of detected ingredient-adverse event and product-adverse event associations is available at https://github.com/zhang-informatics/DDSAE.

Not only do adulterated products pose a risk to military readiness, but inappropriate use of DS can be problematic. A convenience sample conducted in 2010-2011 of Service Members noted that combination product users were more than two times more likely to self-report experiencing abnormal heart beats, stomach pain, dizziness, tremors, and numbness/tingling.[13] Users of purported steroid analogues were more than 2.5 times more likely than non-users to report experiencing dizziness.[13] Of great concern however, are the deaths of several Service Members potentially associated with DS use, and others who were hospitalized with hepatic injury or suffered other AEs from taking DS containing harmful ingredients.[14–18] Although the evidence is limited, even excessive use of some vitamin and mineral supplements may be associated with higher risk of serious harms (hip fracture [vitamin A], hemorrhagic stroke [vitamin E], and kidney stones [vitamin C, calcium]).[18] Therefore, identifying supplements that are safe to consume and have scientifically validated efficacy are critical for sustaining military health and performance.

How Best to Capture Use of Dietary Supplements?

Since the publication of the IOM Report in 2008, the DoD, primarily by the Consortium for Health and Military Performance (CHAMP) at the Uniformed Services University and the DoD Dietary Supplement and Other Self Care Products Subcommittee, has sought to address the issue of how best to capture AEs from DS by Service Members to inform leadership of potential problems and to mitigate future AEs. From 2008 to 2022 multiple activities and actions were taken to encourage and adopt an AEs reporting system military wide. Many of these activities either failed to be acted on or were short-lived. One action

taken in 2017 was to propose ICD-10 codes that could be developed and implemented within the DoD electronic health record (EHR) to simplify and enhance the capture of DS. The codes were categorized by the intended use and/or composition of the DS as shown below:

T43.615X: Caffeine and other dietary stimulant-containing supplements	**T50.4X5:** Protein Supplements (Protein, creatine, amino acids)
T45.2X5: Vitamins and/or mineral supplements	**T50.5X5:** Weight Loss Supplements
T50.0X5: Health Supplements (Joint, Heart, Brain, Gut, Immune health)	**T50.7X5:** Androgenic/Anabolic and/or Anabolic-like substances
T50.1X5: Other types of supplements (unclear as to intended use and/or ingredients)	**T50.995X:** Herbals and other botanical supplements
T50.3X5: Sexual Enhancement	

For example, under the code, T43.615X:

Caffeine and other dietary stimulant-containing supplements/products, the following DS ingredients and products could further be described in the EHR.

- Stimulant ingredients: DMAA, DMBA, DMHA, ephedra, higenamine, hordenine, methylsynephrine, octopamine, rauwolscine
- Examples of pre-workouts products: Cellucor C4 Original, Condemned Labz Arsynist, Insane Labz Psychotic Gold, Metabolic Nutrition Synedrex, Muscletech #Shatter SX-7, ProSupps Mr. Hyde, Beyond Raw Lit, BSN N.O.-Xplode
- Examples of energy drinks products: Monster, Red Bull, Rockstar, Amp, Full Throttle, Venom, Xyience, Rip It, NOS High Performance Energy Drink
- Examples of energy shot products: 5-Hour Energy, MTN OPS, Rip It Energy Shot

Can Electronic Health Records Facilitate Capture of Dietary Supplement Use?

—In many EHRs DS are recorded in the medications list, a structured field within the record to facilitate uniformity of recording and provide for the ability to retrieve data. Use of ICD codes, also presented in a structured format allows for greater interoperability of the EHR so DS recorded in the medications list could be linked to ICD codes and the reporting of adverse events. Within the current DoD EHR this feature is not available. This interoperability gap was also pointed out in a survey of EHR systems and practices within four federal agencies - DoD (Army and Air Force, Indian Health Service, Department of Veterans Affairs, and the NIH Clinical Center) - that deliver clinical services.[19] Below is a list of what would be needed for a robust EHR for collecting DS and Adverse Events:

- Uniform reporting of DS in a structured field and format
- Built in functionality to implement drug-drug and drug-allergy interaction checks with automatic real-time notifications to the healthcare provider

- A DS/drug interaction check as many DS have multiple active ingredients that increase the likelihood of an AE
- Full listing of available DS in drug-knowledge software programs
- Instructions and training on processes
- Ease of automatic filing reports with HHS/FDA Safety Reporting Portal

How the DoD Instruction can Promote Capture of the Use of DS by Service Members?—Another action of a long awaited approval and enforcement was a new DoD Instruction, signed and issued on 9 March 2022, regarding the use of DS by members of the U S. military. It was signed: DoDI 6130.06: Use of Dietary Supplements in the DoD (referred to below as just "the DoDI" https://www.esd.whs.mil/Directives/issuances/dodi/). This DoDI provides guidelines to establish an official list of prohibited substances. The DoDI also identifies Operation Supplement Safety (OPSS) at CHAMP as DoD's "go to" program for DS use and information about dietary supplements and ingredients. The OPSS website (OPSS.org) (Figure 1) hosts the official *"DoD Prohibited Dietary Supplement Ingredients list."* This list will be updated when an FDA action occurs, or new scientific information becomes available regarding DS ingredients. Service Members are not allowed to use any product with an ingredient on the DoD Prohibited Dietary Supplement Ingredients list.

The policy applies to "Office of the Secretary of Defense (OSD), the Military Departments, the Office of the Chairman of the Joint Chiefs of Staff and the Joint Staff, the Combatant Commands, Office of the Inspector General of the Department of Defense, the Defense Agencies, the DoD Field Activities, and other organizations within DoD. DoDI 6130.06 also explicitly states that *"No retail facility on a military installation can sell products containing ingredients on the DoD Prohibited Dietary Supplement Ingredients list on the OPSS website."* Dietary supplement education is required for all Service Members and those who provide health-related services to military members. This includes healthcare personnel, health promotion specialists, fitness leaders, athletic trainers, and strength-and-conditioning specialists. *The DoDI also requires DoD healthcare providers to document the use of all dietary supplements in the Service Member's EHR, and to report "suspected serious adverse events resulting from use of dietary supplements" both via the adverse events button on the main page of the OPSS website and in the user's EHR.*

Gaps in AE Reporting that need to be Filled

The DoDI 6130.06 is a major accomplishment to ensure the health and safety of Service Members and their families. However, a number of gaps remain in the full implementation of the DoDI. As demonstrated, enhancements to the EHR are needed, followed by implementation, and then a mechanism whereby the information would automatically go to FDA. In addition, DoD needs support from Federal Partners, and outside collaborators to ensure the safety of our Service Members. Currently the FDA has neither the authority nor the resources to limit what comes on the market and although it has an Adverse Event Reporting System, it is not possible within the system to identify Service Members, what

service and other information needed to track within the DoD. What we do know is that most health care providers (HCP) have seen AEs in association with DS. Published reports indicate that 60 to 81% of HCP have encountered an AE in association with a DS.[20–22] Despite observing such events, most HCP report lacking the knowledge as to where and how to report such AE.[20–22] Interestingly, many do report the observed AE (10 to 41%), but to various sources, including the hospital database, other specialists, Poison Control Center and the like. The FDA's Safety Reporting Portal (SRP) is intended to streamline the process of reporting product safety issues to the FDA and the National Institutes of Health (NIH). However, when data from the various studies are combined, estimates for reporting AEs to FDA's Safety Reporting Portal range from 0% to 15%.[20–23] Most of the AEs submitted to the FDA are not voluntary, but rather related to the post-market surveillance requirement for manufacturers to report all serious AEs to the agency within 15 business days of receipt.[24] Also, if one wanted to review a FDA case record, a request must be filed under the Freedom of Information Act. Finally, the FDA reporting system was not designed to accommodate the work-flow of busy HCP, so it is not surprising that voluntary reporting rates are so low. Health care providers need to be educated on the importance of AE reporting, but the process must be simple – a coding and note in the EHR, extract data and have it submitted to the FDA. Only when the AE reporting process for providers is simple, will AEs be able to serve as a signal for action. If DoD had such a system, they would be able to calculate the costs of lost duty time, medevac'ing from theater and both short- and long-term health-care costs associated with treating AE associated with DS.[25]

A simple process is within reach, as the mechanism is there. OPSS started as an educational campaign back in 2012 due to several deaths and other adverse events in Service Members taking products containing DMAA (1,3-dimethylamylamine).[15] Now an established program, with the DoD Prohibited Dietary Supplement Ingredients list containing over 800 ingredients, it is time to ensure all Service Members and HCP are adequately educated on the risks and benefits of DS. We need to work together to find a practical way to report AE from DS within the EHR to ensure DoD can identify any pertinent signals, in cooperation with the FDA so they can take action.

Lastly, industry continues to show it does not have the will to self-regulate and strives to control what happens in the DS world, even when some DS are a threat to Force readiness. Exploitation of the unique health needs of military personnel with misleading and irresponsible marketing claims and misbranded and adulterated products is both reprehensible and frequently illegal. At least one dietary supplement trade association has gone on record by stating that responsible industry has a role in ensuring that supplements are safe for all consumers, including military personnel and supports FDA enforcement against violative products.[26] Other trade associations and businesses selling DS should also demand such practices be stopped. Service Members should feel assured that products they purchase will not cause them an adverse health event or a positive drug test. It's time for Service Members and the public to have access to only safe DS products.

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Biographies

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Figure 1.

The Operation Supplement Safety (OPSS) program at the Consortium for Health and Military Performance at the Uniformed Services University of the Health Sciences. Materials posted on the OPSS website (opss.org) are free and available to military servicemembers, federal agencies, health care professionals, and consumers.