Stimulant Medications and Supplements: Clinical Implications for the Sports Medicine Provider

Collaborative Solutions for Safety in Sport

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DISCLOSURE

- I have no relevant financial disclosures in reference to this lecture.
- That being said, I am a physician in the US Army, and work for the DoD.

My opinions and assertions contained herein are private views and are not to be construed as official or as reflecting the views of the U.S. Army Medical Department, Uniformed Services University or the Department of Defense at large.
Case Presentation 1

- 25 y/o soldier presents to the sports medicine clinic for heat tolerance testing and a return to duty assessment;
- He sustained an exertional heat stroke (EHS) during Special Forces accession.
- Soldier was acclimatized with no history of EHS; he had been using a pre-workout stimulant.
Case Presentation 2

- 25 y/o soldier presents to the medical aid station complaining of palpitations, agitation and insomnia.
- He has **sinus tachycardia** on the monitor and reports regular use of **Red Bull** and caffeine gum.
- Unit is requesting guidance on strategies for sleep.
Case Presentation 3

A warfighter contacts the Human Performance Resource Center looking for help.

Recently using a **new pre-workout supplement** to enhance training.

Unfortunately the soldier “popped positive” on a recent urine drug screen.
Case Presentation 4

- Alison is a 19 y/o **transfer** female basketball player.
- She states she has a **personal history of ADHD** and would like to renew her prescription for Ritalin.
- At the present point in time, she has **no supporting documentation** in her medical record.
Objectives

- Review the epidemiology, purported performance benefits, and adverse effects of stimulants.
- Discuss stimulant use in the NCAA athlete with ADHD.
- Identify resources to assist with patient education, physician reporting and athletic participation.
Stimulant Use In Athletes
Epidemiology: NCAA

- NCAA study of 21,000 college students from 713 NCAA member institutions in 2001 showed an increase in ephedrine use from 3.5% to 3.9% c/w rates in 1997.

- Men's lacrosse (5.5%) and women's gymnastics (8.3%) had the highest rate of ephedrine use among NCAA athletes.

- Reasons: improved athletic performance (27.3%), improved physical appearance (27.3%), and weight control (19.7%).

Epidemiology: Stimulants

- 139 collegiate hockey players were surveyed;
- 52% of hockey players admitted to using stimulants.
- 17% utilization of pseudoephedrine.
- 33% would use if it would help them get in the NHL.

Eighty-two percent of deployed and 74% of garrison soldiers used DSs ≥1 time·week⁻¹.

Logistic regression analyses, adjusted for significant demographic and health predictors of DS use, showed deployed personnel were more likely than garrison soldiers to use protein, amino acids, and combination products.

Stimulant Use in Deployed Marines

- A total of 329 active duty Marines completed the survey.
- The prevalence of supplement use was 72% for males and 42% for females (p = 0.009).
- Of the 12% of Marines reporting side effects, 79% were taking multiple supplements and 89% were using stimulants.
- Deployment was significantly associated with new supplement use (p < 0.001).

Epidemiology: Energy Drinks (ED)

- 692 college students completed surveys at a large private university.
- 36% (197 non-athletes, 58 student athletes) of participants reported ED consumption in the preceding 30 days.
- No difference in ED consumption based on status.
- Episodic drinking and prescription stimulant misuse were both correlated with increased ED consumption.

Epidemiology: ADHD
Medication Diversion

- Majority of nonprescription stimulant users reported obtaining the drugs from a peer with a prescription – termed diversion.
- Lifetime rates of diversion ranged from 16% to 29% of students asked to give, sell, or trade their medications.
- A study of 9161 undergraduates reported an 8.1% lifetime nonprescription stimulant misuse rate among college students.

Stimulants and
the Athlete:
Do They Work!
Yes they Do!

- CNS stimulants are used to reduce fatigue and increase alertness, competitiveness, and aggression.
- Accepted ergogenic aid for endurance performance.
- “Recent studies with trained subjects support observation that caffeine seems highly ergogenic for speed endurance exercise ranging in duration from 60 to 180 seconds.”
- Studies employing sport-specific methodologies (i.e. hockey, rugby, soccer, basketball, volleyball) with shorter duration (i.e. 4-6 seconds) show caffeine to be ergogenic during high-intensity intermittent exercise.

Caffeine and Exercise

- Caffeine acts antagonistically on adenosine receptors, inhibiting the negative effects adenosine induces on neurotransmission, arousal and pain perception.

- The hypoalgesic effects of caffeine have resulted in dampened pain perception and blunted perceived exertion during exercise.
Stimulants and the Athlete: Adverse Effects
Korey Stringer Cause of Death

- In (his) locker, Kelly said, were an empty bottle of the supplement Ripped Fuel; a vial of Celebrex, an anti-inflammatory prescription drug; an unopened bottle of the weight-loss product Xenadrine, and the herbal supplement Mo' Power, a performance-enhancing product…
- The St. Paul Pioneer Press…, cited team sources who said one player told team officials he'd seen Stringer take two Ripped Fuel capsules before the morning practice on July 31.
CLEARWATER, Fla. — The Broward ( Fla.) County medical examiner said Thursday the dietary supplement ephedra definitely contributed to the heatstroke death of Baltimore Orioles pitching prospect Steve Bechler on Feb. 17. Dr. Joshua Perper, in releasing the results of toxicology tests on the 23-year-old, confirmed that "significant amounts" of the over-the-counter supplement containing the herb ephedra were partly to blame for the death. (2003)
Increase in Heat Stroke Fatalities?

- Recent trends in football heatstroke fatalities toward significant increases may, in part, be attributable to or aggravated by the use of dietary supplements.
- Credible scientific evidence has been found that amphetamine derivatives and the ergonomic aid creatine may contribute to subclinical dehydration and heatstroke in selected individuals.
- Caution is urged in the education and evaluation of football players who train during the hot summer months.

Bailes JE, Cantu RC, Day AL
A 21-year-old healthy man had a witnessed out-of-hospital cardiac arrest while exercising at a gym.

The patient confirmed using the supplement for the first time before exercising on the day of admission.
The Danger of Combination Ingredients

- Case of a previously healthy 22-year-old man who presented with anginal chest pain and was diagnosed with a non-ST-elevation MI.
- For 3 weeks, he had been ingesting the dietary supplements Jack3d® (principal ingredient, 1,3-dimethylamylamine) and Phenorex™ (ingredient, Citrus aurantium) daily, before undertaking physical activity.
- Coronary angiograms revealed a proximal left anterior descending coronary artery thrombus with distal embolization.

Sudden Unexplained Cardiac Death (SUD)

- The incidence of SCD in Division 1 male basketball athletes was 1:5,200 AY.
- The most common findings at autopsy were autopsy-negative sudden unexplained death in 16 (25%), and definitive evidence for hypertrophic cardiomyopathy was seen in 5 (8%).

Military Perspective

O’Connor FG: Dietary supplements and warfighters: a challenge for military providers. Mil Med. 2012 Dec;177(12):1448-9
Don’t Forget the Supplements!

- Of the 48 sudden deaths temporally associated with supplement use, the mean age was 34.2 ± 10.0 years and predominantly male (n = 44, 91.7%).
- The underlying cause of death was fatal atherosclerotic coronary disease in 18 (37.5%), sudden unexplained death in 16 (33.3%), and hypertrophic cardiomyopathy in six (12.5%).
- Compared with controls, there were no statistically significant differences in adjudicated cause of death.
- Ergogenic supplements increase risk of SCD 5 fold in soldiers >35 years.

1,3-dimethylamylamine (DMAA)

- Case reports for **two soldiers** who were taking commercially available dietary supplements containing multiple ingredients to include the sympathomimetic, **1,3-dimethylamylamine (DMAA)**; both collapsed during physical exertion from cardiac arrest and ultimately died.

- Our cases highlight concerns that **DMAA in combination with other ingredients** may be associated with significant consequences, reminiscent of previous adverse events from other sympathomimetic drugs removed from the market.

Eliason MJ, Eichner A, Cancio A, Bestervelt L, Adams BD Deuster PA
Case reports: Death of active duty soldiers following ingestion of dietary supplements containing 1,3-dimethylamylamine (DMAA).
The Danger of Pushing Too Hard!

- Case report of a highly trained, heat-acclimatized infantry soldier who suffered from **exertional heatstroke** during a 12-mile road march shortly after taking an ephedra-based supplement.
- Clinicians and military commanders should strongly discourage the use of ephedra-containing substances in active duty soldiers undergoing strenuous exercise.

What’s Really in There!

Supplement Facts
Serving Size 1 Scoop (5.3 g)
Servings Per Container 45

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>% Daily Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C (as Ascorbic Acid)</td>
<td>250 mg</td>
</tr>
<tr>
<td>* Kineses Proprietary Blend</td>
<td>4580 mg</td>
</tr>
<tr>
<td>Trimethylglycine (Betaine Anhydrous)</td>
<td></td>
</tr>
<tr>
<td>Creatine Monohydrate</td>
<td></td>
</tr>
<tr>
<td>L-Citrulline</td>
<td></td>
</tr>
<tr>
<td>Dendrobex (Dendrobium Extract)(stem) (Concentrated for alkaloid content including Dendrobine, Dendroxine, Dendramine, B-Phenylethylamine, N,N-Dimethyl- B-Phenylethylamine, and N,N-Diethyl-B-Phenylethylamine)</td>
<td></td>
</tr>
<tr>
<td>B-Phenylethylamine HCl</td>
<td></td>
</tr>
<tr>
<td>Citramine (Citrus Reticulata Extract) (fruit) (Concentrated for N-Methyltyramine content)</td>
<td></td>
</tr>
<tr>
<td>Caffeine Anhydrous</td>
<td></td>
</tr>
</tbody>
</table>

* Daily Value not established.

Other Ingredients: Citric Acid, Malic Acid, Natural and Artificial Flavors, Sucralose, Acesulfame Potassium, FD&C Red #40, RD&C Blue #1.
Analysis of Craze

- β-Methylphenethyamine
- B (2-) Phen(yl)ethylamine
- N-Methylphenethylamine
- Ethylamphetamine
- Amphetamine
- Synephrine
Stimulants and the Adverse Events: Why?
Stimulants and Exercise

- Vasoconstrictor
  - Inability to properly thermoregulate
- Strain to Cardiovascular System
  - Increased BP
- Increased Metabolic Heat
  - Increased cellular metabolism
- Excessive Sense of Energy
  - Loss of “governor” to regulate activity

Cardiovascular Mechanisms for Adverse Events

- Coronary vasoconstriction, tachycardia, and hypertension are principal mechanisms for myocardial ischemia and infarction.

- Reentrant cardiac arrhythmias are thought to be secondary to adrenergic shortening of cardiac refractory periods.

Potential Mechanism with Long Term Use

- **Two cases of ventricular arrhythmias** induced by abuse of ephedrine in two competitive athletes.
- Endomyocardial biopsies guided by electroanatomic mapping revealed **contraction-band necrosis**, a myocardial injury frequently observed in cases of catecholamine excess.
- Our cases suggest that **long-term abuse** of ephedrine may result in **myocardial damage**, and that these structural alterations may promote areas of slow conduction **favoring re-entrant ventricular tachyarrhythmias** and a long-lasting risk of ventricular arrhythmias.

**Casella M et al:** Ventricular arrhythmias induced by long-term use of ephedrine in two competitive athletes. *Heart Vessels.* 2015 Mar;30(2):280-3.
Cardiovascular Effects of Stimulants

- The caffeine concentration in these drinks is high and their overconsumption could lead to insomnia, agitation, tremors and cardiovascular complications including sudden death.

Stimulants and the Adverse Events: The Lack of Reporting
Know How and Where to report Adverse Events

Percent of Respondents (%)

- **Observed AE**
  - Study 1 n = 401
  - Study 2 n = 251
  - Study 3 n = 308

- **Know How**
  - Study 1 n = 401
  - Study 2 n = 251
  - Study 3 n = 308

- **Reported**
  - Study 1 n = 401
  - Study 2 n = 251
  - Study 3 n = 308
RESULTS:

- A total of 311 AMSSM physicians.
- Only 51% of respondents had a reliable source for information on DS safety; 58% routinely discussed DS use with their patients.
- Although a majority (71%) of respondents had encountered adverse events associated with DS use, few of those (10%) confirmed reporting such events.
- Reasons that physicians did not report adverse events were lack of knowledge regarding where to report (68%), how to report (61%), and availability of time (9%).

Stimulants and the Athlete with ADHD
Student athletes (SA) require **formal documentation** of a comprehensive evaluation that supports a diagnosis of ADHD.

SA with a diagnosis of ADHD require documentation of an **annual clinical examination**.

Clinicians must provide statement that non-stimulant medication was considered.
ADHD Medications and the Need for a Baseline ECG

“... statement advocates a thorough history and physical examination before starting stimulant medications, with an emphasis on the identification of risk factors for sudden death, but does not routinely recommend electrocardiographic screening or cardiac subspecialist consultation ...”

References for the Team Physician on the Utilization of Stimulants
1. Why is the NCAA instituting a stricter application of the medical exception policy for the use of banned stimulant medications to treat ADHD?

   • The stricter application reflects a stronger stand on policy enforcement, protecting the student-athlete competing while using these stimulants, and the integrity of the sport. This stricter application of the medical exception policy is intended to provide clearer documentation of the student-athlete’s evaluation, and not intended to replace the clinician’s evaluation and treatment.

   As experienced across campus, more and more college students-athletes are being treated with stimulant medications for ADHD. These stimulants are banned for use in NCAA competition for both performance and health reasons, and using them may result in a positive drug test and loss of eligibility, unless the student-athlete provides adequate documentation of a diagnostic evaluation for ADHD and appropriate monitoring of treatment. In recent years, the number of student-athletes testing positive for these stimulant medications has increased 3 fold, and in many cases there has been inadequate documentation submitted in support of the request for a medical exception to the NCAA banned drug policy.

2. Who was consulted in the development of the guidelines?

   • The NCAA sought consultation from MDs, Psychiatrists, Psychologists and others in the development of the guidelines for appropriate documentation requirements. These were then reviewed and approved by the NCAA Committee on Competitive Safeguards and Medical Aspects of Sports.

3. How was the change communicated to the membership?

   • Beginning in January 2008, the membership received notification of the effective date of the stricter application — August 2009 — in the form of NCAA News articles, notices in email communications, and the posting of a video describing the rationale and expectations of the stricter application. This 18 month period of notice would allow member institutions to inform current and incoming student-athletes to be prepared to gather the necessary documentation of the diagnosis, course of treatment and current prescription.

4. Who needs to conduct the evaluation?

   •
The World Anti-Doping Code

THE 2015 PROHIBITED LIST
INTERNATIONAL STANDARD

The official text of the Prohibited List shall be maintained by WADA and shall be published in English and French. In the event of any conflict between the English and French versions, the English version shall prevail.

This List shall come into effect on 1 January 2015
FDA MedWatch

Food and Drug Administration

MedWatch

The FDA Safety Information and Adverse Event Reporting Program

[Image of a MedWatch form with a pen on it]
The Edge You Need For Total Fitness

HPRC encompasses those areas (physical, environmental, nutritional, psychological, social, spiritual, behavioral, and medical conditioning) that will enable our warriors to enhance and sustain their physical and mental performance under any environmental conditions, will provide resilience to resist injury and illness and will enhance recovery for the injured and ill. The result is Total Force Fitness: Warriors “optimized” to carry out their mission as safely and effectively as possible.

FEATURED UPDATES

Strategies to impact your well-being: Week #4

A recent study examined eight different strategies for processing emotions and how they were linked to positive emotions and life satisfaction.
The extreme demands of military performance often require that a Warrior's diet be supplemented with vitamins, minerals, and the like. Making an informed decision about using dietary supplements can be difficult, and a bad decision could adversely affect health.

HPRC provides research-backed information to help users make good decisions about supplements. We provide a portal to the Natural Medicines Comprehensive Database for proven information on supplements and natural medicines. We also provide alerts of recalls, market withdrawals, and safety bulletins, plus links to additional reliable information on supplements.

Dietary Supplements Resources

- **Questions from the Field**
  Articles researched and written by HPRC on topics you asked about.

- **Supplement Alerts**
  Alerts on dietary supplements to keep you informed on recalls, market withdrawals, and safety alerts.

- **Natural Medicines Comprehensive Database**
  Many warriors use supplements to improve their health and performance, but getting good information isn’t always easy. Check out resources from our partners at the Natural Medicines Comprehensive Database.

- **Dietary Supplements Classification System**

**DIETARY SUPPLEMENTS NEWS**

- **FDA warning: “Black Ant” drug content could be dangerous**
  The FDA found an ingredient in this sexual enhancement supplement that could have dangerous interactions with some prescription drugs.

- **Tainted dietary supplements: How do you know?**
  Dietary supplements do not require approval by the FDA, so how can you know if the supplement you are considering is tainted? Read on for warning signs and new actions by the FDA that can help.
Many warfighters use supplements to improve their health and performance, but getting good information isn’t always easy. Check out resources from our partners at the Natural Medicines Comprehensive Database.

The Natural Medicines Comprehensive Database provides scientifically reliable answers to questions about dietary supplements and alternative therapies. Updated daily, the Database has information on supplements' safety, benefits, side effects, drug interactions and more.
Dietary Supplements Classification System

Make informed decisions about supplements with the Dietary Supplement Risk Table.

Dietary Supplements Classification System—Risks and Benefits

Before using any dietary supplement, a Warfighter—or anyone—should ask: "What are the potential benefits?" and "What are the risks associated?" And finally, "Are the potential benefits worth the risks?" This Dietary Supplement Risk Table was developed to assist healthy military personnel in making informed decisions about supplements. Benefits were ranked on a scale of low, moderate, or high potential benefit. Safety concern was similarly ranked on a scale of minimal, low, moderate, or high concern.

<table>
<thead>
<tr>
<th>Potential Benefit</th>
<th>Safety Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimal</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Low</td>
<td>5</td>
</tr>
</tbody>
</table>

Disclaimer: This table includes consideration of the safety and potential benefits of dietary supplements based on use at appropriate doses and availability of current data in the literature. The matrix is meant to be informative and not prescriptive. For individual guidance, consult with a designated health professional for your respective service or specific organization.

Scores of 1-3 are in the "green zone," 4-8 in the "yellow zone," and 9-12 in the "red zone."
# Supplements

<table>
<thead>
<tr>
<th>Green Zone</th>
<th>Yellow Zone</th>
<th>Red Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidants</td>
<td>Beta-Alanine (B-Alanine)</td>
<td>Ephedra</td>
</tr>
<tr>
<td>Branched-Chain Amino Acids</td>
<td>*Caffeine</td>
<td>Melatonin (for flight personnel)</td>
</tr>
<tr>
<td>Fish Oil/Omega-3 Fatty Acids</td>
<td>Carnitine</td>
<td>Nitric Oxide (NO) Products</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Chromium picolinate</td>
<td>Synephrine (Bitter Orange)</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Coenzyme Q10</td>
<td>Testosterone Precursors/Boosters and Anabolic Compounds</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>Creatine</td>
<td>Weight-loss Supplements</td>
</tr>
<tr>
<td>Vitamin B Complex</td>
<td>Glutamine</td>
<td></td>
</tr>
<tr>
<td>Multivitamins &amp; Minerals</td>
<td>Megavitamins &amp; Minerals</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quercetin</td>
<td></td>
</tr>
</tbody>
</table>

## Food-based Products

<table>
<thead>
<tr>
<th>Sports Bars</th>
<th>Protein Powder (including whey)</th>
<th>**Energy Boosters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sports Drinks</td>
<td>*Energy Drinks</td>
<td></td>
</tr>
<tr>
<td>Sports Gels</td>
<td>**</td>
<td></td>
</tr>
</tbody>
</table>

*Excessive consumption is potentially dangerous and could lead to side effects and/or adverse reactions.

**Insufficient evidence to support a recommendation for use.

**Note: Supplements in bold appear in more than one zone.**
OPSS: Operation Supplement Safety

You could be putting yourself at risk every day in a way that might surprise you—by using dietary supplements. Some dietary supplements, including ones sold on military installations, may contain problematic and potentially harmful ingredients.

OPSS: Operation Supplement Safety is a joint initiative between the Human Performance Resource Center and the DoD to educate warrior athletes and consumers about the risks associated with dietary supplement use and how to choose supplements wisely.

Operation Supplement Safety—What's the scoop on supplement safety?

Dietary supplement use among military service members is high. HPRC's Operation Supplement Safety outlines what you can do to determine if a dietary supplement product is relatively safe or not.

Resources
Organizations
Databases
General Information
Publications
Operation Supplement Safety (OPSS) Resources
Publications and databases for detailed dietary supplements information
RIPPED or RIPPED OFF?

YOU WANT RESULTS, BUT AT WHAT COST?

NOT ALL SUPPLEMENTS ARE WHAT THEY CLAIM.

Worse, some supplements contain undisclosed ingredients that may be illegal and/or potentially dangerous.

CHOOSE “CLEAN” SUPPLEMENTS ONLY.

Products with a seal from an independent organization such as USP or NSF have been evaluated for authenticity and safety.

www.hprc-online.org/dietary-supplements/OPSS

OPERATION SUPPLEMENT SAFETY

Know the red flags. Know the risks. Know the reputable sources.

www.hprc-online.org/dietary-supplements/OPSS

iPhone Apps

Natural Medicines Comprehensive Medical
Updated Apr 26, 2012
FREE

iPad Apps

Natural Medicines Comprehensive Medical
Updated Apr 26, 2012
FREE

Warfighter App to come!