Systematic review of the potential adverse effects of caffeine consumption in healthy adults, pregnant women, adolescents, and children:

Behavior Outcome

DR. HARRIS LIEBERMAN
MILITARY NUTRITION DIVISION, US ARMY RESEARCH INSTITUTE OF ENVIRONMENTAL MEDICINE
AND
DR. CHARLES O’BRIEN
DEPARTMENT OF PSYCHIATRY, UNIVERSITY OF PENNSYLVANIA
Disclosure

Harris Lieberman:

Member of the ILSI North America Caffeine Systematic Review Team (uncompensated)

Government Liaison ILSI North America Caffeine Working Group (uncompensated)

The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or reflecting the views of the Army or the Department of Defense. Any citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement of approval of the products or services of these organizations. In the conduct of research involving human subjects, the investigators adhered to the policies for protection of human subjects as prescribed by DOD Instruction 3216.02, and the research was conducted in adherence with the provisions of 32 CFR Part 219.

Charles O’Brien:

Member of the ILSI North America Caffeine Systematic Review Team

ILSI North America provided an honorarium and travel to attend this meeting.
Population, Exposure, Comparator, Outcome (PECO) Questions for the Behavior Outcome

For [population], is caffeine intake above [dose], compared to intakes [dose] or less, associated with adverse effects on behavior health outcomes?

Example: For healthy adults, is caffeine intake above 400 mg/day, compared to intakes of 400 mg/day or less, associated with adverse effects on behavior health outcomes?

<table>
<thead>
<tr>
<th>Population</th>
<th>Healthy Adults</th>
<th>Healthy Pregnant Women</th>
<th>Healthy Adolescents</th>
<th>Healthy Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>&gt; 400 mg/day</td>
<td>&gt; 300 mg/day</td>
<td>&gt; 2.5 mg/kg-day</td>
<td>&gt; 2.5 mg/kg-day</td>
</tr>
<tr>
<td>Comparator</td>
<td>≤ 400 mg/day</td>
<td>≤ 300 mg/day</td>
<td>≤ 2.5 mg/kg-day</td>
<td>≤ 2.5 mg/kg-day</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td>Adverse behavioral effects</td>
</tr>
</tbody>
</table>
## Characterization of Data for Behavior Outcome

<table>
<thead>
<tr>
<th>Data Type</th>
<th>Characterization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>81 included; 123 excluded (no quantitative value of caffeine – “association studies”; other exclusionary criteria such as unhealthy study population or no data on adverse effects)</td>
</tr>
<tr>
<td>Study types</td>
<td>Randomized controlled trials; some cross-sectional and cohort studies; a single case-control study</td>
</tr>
<tr>
<td>Populations</td>
<td>Adults, adolescents, children (no data available on pregnant women)</td>
</tr>
</tbody>
</table>
| Exposure           | • Primarily controlled exposure to some form of pure caffeine, though some provided measured doses of coffee, energy drinks or another source  
  • Others quantified dietary intake (e.g., food frequency questionnaires) – coffee, soda, tea, chocolate  
  • ~2/3 specifically evaluated caffeine  
  • Categorical groupings (e.g., <1 cup/day, >3 cups/day) or specific quantification                                                                                                                                                                                                 |
| Outcome (Endpoints)| • Adverse Mood States (Anxiety, Anger and Confusion, Depression); Sleep (Objective and Subjective measures); Withdrawal; Headache; Risk-taking                                                                                                                                                                                                 |
Behavior End Points (All Potentially Adverse)

• Mood – Adults
  o Increased anxiety
  o Increased anger
  o Increased confusion
  o Increased depression

• Mood – Children and Adolescents

• Headache – Adults

• Headache – Children and Adolescents
Behavior End Points – All Potentially Adverse (cont’d)

• Sleep – Adults
  o Subjective (self-report questionnaires) – increased fatigue, drowsiness
  o Objective – decreased sleep duration and/or quality assessed by polysomnography (EEG) or wrist activity monitoring

• Sleep – Children and Adolescents

• Problematic and Risk-Taking Behavior – Adults
  o Substance abuse
  o Smoking
  o Disorderly behavior
  o Risk-taking

• Problematic and Risk-Taking Behavior – Children
Through a Different Lens Other than “Safety and Toxicology”

• Caffeine is frequently consumed for its behavioral effects
  o Increased alertness
  o Decreased sleepiness

• European Food Safety Authority (EFSA) Panel concluded consumption of caffeine increased alertness and attention in doses of at least 75 mg caffeine in the general adult population.
The Behavioral Data

• 81 studies included after eliminating 123 (only 5 on children and adolescents, none on pregnant women)
  o Only 6 were dose-response studies
  o 19 used doses of 400 mg or above (the comparator for adults)

• Most **not** conducted for studying ‘adverse events’ *per se*

• Many were conducted to test behavioral hypotheses
  o Does caffeine in moderate doses found in foods increase alertness?
  o Does caffeine given before bedtime interfere with sleep?
Results

• Mood – Adults
  o Anxiety
    • Findings across studies very variable, over ½ below 400 mg were negative
    • Concluded: caffeine can produce a small increase in anxiety above and below 400 mg/day
    • For future research, dose-response studies should be conducted
  o Anger and Confusion
    • Generally no effects below or above comparator
  o Depression
    • No negative effects below or above comparator

• Mood – Children and Adolescents
  o Insufficient data overall – two studies available are both negative
Results (cont’d)

• Headache – Adults
  o Difficult, complex area; some studies suggest:
    • Caffeine withdrawal can sometimes cause headache
    • Caffeine administration during withdrawal can mitigate headache
  o Conclusion based on 15 studies – caffeine doses below 400 mg comparator are not associated with headache

• Headache – Children and Adolescents
  o Insufficient evidence
Results (cont’d)

• Sleep – Adults
  o “Subjective” effects on alertness, fatigue
    • No adverse effects below comparator (a decrease in fatigue)
    • At very high doses (1200 mg/day) increase in fatigue due to disruption of sleep
  o Objective measures of sleep with polysomnography (EEG) or wrist activity monitor (a decrease in sleep duration/quality)
    • Caffeine administration above or below 400 mg comparator can disrupt sleep especially when given later in the day

• Sleep – Children and Adolescents
  o Insufficient data

• Problematic and Risk-Taking Behavior (substance abuse, etc.)
  o Insufficient data – adults and children
Evaluation of Individual Study Quality (Risk of Bias)

Overall “probably low” risk of bias for studies in adults; few qualified studies in children and adolescents which were generally of lower quality.

Limited by exposure characterization (Q8, Q11) and Outcome Assessment (Q9).
Behavior: Weight of Evidence (WoE)

Conclusion

• Adults: When the weight of evidence was considered, with particular emphasis on level of adversity, 400 mg caffeine/day was found to be an acceptable intake that is not associated with significant concern regarding adverse behavioral effects.
  ◦ There were some adverse noted effects below the comparator:
    • Anxiety and sleep may be affected below the comparator depending on dose, time of administration, history of caffeine intake, genetics, etc.

• There is moderate to high level of confidence in the body of evidence supporting this conclusion

• Children and adolescents: the evidence base was insufficient to develop a conclusion

• No data on pregnant women
Anxiety (Adults)

• The evidence demonstrates that caffeine has adverse effects on anxiety both above and below the comparator of 400 mg caffeine/day in healthy adult populations
  ◦ At intakes above the comparator, up to 1200mg/day, reported adverse effects are more consistent
• Studies reporting effects that were often
  ◦ Low in magnitude
  ◦ Only in sensitive sub-populations (ADOR2A polymorphisms)
• Moderate level of confidence in the body of evidence
Sleep (Adults)

- Evidence supports that 400 mg caffeine/day in healthy adult populations is an acceptable intake that is not associated with significant concern regarding subjective measures of sleep
  - Most studies indicate that caffeine improves measures of fatigue
  - One study at the high end (1200 mg/day for 7 days) observed adverse effects related to cumulative loss of sleep
- Evidence suggests that 400 mg caffeine/day in healthy adult populations is associated with adverse effects on objective measures of sleep
  - Most studies indicate that timing of the dose is important and that sleep disruption occurs most frequently when administered close to bedtime.
- High level of confidence in the evidence base
Behavior in Children and Adolescents

• Relatively little data available for each of the major behavioral endpoints
  ◦ Only one study provided data above the comparator

• No major adverse effects seen in children or adolescents at doses near or less than 2.5 mg/kg

• Many non-quantitative (i.e. association studies) available in the literature could not be used

• Few studies available to effectively evaluate the comparator of 2.5 mg/kg/day in this population

• Lower quality evidence base due to issues with study design, indirectness and reverse causation

• More research is required, particularly in the key areas of sleep and risk-taking behavior
Clinical Considerations in Weigh-of-Evidence (WoE) Conclusions

Relationship of caffeine to anxiety disorders, caffeine and addiction, caffeine withdrawal.

Caffeine and sleep disorders.

Caffeine and children (strongly need more studies).

Caffeine and cardiac disease, hypertension.

Effects of caffeine on performance, cognitive, motor, at what dose?
Anxiety (Adults)

- The evidence demonstrates that caffeine has adverse effects on anxiety both above and below the comparator of 400 mg caffeine/day in healthy adult populations
  - At intakes above the comparator, up to 1200mg/day, reported adverse effects are more consistent

- Studies reporting effects that were often
  - Low in magnitude
  - Only in sensitive sub-populations (ADOR2A polymorphisms)

- Moderate level of confidence in the body of evidence
Sleep (Adults)

- Evidence supports that 400 mg caffeine/day in healthy adult populations is an acceptable intake that is not associated with significant concern regarding subjective measures of sleep
  - Most studies indicate that caffeine improves measures of fatigue
  - One study at the high end (1200 mg/day for 7 days) observed adverse effects related to cumulative loss of sleep

- Evidence suggests that 400 mg caffeine/day in healthy adult populations is associated with adverse effects on objective measures of sleep
  - Most studies indicate that timing of the dose is important and that sleep disruption occurs most frequently when administered close to bedtime.

- High level of confidence in the evidence base
Future Research Needs

More research necessary on children and adolescents; particularly with regards to caffeine’s effects on sleep and risk-taking behavior.

More consideration for/or better understanding of the effects of caffeine withdrawal on these endpoints.

No data available on pregnant women.

Better understanding of the effects of caffeine on anxiety and sleep in sensitive subpopulations, individuals with polymorphisms (e.g. ADORA2A).