Addictive Properties of Caffeine

Roland R. Griffiths, Ph.D.
Departments of Psychiatry and Neuroscience
Johns Hopkins University School of Medicine
Caffeine

- Subjective Effects
- Reinforcing Effects (i.e. caffeine self-administration)
- Tolerance
- Physical Dependence (i.e. withdrawal)
- Addiction (i.e. DSM-5 Substance Dependence Syndrome)
Caffeine Subjective Effects

• Drug-induced changes in an individual’s experience or feelings

• Numerous studies show that the qualitative subjective effects of caffeine are dose-dependent
Lower doses (20-200 mg) produce predominantly positive subjective effects

- Increased
  -- well-being/happiness
  -- energy/active
  -- alertness/concentration
  -- desire to socialize
  -- motivation for work
High dietary doses (300-500 mg) produce predominately “dysphoric” subjective effects

- Increased -- anxiety
  -- nervousness
  -- jittery
  -- shaky
  -- bad effects
Caffeine

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Self-Injection of Caffeine in Baboons

![Graph showing self-injection of caffeine in baboons]
Circumstantial Evidence for Reinforcing Effects of Caffeine

1. Regular daily consumption at pharmacologically-active doses is widespread

2. Historically, caffeine consumption has been long-term, relatively stable, and resistant to suppression

3. Consumption occurs in widely different vehicles (e.g. coffee, tea, mate, soft drinks, energy drinks; chewing kola nuts)

4. Consumption occurs in widely varying cultural and social contexts
Reinforcing Effects of Caffeine

- Caffeine can function as a reinforcer when administered in capsules, coffee or soft drinks
- The range of conditions under which caffeine functions as a reinforcer is not as broad as with classic abused stimulants
- Caffeine reinforcement is an inverted U-shaped function of dose
- In normal subjects there are wide individual differences in susceptibility to caffeine reinforcement
- Avoidance of abstinence-associated withdrawal symptoms plays a central role in reinforcement among regular consumers. However, such a history is not necessary for demonstrating caffeine reinforcement.
Caffeine

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• Tolerance
• Physical Dependence (i.e. withdrawal)
• Addiction (i.e. DSM Substance Dependence Syndrome)
Caffeine Tolerance

• Tolerance is refers to reduced responsiveness due to drug exposure
  - Tolerance has been clearly demonstrated in both animals and humans
Complete Insurmountable Tolerance in Rats
Complete tolerance in humans (300 mg challenge; 900 mg/day)
Caffeine

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Caffeine Withdrawal

• Time-limited disruption of mood or behavior after cessation of chronic dosing
Caffeine withdrawal in rats
Time-course of caffeine withdrawal in humans

- **Headache**
- **Lethargy / Fatigue / Tired / Sluggish**
- **Able to Concentrate**
Caffeine
Placebo

Placebo

330
340
350
360
370
380

Base line
Tapping

Trials
Number Per Minute

1 2 3

Tapping

- Base line
- Caffeine
- Placebo

Number Per Minute

330
340
350
360
370
380

Trials
Unauthorized Medication Use

Placebo

Caffeine
Headache - the most commonly reported symptom

• In experimental studies, 50% of individuals report headache

• Although headache is common, withdrawal symptoms without headache also occur
Symptom Clusters in Caffeine Withdrawal

- Headache
- Fatigue or drowsiness
- Dysphoric mood, depressed mood, irritability
- Difficulty concentrating
- Flu-like somatic symptoms
  - nausea, vomiting, or muscle pain/stiffness
Incidence of clinically significant or functional impairment

- 13% in prospective experimental studies
- 9% in retrospective survey studies
Examples of functional impairment from volunteers in a double-blind caffeine withdrawal study

1. Missed work; emesis
2. Could not perform work responsibilities; needed spouse to care for children, went to bed early
3. Multiple costly mistakes at work, left work early, went to bed early
4. Cancelled son’s birthday party, called spouse home early because could not care for children
5. Screaming at his children
Parametric determinants of caffeine withdrawal

- Chronic caffeine maintenance dose (100-600 mg/day)
- Duration of caffeine maintenance (3-14 days)
- Within-day frequency of dosing during caffeine maintenance
  - once-a-day administration is sufficient
- Re-administration of caffeine reverses abstinence effects
  - rapid (30-60 minutes) and dose-dependently
Role of withdrawal in habitual use of caffeine

- Avoidance of abstinence-associated withdrawal symptoms plays a central role in the habitual consumption of caffeine
  - Studies show that withdrawal potentiates the reinforcing effects of caffeine
  - Studies also show that withdrawal plays an important role in the development of preferences for flavors paired with caffeine
Caffeine

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DSM Substance Dependence Syndrome on Caffeine

Eight studies showed that some people fulfill DSM-IV or 5 criteria for a diagnosis of Substance Dependence applied to caffeine

- Strain et al., 1994
- Hughes et al., 1998
- Bernstein et al., 2002
- Jones and Lejuez, 2005
- Svikis et al., 2005
- Ciapparelli et al., 2010
- Striley et al., 2011
- Juliano et al., 2012
PURPOSE

- to determine whether there are individuals who are sufficiently distressed by their caffeine use to seek outpatient treatment
- describe them demographically and psychiatrically, and characterize their problematic caffeine use
Method

• Adult caffeine users were recruited from the community using advertisements and invited to participate in a treatment program for Caffeine Dependence. Individuals with current drug dependence other than nicotine were excluded.

• A clinical psychologist assessed for Caffeine Dependence and other psychiatric disorders using structured interviews
Characteristics of the population (N=94)

A high-functioning, educated group of adults

- Mean Age -- 41 years
- 55% Female
- 86% College or Post-Graduate Education
- Mean caffeine use 548 mg/day
DSM-5 Criteria Fulfilled

- 89% Persistent desire or unsuccessful efforts to cut down or control substance use
  - 88% reported unsuccessful past attempts to quit. Some described short term success (e.g. 1-2 days to 2 weeks), but subsequently relapsed to higher use
DSM-5 Criteria Fulfilled

- 96% Characteristic withdrawal symptoms or use to relieve or avoid withdrawal symptoms
  - 43% reported functional impairment (severity sufficient to produce a impairment of normal activities such as being unable to work or sleeping at work)
DSM-5 Criteria Fulfilled

- 87% Continued use despite persistent or recurrent physical or psychological problems
  - 83% reported a physical problem. Examples include stomach problems, cardiovascular problems, pregnancy, sleep problems, urinary problems
  - 67% reported a psychological problem. Examples include anxiety, irritability, and anger problems
  - 43% had been told by a physician or other medical professional to modify caffeine use because of various medical conditions (e.g. pregnancy, headaches, etc.)
Conclusions: Caffeine Withdrawal and Addiction

- **Caffeine Withdrawal:**

  - Numerous studies (about 75). Indicate that cessation of caffeine consumption after a period of daily intake can result in a distressing withdrawal syndrome resulting in functional impairment. This conclusion is consistent with the DSM-5 committee recognition of Caffeine Withdrawal as a diagnosis. It is also consistent with a survey study of 500 addiction professionals the majority of whom endorsed that caffeine withdrawal can be of clinical importance (Budney et al., in press).
Conclusions: Caffeine Withdrawal and Addiction

- Caffeine Addiction:
  
  - Eight studies suggest that some people become clinically dependent on caffeine: unable to quit, continue to use despite medical problems, and are sufficiently distressed to seek treatment. This less well established effect is consistent with the DSM-5 committee recommendation that Caffeine Use Disorder be recommended as a diagnosis for further study. It is also consistent with a survey study of 500 addiction professionals the majority of whom endorsed that Caffeine Use Disorder occurs and some people could benefit from professional help for quitting (Budney et al., in press).
Tolerance: Implications for Youth as a Vulnerable Population

- Individuals who do not use caffeine regularly will be substantially more sensitive to caffeine acute effects including adverse effects. Most studies characterizing the adverse effects of caffeine (e.g. cardiovascular effects) have examined effects in habitual consumers. These are important studies to do, however, given that tolerance readily occurs, these studies are of little relevance to estimating the risk of adverse events in caffeine non-tolerant individuals.
Dose-Dependence: Implications for Youth as a Vulnerable Population

- Individuals who weigh less receive a proportionally greater dose of caffeine for a given serving size -- (a 13 year old boy weighs about 55% as much as a 50 year old man).
Conditioned Taste Preference and Addiction: Implications for Youth as a Vulnerable Population

It is well known that consumers often develop strong preferences for specific types and brands of caffeinated beverages (e.g. Coke vs. Pepsi). The likely mechanism behind this is that caffeine readily conditions preference for specific flavors. Initial favor preferences are likely to evolve into habitual brand preferences, perhaps lasting a lifetime. These facts will not be lost on those marketing energy drinks, and they may incentivize promotion of products to younger and younger populations -- much as the tobacco companies were accused of doing until the marketing of tobacco products was more tightly regulated.
Withdrawal and Addiction: Implications for Youth as a Vulnerable Population

- If physical dependence develops, youth are less likely than adults to have the financial and/or transportation resources to assure their uninterrupted supply of caffeine. If they are withdrawal-sensitive and their habitual pattern of intake is delayed or interrupted they will experience adverse emotional, cognitive, and behavioral consequences.
Added Caffeine and Public Policy

- In the 1950s, the FDA approved the use of adding caffeine to cola beverages (up to 200 ppm, about 70 mg/12 oz).

- In 1980 the FDA proposed to delete caffeine from cola-type beverages

- In response, the soft drink manufacturers justified adding caffeine to soft drinks on the basis that caffeine is a flavor enhancer. No claims were made for the behavioral or subjective effects of caffeine. In fact, representations to FDA and the public appeared to assiduously avoid even the suggestion that these added doses had such effects. Therefore, there were no advertising claims that caffeine-containing soft drinks were stimulants.
Added Caffeine and Public Policy

- That situation changed radically with the recent entry of energy drinks (starting in 1997 with Red Bull), whose advertising prominently promotes the psychomotor stimulant effects of caffeine.

- Furthermore, today’s advertisements are often targeted to youth (e.g., 13-year-olds), who we can expect to have increased sensitivity to caffeine because of their smaller body size, lack of tolerance.

- Significant unknowns include: 1. various chemical additives so prevalent in energy drinks, and 2. the effects on emotional and behavioral development.
Added Caffeine and Public Policy

- The total amount of caffeine and other ingredients should appear on the container

- Product label warnings about risks and guidance about use would seem appropriate, similar to the labeling required of caffeine marketed in over-the-counter stimulant products (e.g. NoDoz).

- Restrictions on advertising to children or young adolescents could be considered.
Some addiction professionals expressed concerns about inclusion in DSM for reasons such as it might trivialize other substance use disorders, might cause problems billing for disorders, only rare cases are clinically important
Caffeine Tolerance in Humans

• Complete tolerance to subjective, pressor, and neuroendocrine effects occurs when very high doses of caffeine are administered daily (e.g. >750 mg/day)

• Partial tolerance to the sleep disruptive effects of caffeine has been demonstrated

• However, at lower doses complete caffeine tolerance may not occur
- Tolerance:
  - Individuals who do not use caffeine regularly will be substantially more sensitive to caffeine acute effects including adverse effects.
  - Most studies characterizing the adverse effects of caffeine (e.g. cardiovascular effects) have looked at effects in habitual consumers. These are important studies to do, however, given that tolerance readily occurs, these studies are of little relevance to estimating the risk of adverse events in caffeine non-tolerant individuals.
Severity of DSM-5 Substance Use Disorder

- 59% fulfilled DSM-5 generic criteria for a severe Substance Use Disorder by endorsing
  - Persistent desire to cut down
  - Characteristic withdrawal symptoms
  - Continued use despite problems
  - Plus 3 or more additional diagnostic criteria
Added Caffeine and Public Policy

- The FDA is interested in an update of the adverse effects of caffeine, particularly in light of new caffeine-containing products (e.g. caffeinated energy drinks, gum, and other foods) that are being introduced to the market to potentially new populations (e.g., young adolescents).

- Earlier this year FDA issued a statement that the only time FDA explicitly approved the use of added caffeine was for cola drinks in the 1950s. That approval limited added caffeine to 200 ppm (about 70 mg/12 oz).
- That Consider how those muted claims compare with the direct appeal to psychomotor stimulant effects of caffeine so prominent in today’s advertising for energy drinks.

- Furthermore, today’s advertisements are often targeted to youth (e.g. 13 year olds), who we can expect to have increased sensitivity to caffeine because of their smaller body size, lack of tolerance, and possibly faster rate of consumption than coffee.

- Significant unknowns include: 1. various chemical additives so prevalent in energy drinks, and 2. the effects on emotional and behavioral development.
- In 1980 the FDA proposed to delete caffeine from cola-type beverages.

- The soft drink manufacturers justified adding caffeine to soft drinks on the basis that caffeine is a flavor enhancer. No claims were made for the behavioral or subjective effects of caffeine. In fact, representations to FDA and the public appeared to assiduously avoid even the suggestion that these added doses had such effects. Therefore, there were no advertising claims that caffeine-containing soft drinks were stimulants (other than perhaps that Coca-Cola was “refreshing” or the Dr. Pepper’s ad “Be a Pepper”).
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- Earlier this year FDA issued a statement that the only time FDA explicitly approved the use of added caffeine was for cola drinks in the 1950s. That approval limited added caffeine to 200 ppm (about 70 mg/12 oz).
Headache - the most commonly reported symptom

• In experimental studies, 50% of individuals report headache

• Phenomenologically described as gradual in development, diffuse, throbbing, severe, intensified with exercise and Valsalva maneuver, and distinct from migraine headache

• Although headache is common, withdrawal symptoms without headache also occur
Conclusion

• Caffeine, the world’s most widely used mood-altering drug, shares many behavioral-pharmacological features in common with classic drugs of abuse and provides an intriguing model system for understanding drug dependence processes.

• Caffeine intoxication, withdrawal, and dependence are problems, but their severity and social import pale in comparison to the life threatening health risks associated with classic drugs of abuse.

• Caffeine dependence is a useful, but almost completely unexplored clinical marker for vulnerability to dependence on other drugs of abuse. Because there is so little stigma attached to caffeine use, self-reports may be more accurate for caffeine dependence than for problematic use of other alcohol and other drugs.

• Whether caffeine use increases vulnerability to other drug use (e.g. cigarette smoking; non-medical use of stimulants) should also be a target of future research.
Conclusion

• As the world’s most widely used mood-altering drug, caffeine provides an intriguing model system for understanding drug dependence processes.

• Caffeine intoxication, withdrawal, and dependence are problems, but their severity and social import pale in comparison to the life threatening health risks associated with classic drugs of abuse.

• Caffeine dependence is a useful, but almost completely unexplored clinical and scientific marker for vulnerability to dependence on other drugs of abuse. Because there is so little stigma attached to caffeine use, self-reports may be more accurate for caffeine dependence than for problematic use of other alcohol and other drugs.

• Whether caffeine use increases vulnerability to other drug use (e.g., cigarette smoking; non-medical use of stimulants) should be a target of future research.
In conclusion, I hope that I have clearly demonstrated that caffeine has many features in common with classic abused drugs. However, caffeine is the most widely used mood altering drug in the world. As with everything in life, there are risks and benefits.
Chronic caffeine maintenance dose

**Headache**

- 100 mg: Rating 1.0 (no significant change)
- 300 mg: Rating 1.5 (* significant change)
- 600 mg: Rating 2.0 (* significant change)

**Tiredness**

- 100 mg: Rating 1.5 (* significant change)
- 300 mg: Rating 2.0 (* significant change)
- 600 mg: Rating 2.5 (* significant change)
Duration of caffeine maintenance

**Headache**

- Duration of Caffeine Exposure (# days)
- Rating

**Tiredness**

- Duration of Caffeine Exposure (# days)
- Rating
Individual differences in caffeine withdrawal

- There are differences within and across individuals with respect to the incidence of caffeine withdrawal
  - 50% of individuals experience headache; 13% have clinically significant symptoms
Individual differences in caffeine withdrawal

- There are differences within and across individuals with respect to the incidence of caffeine withdrawal
- Genetic factors may play a role
  - Female twin study show greater concordance of DSM-IV defined caffeine withdrawal among monozygotic (41%) than dizygotic (18%) twins -- heritability of 35%
Mechanisms underlying caffeine withdrawal

- Caffeine is a potent, selective, competitive antagonist of adenosine, an endogenous neuromodulator

- Chronic caffeine has been reported to
  - Increase the number of brain adenosine receptors
  - Shift brain A1 adenosine receptors into a high affinity state
  - Increase functional sensitivity to adenosine

- Increased functional sensitivity to adenosine may be the mechanism of caffeine withdrawal
  - Adenosine dilates cerebral vasculature - a possible mechanism of withdrawal headache
  - Centrally, adenosine decreases locomotor activity and operant behavior, which may be related to symptoms of fatigue and drowsiness in withdrawal
DSM-5 Criteria Fulfilled

- 70% Tolerance -- a need for markedly increased amounts to achieve desired effects or markedly diminished effect with continued use