

CAFFEINE DEPENDENCE

USE AND COMMON SOURCES OF CAFFEINE

Caffeine is the most commonly used mood-altering drug in the world. Caffeine is found in numerous plants, the most widely consumed being coffee, tea, cola nut, cacao pod, guarana, and maté. It is estimated that in North America between 80 and 90 percent of adults and children habitually consume caffeine. About 15% of the general population report having stopped caffeine use completely, citing concern about health and unpleasant side effects.

In the United States the average per capita daily intake among adult caffeine consumers is 280 milligrams (the equivalent of 17 ounces of brewed coffee or 84 ounces of soft drink). Studies show that 30 milligrams or less of caffeine can alter self-reports of mood and affect behavior and 100 mg per day can lead to physical dependence and withdrawal symptoms upon abstinence.

Coffee is the leading dietary source of caffeine among adults in the United States, while soft drinks represent the largest source of caffeine for children. Caffeine consumption from soft drinks has dramatically increased over the last few decades and 70% of all soft drinks contain caffeine.

The table below shows the range of caffeine contents from common foods and medications as well as estimated "typical" caffeine contents. Of the three major dietary sources of caffeine, servings of tea and soft drinks usually contain about one-half to one-third the amount of caffeine in a serving of coffee.

Although most people are aware that coffee, tea and most cola beverages contain caffeine, there several sources of caffeine about which there is less awareness. In the United States, about 70% of all soft drinks consumed contain caffeine. A number of non-cola drinks such as root beer, orange soda, cream soda, and lemon-lime drinks contain caffeine in amounts similar to those in the cola drinks. Some, but not all, coffee ice creams and yogurts deliver a significant dose of caffeine. Although chocolate milk, cocoa, and milk chocolate candy also contain caffeine, the dose delivered in a usual serving is generally below the threshold for readily detectable mood and behavioral effects (<10 mg). The one exception is that a serving of dark chocolate candy may contain about 30 mg of caffeine.

Medicinal products also often contain significant amounts of caffeine. Over-the-counter stimulant medications such as NoDoz and Vivarin contain between 100-200 milligrams per tablet, while caffeine-containing analgesics such as Anacin, Excedrin, and Midol deliver 64 to 130 milligrams per two tablet dose.

Typical Caffeine Content of Common Foods and Medications

| Substance | Serving Size | Caffeine Content | Caffeine Content |
|---------------|--------------------|------------------|------------------|
| | (volume or weight) | (range) | (typical) |
| Coffee | | | |
| Brewed/Drip | 6 oz | 77-150 mg | 100 mg |

| | | | |
|---|--------------|-----------|---------------|
| Instant | 6 oz | 20-130 mg | 70 mg |
| Espresso | 1 oz | 30-50 mg | 40 mg |
| Decaffeinated | 6 oz | 2-9 mg | 4 mg |
| Tea | | | |
| Brewed | 6 oz | 30-90 mg | 40 mg |
| Instant | 6 oz | 10-35 mg | 30 mg |
| Canned or Bottled | 12 oz | 8-32 mg | 20 mg |
| Caffeinated Soft Drinks | 12 oz | 22-71 mg | 40 mg |
| Caffeinated Water | 16.9 oz | 50-125 mg | 100 mg |
| Cocoa/Hot Chocolate | 6 oz | 2-10 mg | 7 mg |
| Chocolate Milk | 6 oz | 2-7 mg | 4 mg |
| Coffee Ice Cream or Yogurt | 1 cup (8 oz) | 8-85 mg | 50 mg |
| Chocolate Bar | | | |
| Milk Chocolate | 1.5 oz | 2-10 mg | 10 mg |
| Dark Chocolate | 1.5 oz | 5-35 mg | 30 mg |
| Caffeinated Gum | 1 stick | 50 mg | 50 mg |
| Caffeine-Containing OTC Products | | | |
| Analgesics | 2 tablets | 64-130 mg | 64 or 130 mg |
| Stimulants | 1 tablet | 75-350 mg | 100 or 200 mg |
| Weight-loss products | 2-3 tablets | 80-200 mg | 80-200 mg |
| Sports Nutrition | 2 tablets | 200 mg | 200 mg |

As shown in the table above, it can be difficult for a person to accurately estimate his/her caffeine consumption because of the wide differences in the amount of caffeine delivered in common foods as well as large differences in common serving sizes. For instance, the amount of caffeine in a serving of coffee can vary over a 10-fold range, from as little as 20 mg for a small 5 oz cup of instant coffee to 300 mg for a large 12 oz. cup of strong drip coffee. A similar 10-fold variation can occur with soft drinks, with a small glass of one of the weaker cola drinks containing as little as 12 mg of caffeine in contrast to about 120 mg from a 20 oz bottle one of the stronger colas.

CAFFEINE AND HEALTH

Caffeine use can be associated with several distinct psychiatric syndromes: caffeine intoxication, caffeine withdrawal, caffeine dependence, caffeine-induced sleep disorder, and caffeine-induced anxiety disorder. Studies have not proven that caffeine produces significant life-threatening health risks such as cancer, heart disease, and human reproduction abnormalities. Nevertheless, individuals with various conditions such as generalized anxiety disorder, panic disorder, primary insomnia, gastroesophageal reflux, pregnancy and urinary incontinence are often advised to reduce or eliminate regular caffeine use. With

regard to cardiovascular health, caffeine produces modest increases in blood pressure and studies have established that unfiltered caffeinated and decaffeinated coffee (including espresso and French Press) contain lipids which raise serum cholesterol. In addition, concerns have been raised about a role of caffeine in cardiovascular disease. Finally, studies suggest that there may be an association between high daily caffeine consumption and delayed conception and lower birth weight.

MOOD ALTERING AND REINFORCING EFFECTS OF CAFFEINE

Mood Altering Effects: The mood altering effects of caffeine depend on the amount of caffeine consumed and whether the individual is physically dependent on or tolerant to caffeine. In caffeine non-users or intermittent users, low dietary doses of caffeine (20-200 mg) generally produce positive mood effects such as increased well-being, happiness, energetic arousal, alertness, and sociability. Among daily caffeine consumers, much of the positive mood effect experienced with consumption of caffeine in the morning after overnight abstinence is due to suppression of a low grade withdrawal symptoms such as sleepiness and lethargy (see section on Caffeine Withdrawal). Large caffeine doses (200 mg or greater) may produce negative mood effects. Although generally mild and brief, these effects include increased anxiety, nervousness, jitteriness, and upset stomach. However, individual differences in sensitivity and tolerance affect the severity and likelihood of experiencing negative effects.

Reinforcing Effects: Drug reinforcement refers to the ability of a drug to sustain regular self-administration (i.e. drug-taking). As the most widely consumed mood altering drug in the world, it is clear that caffeine is a reinforcer. Furthermore, historical efforts to restrict or eliminate use of caffeine containing foods in various cultures have invariably met with failure. Contemporary research has shown that caffeine functions as a reinforcer when it is delivered in coffee, soft drinks, tea, or capsules. For regular caffeine users, the avoidance of low grade withdrawal symptoms, such as drowsiness after overnight abstinence, has been identified as a central mechanism underlying the reinforcing effects of caffeine.

ANXIETY AND CAFFEINE

Studies have shown that high dietary doses of caffeine (200 mg or more) increase anxiety ratings and induce panic attacks in the general population. Individuals with panic and anxiety disorders are especially sensitive to the effects of caffeine. Although highly anxious individuals tend to be more likely to limit their caffeine use, not all individuals with anxiety problems naturally avoid caffeine, and some may fail to recognize the role that caffeine is playing in their anxiety symptoms.

SLEEP AND CAFFEINE

Studies have demonstrated that caffeine disrupts sleep. When caffeine is consumed immediately before bedtime or continuously throughout the day, sleep onset may be delayed, total sleep time reduced, normal stages of sleep altered, and the quality of sleep decreased. Because of its ability to cause insomnia, sleep researchers have used caffeine as a challenge agent in order to study insomnia in healthy volunteers. Caffeine's effects on sleep appear to be determined by a variety of factors including dose, the time between caffeine ingestion and attempted sleep, and individual differences in sensitivity and/or tolerance to caffeine. The effects of caffeine on sleep are dose-dependent with higher doses showing greater disruption on a number of sleep quality measures. Caffeine administered immediately prior to bedtime or throughout the day has been shown to delay sleep onset, reduce total sleep time, alter the normal stages of sleep, and decrease the reported quality of sleep. There is some evidence to suggest that caffeine taken early in the day also negatively affects nighttime sleep. Caffeine-induced sleep disturbance is greatest among individuals who are not regular caffeine users. Although there is evidence for some tolerance to the sleep disrupting effects of caffeine, complete tolerance may not occur and thus habitual caffeine consumers are still vulnerable to caffeine-induced sleep problems.

CAFFEINE TOLERANCE

Tolerance refers to a decrease in responsiveness to a drug after repeated drug exposure. High doses of caffeine (750 to 1200 mg/day spread throughout the day) administered daily, have been shown to produce "complete" tolerance (i.e., caffeine effects are no longer different from baseline or placebo) to some, but not all of the effects of caffeine. However, lower or typical dietary doses of caffeine produce incomplete tolerance. For example, sleep may continue to be disrupted in regular caffeine users.

CAFFEINE WITHDRAWAL

The caffeine withdrawal syndrome has been well-characterized in numerous rigorous double-blind studies. The potential for caffeine withdrawal to cause clinically significant distress or impairment in functioning is reflected by the inclusion of caffeine withdrawal as an official diagnosis in ICD-10 (World Health Organization) and as a proposed diagnosis in DSM-IV (American Psychiatric Association). Although most research on withdrawal has been performed with adults, there is also evidence that children experience withdrawal effects during caffeine abstinence.

Signs and symptoms. The most commonly reported withdrawal symptoms are listed below:

- **Headache** – (often described as being gradual in development and diffuse, and sometimes throbbing and severe)
- **Fatigue** -- (e.g., fatigue, tiredness, lethargy, sluggishness)
- **Sleepiness/drowsiness** -- (e.g., sleepy, drowsy, yawning)
- **Difficulty concentrating** -- (e.g., muzzy)
- **Work difficulty** -- (e.g., decreased motivation for tasks/work)
- **Irritability** -- (e.g., irritable, cross, miserable, decreased well-being/contentedness)
- **Depression** -- (e.g., depressed mood)
- **Anxiety** -- (e.g., anxious, nervous)
- **Flu-like symptoms** -- (e.g., nausea/vomiting, muscle aches/stiffness, hot and cold spells, heavy feelings in arms or legs)
- **Impairment in psychomotor, vigilance and cognitive performances**

Dosing parameters. The incidence and severity of caffeine withdrawal is an increasing function of daily self-reported caffeine dose. Significant caffeine withdrawal has been shown to occur after abstinence from a dose as low as 100 mg/day, which is the caffeine equivalent of one 6 oz. cup of brewed coffee or two to three 12 oz. servings of caffeinated soft-drink. Caffeine withdrawal has also been shown to occur after stopping regular once-a-day consumption of caffeine (e.g. daily consumption of a single cup of coffee).

Incidence of caffeine withdrawal. Blind experimental studies in healthy normal caffeine consumers who abstain for „ 24 hours indicate that the incidence of withdrawal headache is about 50%. When all withdrawal symptoms are considered, the incidence of caffeine withdrawal is higher. In a population-based random digit dial telephone survey study, 40 to 70% of individuals who tried to quit caffeine use reported experiencing withdrawal symptoms.

Many caffeine consumers may be unaware of their physical dependence on caffeine because their frequent habitual consumption precludes a period of sustained abstinence (e.g. 2 days). Furthermore, relatively low doses of caffeine (e.g. as little as 25 mg) can partially suppress withdrawal symptoms. Thus, some people may report never experiencing withdrawal because they unknowingly consumed small amounts of caffeine on days they thought they had been caffeine free. Finally, caffeine withdrawal symptoms (e.g., headache, nausea, muscle aches) may be misattributed to other causes or ailments (e.g., viral infection).

Severity of caffeine withdrawal. When signs or symptoms of caffeine withdrawal occur, the severity can vary from mild to extreme. At its worst, caffeine withdrawal has been repeatedly documented to produce clinically significant distress or impairment in daily functioning and, on rare occasions, to be totally incapacitating. For example, in a double-blind caffeine-withdrawal evaluation, 73% of individuals who met criteria for DSM-IV substance dependence on caffeine reported functional impairment in normal activities

during an experimental withdrawal phase. The table below gives some examples of the types of functional impairments experienced during caffeine withdrawal. The proportion of regular caffeine consumers who are at risk for experiencing such functional impairment during caffeine withdrawal is difficult to estimate. In one double-blind study with individuals from the general community, 52% of individuals from the general community with an average caffeine intake of 260 mg/day reported moderate to severe headache, and 8-11% showed abnormally high scores on standardized depression, anxiety and fatigue scales. In another double-blind study, 45% of individuals experienced a diffuse, throbbing headache, with almost a third also reporting nausea and sickness.

Individual differences in caffeine withdrawal. There are substantial differences within and across individuals with regard to incidence and/or severity of caffeine withdrawal. As discussed above, only about 50% of regular caffeine consumers report headache after any single episode of caffeine abstinence. One study that examined repeated abstinence trials clearly showed differences within and across subjects: one individual never showed caffeine withdrawal headache, some showed consistent headaches, while others reported headaches on some trials but not other trials. Little is known about the determinants of these differences within and across individuals.

Time course of caffeine withdrawal. The caffeine withdrawal syndrome follows an orderly time course. Onset usually occurs 12 to 24 hours after terminating caffeine intake, although onset as late as 36 hours has been documented. Peak withdrawal intensity has generally been described as occurring 20 to 48 hours after abstinence. The duration of withdrawal has most often been described as ranging between 2 days and 1 week, although longer durations have been occasionally noted.

Examples of functional impairment observed during a double-blind caffeine withdrawal trial in eleven individuals who fulfilled DSM-IV criteria for substance dependence on caffeine.

| Subject | Primary Vehicle | Caffeine Intake (mg/day) | Functional Impairment |
|---------|-----------------|--------------------------|--|
| 1 | Soft drink | 231 | Missed work; emesis |
| 2 | Soft drink | 270 | Failure to complete daily responsibilities, e.g., stopped doing errands, didn't make child's lunch, did not exercise |
| 3 | Coffee | 295 | None |
| 4 | Soft drink | 302 | Unable to complete schoolwork |
| 5 | Soft drink | 342 | Couldn't perform work responsibilities; needed spouse to care for children, went to bed early |
| 6 | Soft drink | 371 | Data entry errors at work, went to bed early, unable to do normal recreational reading |
| 7 | Soft drink | 430 | Cancelled son's birthday party, called spouse home early because could not care for children |
| 8 | Coffee | 516 | None |
| 9 | Coffee | 642 | None |
| 10 | Coffee | 1029 | Multiple costly mistakes at work, manufacturing wrong lenses for glasses, left work early, went to bed early |
| 11 | Coffee | 2548 | Screaming at his children |

CAFFEINE ADDICTION (i.e. CAFFEINE DEPENDENCE)

Although caffeine does not produce with life-threatening health risks commonly associated with the use of classic drugs of addiction such as cocaine, heroin and nicotine, some caffeine users report becoming "addicted" to caffeine in the sense that they report an inability to quit or to cut down their caffeine use, they continue to use caffeine despite having medical or psychological problems made worse by caffeine, and they continue to use caffeine to avoid experiencing caffeine withdrawal symptoms.

Caffeine dependence (ICD-10 diagnosis and DSM-IV criteria for substance dependence applied to caffeine). Substance dependence is characterized by a cluster of cognitive, behavioral and physiological symptoms indicating that the individual continues use of the substance despite significant substance-related problems (American Psychiatric Association). The clinical diagnosis of substance dependence encompasses several features which may or may not include physical dependence (i.e., withdrawal). The World Health Organization (ICD-10) recognizes a diagnosis of substance dependence due to caffeine. Despite the fact that DSM-IV uses very similar criteria for making a diagnosis of substance dependence, caffeine dependence is not presently included in DSM-IV. The rationale presented for excluding substance dependence on caffeine as a DSM-IV diagnosis was that although it had been established that caffeine produces physical dependence, there was insufficient information pertaining to other features of dependence such as such as inability to stop use and use despite harm.

Since the publication of DSM-IV in 1994, four published studies have described adults and adolescents who report problematic caffeine consumption and fulfill DSM-IV substance dependence criteria on caffeine. One investigation found that 16 of 99 individuals who self-identified as having psychological or physical dependence on caffeine met DSM-IV criteria for substance dependence on caffeine, when a restrictive set of four of the seven DSM-IV criteria that seemed most appropriate to problematic caffeine use were assessed (1. continued use despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance; 2. persistent desire or unsuccessful efforts to cut down or control substance use; 3. characteristic withdrawal syndrome or use of the substance to relieve or avoid withdrawal symptoms; 4. tolerance as defined by a need for markedly increased amounts of the substance to achieve desired effect, or markedly diminished effect with continued use of same amount of substance). Interestingly, among those who met criteria for caffeine dependence, caffeine intake ranged from 129 mg to 2548 mg and the preferred caffeine vehicle was equally divided between coffee and soft drinks. Using the same four criteria, another study identified adolescents who fulfilled diagnostic criteria for caffeine dependence. These studies, which represent a series of case reports, demonstrate that a clinically meaningful caffeine dependence syndrome does exist.

When individuals in the general population are surveyed about their caffeine use, a surprisingly large proportion endorse substance dependence criteria. In a random digit-dial telephone survey in which all seven DSM-IV criteria for substance dependence were assessed, 30% of caffeine users fulfilled diagnostic criteria by endorsing three or more dependence criteria. When the more restrictive set of four criteria were used, as in the studies described above, 9% met criteria for substance dependence. The most commonly reported symptom (56%) was persistent desire or unsuccessful efforts to cut down or control caffeine use.

More research is needed to determine the applicability of substance dependence criteria to caffeine, the prevalence of the disorder, and the utility and clinical significance of the diagnosis. Meanwhile therapeutic assistance should be made available for those who feel that their caffeine use is problematic and have been unable to quit on their own.

CAFFEINE INTOXICATION

The potential for caffeine intoxication to cause clinically significant distress is reflected by the inclusion of caffeine intoxication as a diagnosis in DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*)(American Psychiatric Association, 1994) and in ICD-10 (*International Statistical Classification of Diseases and Related Health Problems, Tenth Edition*)(World Health Organization). Caffeine intoxication has long been recognized as a discrete syndrome associated with excessive

caffeine use. Caffeinism is an older term that has been used to describe the toxic effects of caffeine resulting from acute or chronic use. Caffeine intoxication is currently defined by a number of symptoms and clinical features that emerge in response to recent consumption of caffeine. Common features of caffeine intoxication include nervousness (anxiety), restlessness, excitement, insomnia, rambling flow of thought and speech, gastrointestinal upset, tremors, tachycardia, diuresis, muscle twitching, periods of inexhaustibility, and psychomotor agitation. In addition, there have been reports of patients with caffeine intoxication having fever, irritability, tremors, sensory disturbances, tachypnea, and headaches. High dose caffeine toxicity is very rarely fatal. However, caffeine can be lethal at very high doses (i.e., 5–10 g).

Although DSM-IV diagnostic guidelines indicate that diagnosis is dependent on the recent daily consumption of at least 250 mg of caffeine, the equivalent of just two and a half cups of brewed coffee, intoxication is most often observed at much higher doses of caffeine (i.e., > 500 mg). However, individual sensitivity and tolerance are likely to influence the dose effects. A person with high sensitivity and little tolerance might show signs and symptoms of caffeine intoxication in response to doses of caffeine much lower than a regular user.

Little is known about who may be most vulnerable to caffeine intoxication. Because caffeine intoxication is directly related to excess caffeine ingestion, any individual who consumes caffeine in large excess of their typical consumption may be at risk. It has been noted that caffeine intoxication can occur in someone who has been using caffeine for many years with no prior apparent problems.

Caffeine intoxication usually resolves rapidly (consistent with caffeine's half-life of 4 to 6 hours) and appears to have no long lasting consequences.

Although many may experience the negative effects of caffeine on occasion, caffeine intoxication serious enough to come to clinical attention is considered relatively rare. A random digit telephone survey found that 7% of current caffeine users met DSM-IV criteria for caffeine intoxication by reporting use of more than 250 mg, five or more symptoms, and that symptoms interfered with their functioning at work, school, or home. Other studies that have focused on special populations (e.g., psychiatric patients, college students) have reported caffeine intoxication rates ranging from 2% to 19%.

(Adapted from Griffiths, R.R., Juliano, L.M., & Chausmer, A.L. (2003). Caffeine pharmacology and clinical effects. In: Graham A.W., Schultz T.K., Mayo-Smith M.F., Ries R.K. & Wilford, B.B. (eds.) Principles of Addiction Medicine, Third Edition (pp. 193-224). Chevy Chase, MD: American Society of Addiction)

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