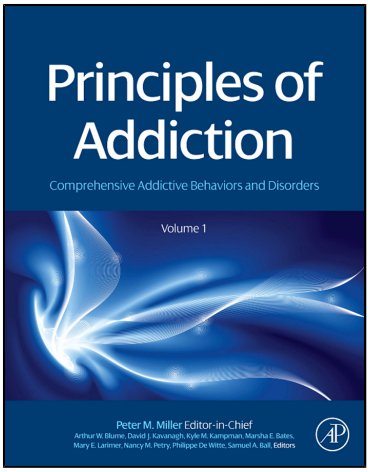

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CHAPTER

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Caffeine and Caffeinated Energy Drinks

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OUTLINE

BACKGROUND

The effects of caffeine have been widely studied and a number of recent reviews cover different outcome measures. Indeed, the present author has written a number of reviews of the behavioral effects of caffeine and has suggested that a cost–benefit analysis is an appropriate way of organizing the literature. The first part of this article will summarize research which demonstrates beneficial effects of caffeine. Earlier reviews suggested that the behavioral effects of caffeine are often positive except when one considers very large doses and sensitive individuals. The issue of dependence and negative effects associated with withdrawal clearly represent an area where one needs to assess possible costs of caffeine consumption. Consumption of energy drinks by children has become an important recent issue. These drinks often have high levels of caffeine and are being consumed by a potentially vulnerable sample. An overview of our current knowledge of these two topics will be given in the second part of the article.

Considerable detail about sources of caffeine, the pharmacology of caffeine, and levels of consumption is available elsewhere. The next section provides a very brief summary of these topics. Caffeine (1,3,7-trimethylxanthine) is a member of a class of naturally occurring substances termed methylxanthines. Plasma levels of caffeine peak 15–45 min after ingestion and the half-life is between 5 and 6 h. A variety of factors influence the metabolism. For example, in pregnant women the half-life can increase to 18 h. Oral contraceptive use

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increases the half-life to 11 h whereas in cigarette smokers the half-life is only about 3 h which may account for the high level of consumption found in this group.

Caffeine acts by blocking the effects of the naturally occurring neuromodulator adenosine. This produces an increase in central nervous system (CNS) activity which is associated with changes in many neurotransmitter systems. Caffeine has other CNS effects (e.g. influencing blood flow to the brain). Many of these CNS effects of caffeine are unlikely to occur with the amounts consumed by humans.

Caffeine occurs naturally in a number of foods, is employed as a food additive, and is added to medications. It occurs naturally in coffee, tea, and cocoa and the exact amount present will depend on growing conditions and preparation. Some rough approximations of the caffeine content of products are: filter coffee – 100–150 mg (5 oz cup); instant coffee – 50–60 mg; tea – 35–45 mg; milk chocolate – up to 15 mg; dark chocolate – up to 35 mg. It is also added to soft drinks (e.g. Cola 40 mg in a 12 oz serving). Higher amounts are added to energy drinks (70 mg+). Caffeine is also added to over-the-counter (OTC) medications (e.g. to analgesics, usually in the region of 30–50 mg per tablet). Caffeine tablets can also be purchased and the recommended dose to increase alertness is 100–200 mg. Several estimates suggest that average intake is about 200 mg per day. Problems usually only occur when excessive amounts are consumed (500 mg a day plus) and these problems usually take the form of an increase in anxiety. Some individuals are very sensitive to effects of caffeine and even small amounts can cause adverse reactions. Most individuals control their consumption of caffeine. For example, consumption usually occurs when alertness is reduced (e.g. early in the morning; after prolonged work; after lunch) and is reduced at times when high alertness is undesirable (e.g. before going to sleep).

BENEFICIAL EFFECTS OF CAFFEINE

In a recent review of the literature on possible beneficial effects of human caffeine consumption, Michael Glade concludes that moderate amounts of caffeine lead to the following benefits:

1. Increased energy availability.
2. Increased daily energy expenditure.
3. Decreased fatigue.
4. Decreased sense of effort associated with physical activity.
5. Enhanced physical performance.
6. Enhanced motor performance.
7. Enhanced cognitive performance.
8. Increased alertness, wakefulness, and feelings of energy.
9. Decreased mental fatigue.
10. Faster reactions.
11. Increased accuracy of reactions.
12. Increased ability to concentrate and focus attention.
13. Enhanced short-term memory.
14. Increased ability to solve problems requiring reasoning.
15. Increased ability to make the correct decisions.
16. Enhanced cognitive functioning capabilities and neuromuscular coordination.

CAFFEINE AND SPORTS PERFORMANCE

A recent position paper on caffeine and sports performance from the International Society of Sports Nutrition can be summarized as follows:

1. Caffeine is effective for enhancing sport performance in trained athletes when consumed in low-to-moderate dosages (~3–6 mg kg^{-1}) and overall does not result in further enhancement in performance when consumed in higher dosages ($\geq$9 mg kg^{-1}).
2. Caffeine exerts a greater ergogenic effect when consumed in an anhydrous state as compared to coffee.
3. It has been shown that caffeine can enhance vigilance during bouts of extended exhaustive exercise, as well as periods of sustained sleep deprivation.
4. Caffeine is ergogenic for sustained maximal endurance exercise, and has been shown to be highly effective for time-trial performance.
5. Caffeine supplementation is beneficial for high-intensity exercise, including team sports such as soccer and rugby, both of which are categorized by intermittent activity within a period of prolonged duration.
6. The literature is equivocal when considering the effects of caffeine supplementation on strength-power performance, and additional research in this area is warranted.
7. The scientific literature does not support caffeine-induced diuresis during exercise, or any harmful change in fluid balance that would negatively affect performance.

CAFFEINE AND SLEEP DEPRIVATION

The American Academy of Sleep Medicine has examined the efficacy and safety of caffeine use during sleep loss and their main conclusions are summarized below:

The most commonly reported measure used to study this topic is the ability to stay awake or fall asleep. Fourteen out of 15 studies reviewed have shown increased wakefulness measured by sleep latency tests following ingestion of caffeine by sleep-deprived volunteers.

Choice reaction time performance of sleep-deprived individuals has been improved by caffeine in eight studies. Similarly, working memory performance of sleep-deprived individuals has been shown to be improved by caffeine in over 10 studies. The effects of caffeine during sleep loss have been examined over a dose range from 75 to 1200 mg per 24 h. Recommended doses are usually in the range of 200–300 mg, mainly because side effects are more prevalent with higher doses. Caffeine administration typically improves performance during sleep loss as compared with placebo, but performance and alertness often continue to decline even when caffeine is given due to further sleep loss, circadian rhythms, and caffeine half-life.

Subjective alertness decreases with sleep loss and ratings of fatigue increase. Studies that have monitored mood typically show that caffeine ameliorates these subjective changes with a similar time course to that seen for performance variables. However, some studies have not obtained these results and it has been suggested that some "subjective tolerance" to caffeine may develop with prolonged testing.

Studies have generally shown that doses of 200–300 mg caffeine produce few side effects whereas higher doses (600 mg+) may increase mild symptoms (e.g. gastrointestinal upset, nervousness, muscle twitching). Based on these findings, the review concluded that caffeine can increase alertness and improve performance at doses of 75–150 mg after acute restriction of sleep and at doses of 200–600 after a night or more of total sleep loss. Caffeine is unlikely to have major disruptive effects on sleep that follows 8 h or longer after administration. Prolonged administration is not recommended due to the increasing likelihood of side effects with high doses.

CAFFEINE AND SUSTAINED MILITARY OPERATIONS

A number of studies have examined effects of caffeine in sustained military operations. Harris Lieberman and colleagues conclude that "When cognitive performance is critical and must be maintained during exposure to severe stress, administration of caffeine may provide a significant advantage".

Other research has examined beneficial effects of caffeinated tube food on pilot performance during a 9-h simulated U-2 mission. The results showed that the caffeinated tube food (200 mg caffeine consumed every 4 h) maintained cognitive performance at baseline levels over a 9-h overnight period. Research has considered both cognitive and physical performance measures in sustained operations (e.g. performance during 27 h of sustained wakefulness in Special Forces personnel). The results showed that caffeine (200 mg caffeinated gum administered on three occasions) maintained performance of a reconnaissance vigilance task and also improved running times compared to placebo. A similar study was conducted over a period of 4 days and three nights of sustained operations. The results showed caffeine maintained both vigilance and physical performance during sustained operations that require periods of overnight wakefulness and restricted opportunities for daytime sleep.

CAFFEINE AND SHIFT WORK

A recent review has considered the effects of caffeine for preventing injuries, errors, and cognitive problems caused by impaired alertness in persons doing shift work. Thirteen trials were included but none measured injury, two measured error, and the remaining trials assessed cognitive performance. The trials assessing the impact on errors found that caffeine significantly reduced the number of errors. Caffeine improved concept formation and reasoning, memory, orientation, attention, and perception. The results were largely from studies involving young participants under simulated conditions and further research is needed on older workers and real world shift work. The authors conclude that "Based on the current evidence, there is no reason for healthy individuals who already use caffeine within recommended levels to improve their alertness to stop doing so."

CAFFEINE AND SAFETY AT WORK

Research by the author has examined the impact of habitual caffeine consumption on performance and safety at work. In the first study volunteers, all of whom were regular caffeine consumers, rated their alertness and carried out a simple reaction time task before and after work on a Monday and Friday. Caffeine consumption during the day was recorded and volunteers were sub-divided into low and high consumers on the basis of a median split (220 mg day^{-1}). The results showed that those who consumed higher levels of caffeine reported significantly greater increases in alertness over the working day and a significantly smaller slowing of reaction time.

The second study involved secondary analyses of a database formed by combining the Bristol Stress and Health at Work and Cardiff Health and Safety at Work studies. In the first analyses associations between caffeine consumption and frequency of cognitive failures were examined in a sample of 1253 white-collar workers. The second set of analyses examined associations between caffeine consumption and accidents at work in a sample of 1555 workers who were especially at risk of having an accident. The results from the second study demonstrated significant associations between caffeine consumption and fewer cognitive failures and accidents at work. After controlling for possible confounding factors, it was found that higher caffeine consumption was associated with about half the risk of frequent/very frequent cognitive failures and a similar reduction in risk for accidents at work. Overall, the results from the three analyses confirmed that caffeine consumption may have benefits for performance and safety at work.

CAFFEINE AND HUMAN ERROR

Other research by the author has involved secondary analyses of a large epidemiological database to examine associations between caffeine consumption and cognitive failures (errors of memory, attention, and action) in a non-working sample. Associations between caffeine consumption and physical and mental health problems were also examined. After controlling for possible confounding factors significant associations between caffeine consumption and fewer cognitive failures were observed. Overall, the results show that caffeine consumption may benefit cognitive functioning in a non-working population. This confirms earlier findings from working samples. This beneficial effect of caffeine was not associated with negative health consequences.

CAFFEINE AND DRIVING

A number of studies by Jim Horne and colleagues have examined (1) the efficacy of 200 mg caffeine with restricted and completely sleep-deprived drivers, (2) an energy drink containing caffeine with sleep-restricted drivers, and (3) "a functional energy drink" and sleep-restricted drivers. The results from these studies showed that caffeine generally reduced the impaired driving performance that was seen in sleepy drivers given placebo.

Others have extended these results by examining the effects of sleepiness and caffeine on real-life driving. Extended driving and sleepiness resulted in an increase in lane crossing, which was reduced by 200 mg caffeine. As shown in previous sections of this chapter, fatigue can be induced in a number of ways. One study involved 1 h of simulated driving before and after either caffeine or placebo. In addition, volunteers carried out a battery of tasks measuring subjective alertness and sustained attention. Caffeine reduced steering variability (which in real-life driving may lead to lane crossing) and led to an increase in subjective alertness and improved cognitive vigilance. This suggests that results found after caffeine with artificial laboratory tasks may be applicable to real-life activities involving similar functions.

Driving performance can be impaired by a number of factors, the most widely studied being alcohol. One study examined whether caffeine would reduce an alcohol-induced impairment of simulated driving. The results suggested that caffeine may increase alertness and improve reaction time after alcohol use but will not completely counteract the alcohol impairments seen in driving.

Jack James and colleagues argue that many of the effects of caffeine seen in studies of driving can be interpreted in terms of reversal of the effects of caffeine withdrawal. One method of distinguishing a benefit of caffeine from a reversal of caffeine withdrawal is to compare caffeine consumers with non-consumers. There is a need to do this using an epidemiological approach to examine associations between caffeine consumption and road traffic accidents.

Research by the author has examined a community sample from South Wales ($N = 6648$). These respondents provided information on involvement in road traffic accidents. 3.6% of non-consumers of caffeine were involved in a road accident requiring medical attention compared to only 2.2% of caffeine consumers. Logistic regressions, including demographic, lifestyle, and psychosocial characteristics showed that consumption of caffeine nearly halved the risk of being in a road accident (odds ratio [OR] = 0.58 confidence intervals [CI]: 0.35, 0.98). This result confirms previous research showing that caffeine reduces the risk of accidents (at work) and supports the existing literature and information campaigns about the positive benefits of caffeine for road safety.

CAFFEINE AND DEMENTIA

Several epidemiological studies have examined associations between consumption of caffeine and dementia. A recent systematic review and meta-analysis considered nine cohort and two case control studies. The outcomes examined were Alzheimer's disease (four studies), dementia or cognitive impairment (two studies), and cognitive decline (three studies). The

summary relative risk for the association between caffeine intake and the different cognitive measures was 0.84 [95% CI: 0.72–0.99]. This suggests a trend toward a protective effect of caffeine but the large methodological heterogeneity across a small number of studies precludes more definitive conclusions.

CAFFEINE AND ANXIETY AND DEPRESSION

Caffeinism refers to a constellation of symptoms associated with very high caffeine intake that are virtually indistinguishable from severe chronic anxiety. Caffeinism is usually associated with daily intakes of between 1000 and 1500 mg. However, it appears to be a rather specific condition and there is little evidence for correlations between caffeine intake and anxiety in either nonclinical volunteers or psychiatric outpatients. Other research has investigated whether caffeine is capable of increasing the anxiety induced by other stressors. It has been found that 400 mg of caffeine increased anxiety when paired with a stressful task. However, other research has not been able to provide any evidence of interactive effects of caffeine and stress.

Recent research has shown an association between ADORA2A and DRD2 polymorphisms and caffeine-induced anxiety. Adenosine receptors functionally interact with dopamine receptors in the brain. Functional polymorphisms in the genes for either adenosine or dopamine receptors may, therefore, affect responses to caffeine. A recent study found that 50 mg caffeine did not increase anxiety in any individuals whereas 450 mg caffeine increased it in the majority of the volunteers. With a dose of 150 mg caffeine anxiety was associated with ADORA2A and DRD2 polymorphisms.

In contrast, moderate caffeine intake has been associated with fewer depressive symptoms and a lower risk of suicide. This effect of caffeine on depression may have other knock on effects with regards to health. The author conducted secondary analyses of a large epidemiological database ($N = 2750$) to examine associations between caffeine and both chronic and acute health outcomes. Many of the initial associations between caffeine and health were no longer significant when potential confounders were examined. However, caffeine consumption was still significantly associated with reduced depression in the final regressions. Caffeine consumption was also associated in a dose response fashion with fewer upper respiratory tract symptoms. This suggests that caffeine may influence the immune system, either directly, or by reducing depression (a well-established risk factor for immunosuppression). Other research by the author has shown that caffeine removes the malaise (fatigue, psychomotor slowing) associated with minor illnesses such as the common cold.

CHRONIC HEALTH EFFECTS OF CAFFEINE CONSUMPTION

It is important to conduct a cost–benefit analysis when considering the effects of caffeine. Benefits usually refer to behavioral outcomes and costs reflect possible long-term health effects. Caffeine has been linked with a range of possible health problems but most of these associations are not significant when confounding factors are adjusted for. Indeed, in recent years the trend has been for suggestions that caffeine may have health benefits. It has been suggested that studies of caffeine have played a key part in defining the role of adenosine receptors, phosphodiesterases, and calcium release channels in physiological processes. Caffeine and various analogs, the latter designed to enhance potency and selectivity toward specific biological targets, are potential therapeutic agents for intervention in Alzheimer's disease, asthma, cancer, diabetes, and Parkinson's disease.

CAFFEINE: AN ATYPICAL DRUG OF DEPENDENCE

Roland Griffiths and colleagues have suggested that caffeine is an excellent model compound for understanding drugs of abuse/dependence. Caffeine can be shown to act as a reinforcing agent, a criterion for dependence, under certain conditions. However, the level of responding is lower than that maintained by addictive drugs such as cocaine and amphetamine and there is little or no evidence for upward dose adjustment. Indeed, it is unclear about the contribution of desirable stimulatory effects and undesirable withdrawal symptoms in the reinforcing properties of caffeine.

It has been suggested that caffeine shares four behavioral pharmacological effects with classic drugs of abuse/dependence: reinforcing effects, discriminative/subjective effects, tolerance, and physical dependence. Similarly, it has been suggested that there are some people who report a compulsive pattern of caffeine use and are physiologically dependent on caffeine and there is evidence that just under 20% of caffeine users show some degree of dependence although this is small compared with nicotine (90% of users show dependence) and at a similar level to alcohol (where 14% show a lifetime prevalence of dependence). The most important issue is the severity of the harmful consequences associated with dependence. Compared to nicotine or alcohol the risks associated with moderate

caffeine consumption are generally low. Although caffeine fulfills some of the criteria for drug dependence and shares with amphetamines and cocaine a certain specificity of action on the cerebral dopaminergic system, the methylxanthine does not act on the dopaminergic structures related to reward, motivation, and addiction.

CAFFEINE WITHDRAWAL

Caffeine withdrawal is typically associated with symptoms of headache and drowsiness. These symptoms generally begin slowly, maximize after 1–2 days and are over within a few days. Many of the early studies of this topic used small samples and if one adjusted for the number of analyses carried out one would find few significant effects. The studies also have other undesirable features (e.g. in one study – the subjects were also the authors of the paper). The frequency of caffeine withdrawal has been examined in a population-based survey and in a controlled, blinded experiment. In the survey of over 11 000 people, 61% reported daily caffeine consumption and 11% of the caffeine consumers reported symptoms upon stopping caffeine. When volunteers were unaware that the focus of the study was caffeine withdrawal, reports of symptoms associated with withdrawal were less frequent. Indeed, in another double-blind study by the present author, caffeine withdrawal was associated with an increase in reports of headache but those who continued to consume caffeine also reported more headaches as the study progressed. Volunteers in this study were not very good at discriminating whether they were in the caffeine or no caffeine groups and this suggests that symptoms of caffeine withdrawal may only be apparent if volunteers know that caffeine has been withdrawn. Such a result was obtained in further research by the author which suggests that the dependence associated with caffeine may largely reflect the knowledge that caffeine has been withdrawn rather than a pharmacological dependence.

BENEFICIAL EFFECTS OF CAFFEINE OR REMOVAL OF NEGATIVE EFFECTS OF WITHDRAWAL?

Overall, the previous sections confirm that the effects of caffeine on performance are largely beneficial. However, this view has been questioned by Jack James who argues that the beneficial effects of caffeine are really only removal of negative effects produced by caffeine withdrawal. The author has argued against this general view of caffeine effects on a number of grounds. First, it cannot account for the behavioral effects seen in animals or non-consumers where withdrawal cannot occur. Second, caffeine withdrawal cannot account for behavioral changes following caffeine consumption after a short period of abstinence or the greater effects of caffeine when arousal is low. Finally, claims about the negative effects of caffeine withdrawal require closer examination as they can often be interpreted in ways other than caffeine dependence (e.g. expectancy). Indeed, in most of the studies that have demonstrated increases in negative affect following caffeine withdrawal, the volunteers have not been blind but have been told or even instructed to abstain from caffeine. This is clearly very different from the double-blind methodology typically used to study effects of caffeine challenge.

The view that beneficial effects of caffeine reflect degraded performance in the caffeine-free conditions crucially depends on the strength of the evidence for withdrawal effects. Jack James states that "there is an extensive literature showing that caffeine withdrawal has significant adverse effects on human performance". If one examines the details of the studies cited to support this view one finds that some of them do not even examine performance, and that where they do, any effects are selective, not very pronounced, and largely unrelated to the beneficial effects of caffeine reported in the literature.

Peter Rogers and colleagues have reviewed a number of studies of caffeine withdrawal and performance. They conclude that " in a review of recent studies we find no unequivocal evidence of impaired psychomotor performance associated with caffeine withdrawal". Indeed, they found that caffeine improved performance in both deprived volunteers and non-consumers. Furthermore, other studies which suggest that withdrawal may impair performance can be interpreted in other ways than deprivation (e.g. changes in state).

The effects of caffeine withdrawal are still controversial. One study showed that caffeine withdrawal impaired short-term memory performance but caffeine ingestion had no effect. In contrast, research by the author has shown that caffeine improved attention in both those who had been deprived of caffeine for a short period and those who had no caffeine for 7 days. Other studies suggest that effects of withdrawal are restricted to mood and that performance is unaltered. Like many areas of caffeine research, some of the effects that have been attributed to withdrawal are open to other interpretations. For example, some studies have compared days when mid-morning coffee was either caffeinated or de-caffeinated. Caffeine consumption was associated with better performance and mood. The authors interpret this as a negative effect of caffeine withdrawal whereas one could equally interpret it as a positive effect

of caffeine. Other studies of caffeine withdrawal effects have methodological problems such as the lack of pre-drink baselines or failure to consider possible asymmetric transfer when using within subject designs.

Caffeine withdrawal has been widely studied because it is meant to provide crucial evidence on whether caffeine is addictive or leads to some kind of dependence. The most frequent outcome measure has been reporting of headache, but mood has been examined in other studies. Research has shown that caffeine deprivation led to increased reporting of stress by heavy coffee drinkers. This has been confirmed in another study which showed that caffeine withdrawal was associated with feelings of fatigue and decreased feelings of alertness. Indeed, results show that about 10% of volunteers with a moderate daily intake (235 mg day^{-1}) reported increased depression and anxiety when caffeine was withdrawn. Other research has examined the effects of varying time periods of caffeine deprivation (90 min, overnight and 7 days) on mood. The results showed that overnight caffeine deprivation produced dysphoric symptoms and these mood effects were reduced, but still present, after longer term abstinence. However, close examination of the results does not support this conclusion with only one of the 17 mood scales showing a significant effect.

Recent research in this area has been concerned with two main topics, namely what underlies the increase in symptoms following caffeine withdrawal, and, secondly, whether the positive effects of caffeine reflect removal of negative effects of withdrawal. Peter Dews and colleagues have considered factors underlying caffeine withdrawal and conclude that "non-pharmacological factors related to knowledge and expectation are the prime determinants of symptoms and their reported prevalence on withdrawal of caffeine after regular consumption".

In contrast, some researchers still suggest that caffeine only has beneficial effects on performance when the person has had caffeine withdrawn. One study reported that caffeine improved performance on a sustained attention task and increased rated alertness when volunteers had been caffeine deprived but had no such effects when they were no longer deprived. However, the results showed an effect of order of treatments with those who received caffeine first continuing to show better performance even when subsequently given placebo.

Research by the author has examined effects of caffeine in the evening after a day of normal caffeine consumption. Caffeine improved performance which casts doubt on the view that reversal of caffeine withdrawal is a major component underlying effects on performance. Further evidence against the caffeine withdrawal explanation comes from recent studies of non-consumers. These studies not only detected few negative effects of withdrawal but also showed that caffeine improved the performance of both withdrawn consumers and non-consumers, a finding that argues strongly against the withdrawal reversal explanation.

Other research has compared the effects of caffeine following abstinence and normal caffeine use. Caffeine had a greater effect on mood in the abstained state. The authors also suggest that choice reaction time showed a similar effect although this would not be significant if adjustments were made for multiple statistical tests. Other aspects of performance showed significant effects of caffeine in both abstained and normal caffeine consumption conditions. Failure to adjust for multiple testing is a common problem in this area of research. In addition, it is often unclear why specific sample sizes or tests are used. Consideration of these factors leads to a very different interpretation of some of the literature. For example, Heatherley and colleagues claim that cognitive performance is only improved by caffeine after 8 h of abstinence. Adjustment for multiple testing shows that none of the effects of caffeine are significant which reflects the low power of the study and failure to covary baseline data. Similarly, claims that 9 to 11-year-old children show negative symptoms of withdrawal which are reversed by caffeine do not hold up when adjustments are made for the number of statistical tests conducted.

A review of caffeine withdrawal has been conducted by Roland Griffiths with a view to validate specific symptoms and signs and to define important features of the syndrome. The review covered 57 experimental and 9 survey studies. Symptoms associated with caffeine withdrawal were: headache, fatigue, decreased energy, decreased alertness, drowsiness, depressed mood, difficulty concentrating, and irritability. The incidence of headache was 50% and the incidence of clinically significant distress was 13%. The onset of symptoms occurred 12–24 h after abstinence, with peak intensity at 20–51 h and for a duration of 2–9 days. Abstinence from even low doses (e.g. 100 mg day^{-1}) produced symptoms. Unfortunately, this review was selective and studies which suggested a different view of caffeine withdrawal were excluded. In addition, there was no attempt to distinguish between negative effects of withdrawal and positive effects of caffeine. For example, certain studies are interpreted in terms of negative effects of caffeine deprivation when they could actual be interpreted in terms of positive effects of caffeine ingestion. This review does not look at the details of the studies and, as stated above, many effects of caffeine deprivation are no longer significant when adjusted for multiple statistical tests.

Recent research has demonstrated that acute caffeine abstinence produces changes in cerebral blood flow

velocity, EEG, and subjective effects. These vascular effects of caffeine withdrawal are clearly very different from behavioral effects of caffeine which are thought to reflect changes in a variety of neurotransmitter systems. Astrid Nehlig and colleagues present evidence that in animals caffeine does not trigger metabolic increases or dopamine release in brain areas involved in reinforcement or reward. A single photon emission computed tomography (SPECT) assessment of brain activation in humans showed that caffeine activates regions involved in the control of vigilance, anxiety, and cardiovascular regulation but did not affect areas involved in reinforcement and reward.

TOLERANCE

Developing tolerance is a hallmark of substance abuse and dependence. In adults, caffeine-induced tolerance has been shown for some, but not all, outcomes and only in a sub-set of consumers.

CROSS-SENSITIZATION

Cross-sensitization is the process by which taking one drug enhances the response to other drugs with the same neurobiological mechanisms. It has been suggested that caffeine may increase sensitization to nicotine although the correlation between caffeine use and smoking may reflect the faster metabolism of caffeine by smokers. There is no clear relationship between caffeine use and cocaine in humans and if anything, cocaine users are less likely to consume caffeine than non-cocaine users.

CAFFEINE AND CHILDREN AND ADOLESCENTS

Ingestion of caffeine from naturally occurring sources has been largely restricted to adults but it is now added, sometimes in large quantities, to drinks that are consumed by children. Our knowledge of the effects of caffeine on the behavior of children needs to be extended by further research. The current position on this topic can be briefly summarized as follows.

Older studies of the behavioral effects of caffeine on children have shown similar effects to those observed in adults. Effects in children are often smaller than those observed in adults which may reflect the smaller doses consumed.

It is generally agreed that caffeine intake by pregnant women should be kept at a low level (below 200 mg) because of the possible impact on birth problems and reduced body weight of the child. However, there is no evidence showing that caffeine consumption during pregnancy or childhood influences brain development.

A recent review has shown that caffeine containing drinks are now regularly consumed by children. Indeed, some caffeinated products are even marketed to children as young as 4 years old. Our knowledge of effects of caffeine on children is very limited and further research is needed in the area because children may be more sensitive to negative effects of caffeine than adults. This research should examine possible caffeine dependence and also caffeine intoxication. Caffeine intoxication is characterized by the following symptoms: restlessness, nervousness, excitement, insomnia, flushed face, diuresis, and gastrointestinal complaints. It is likely that low consumers of caffeine, such as children, may experience caffeine intoxication following consumption of a high dose (as found in some energy drinks). No empirical studies have been conducted to examine whether children and adolescents develop tolerance to the effects of caffeine. Surveys suggest that 41.7% of teenagers reported tolerance to caffeine and 77.8% reported symptoms of withdrawal. Consumption of caffeinated soft drinks is also associated with poor diet, excess weight, and dental caries.

There is a growing literature that suggests that caffeine use in adolescents and young adults is associated with impulsivity, risk taking, and sensation seeking. Unfortunately, due to the correlational nature of these studies, it is not possible to determine the direction of causality.

ENERGY DRINKS

Energy drinks represent the fastest growing sector in the beverage industry. These drinks often contain five times the amount of caffeine as soft drinks and may also contain taurine, riboflavin, pyridoxine, and various herbal derivatives. Most energy drinks also contain sugar in an amount that exceeds recommended daily allowances. Studies of the effects of energy drinks on behavior confirm that they increase alertness and attention, improve simulated driving when sleepy and can reduce sleepiness in night workers. However, energy drinks that also contain alcohol (6% by volume) have been shown to impair a global measure of cognitive functioning. Energy drinks have also been shown in laboratory studies to increase heart rate and blood pressure.

Energy drink consumption can lead to caffeine intoxication especially in children. Deaths attributed to energy drink consumption have been reported in Australia, Ireland, and Sweden. Health care providers

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report the following effects after consumption of energy drinks: dehydration, accelerated heart rates, anxiety, seizures, acute mania, and strokes. The risk of caffeine intoxication may be greater for energy drinks than for other sources of caffeine due to inadequate labeling, advertising, and the consumer demographics.

Energy drinks are often combined with alcohol to increase the positive effects of alcohol ingestion and counteract the depressive effects. This can lead to increased alcohol intake and an increase in adverse events due to alcohol. Indeed, combining energy drinks with alcohol gives the person a false sense of control. Recent research has investigated the extent to which energy drink consumption was a risk factor for alcoholism. The results of a study of over 1000 university students showed that weekly or daily energy drink consumption was associated with more frequent and greater consumption of alcohol. This, of course, could be due to alcohol consumption influencing energy drink consumption rather than the other way around.

CONCLUSIONS

In conclusion, there are many beneficial effects of caffeine and negative effects are restricted to consumption of high doses by susceptible individuals. Caffeine is almost certainly the most widely used drug of dependence in the world. Despite this, the evidence of morbidity associated with caffeine consumption is slight. Research on caffeine tells us little about the harmful effects of drugs of dependence and shows that caffeine dependence *per se* is not a problem.

SEE ALSO

Tobacco, Food Addictions, Khat Addiction, The Biopsychosocial Model of Addiction, Tolerance and Withdrawal

List of Abbreviations

OTC	over-the-counter
SPECT	single photon emission computed tomography

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