CHAPTER 22 Caffeine

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Caffeine (1,3,7-trimethylxanthine) is the most widely used mood-altering drug in the world. Caffeine is found in more than 60 species of plants and is the best-known member of the methylxanthine class of alkaloids. The dimethylxanthines, which include theophylline and theobromine, are structurally related compounds that are also found in various plants.

Caffeine is a nonselective A_1 and A_{2A} adenosine receptor antagonist and mild central nervous system (CNS) stimulant that produces various physiologic and psychological effects. It has long been recognized for its mild stimulating effects and has been consumed in one form or another for thousands of years despite repeated attempts throughout history to ban its use on moral, medical, economic, or political grounds. Today caffeine use remains ubiquitous. In fact, caffeine ingestion is so intricately tied to social customs and daily rituals that it is often not perceived as a drug, despite its well-documented pharmacologic effects. Moreover, common foods and other products often contain significant amounts of caffeine, although they may not be labeled as such. Thus, it is possible to significantly underestimate caffeine consumption and the role that it may play in one's daily experiences.

Behaviorally active doses of caffeine are consumed daily by a majority of adults in the United States. Caffeine is generally considered to be safe relative to classic drugs of dependence, and research suggests that it may even offer protective effects against certain diseases (e.g., Parkinson disease). However, caffeine is not a completely innocuous drug. Although there is a lack of agreement on whether caffeine should be formally considered a drug of clinical dependence, some behavioral features of caffeine use closely resemble those associated with classic drugs of dependence. Caffeine can produce tolerance and a characteristic withdrawal syndrome, and heavy use (>400 mg/day) is associated with increased risk for various health problems. Caffeine functions as a reinforcer and many habitual caffeine consumers report an inability to quit or reduce caffeine use despite a desire to do so. Caffeine can cause discrete psychopathology (e.g., caffeine intoxication, caffeine-induced anxiety disorder), exacerbate existing psychopathology (e.g., anxiety, insomnia), and interfere with the efficacy of some medications (e.g., benzodiazepines). There is also evidence that caffeine may interact with classic drugs of dependence. This chapter will review empirical data on the pharmacologic, behavioral, and clinical effects of caffeine. The review will conclude with a discussion of the clinical implications of caffeine use and practical guidelines for modifying caffeine use.

HISTORY

Caffeine was first isolated from coffee in 1820 and tea in 1827, and its chemical structure was first characterized in 1875. Caffeine has been ingested in one form or another throughout various parts of the world for thousands of years. Tea was first cultivated in China; coffee in Ethiopia; guarana, cocao, and maté in South America; and kola nut in West Africa. The word coffee is believed to have been derived from the Arabic word "qahwa," which historically referred to wine. According to legend, coffee was discovered after an Arabian goatherd observed his goats eating berries and subsequently behaving in an energetic manner. The technique of roasting and grinding coffee beans for beverage preparation was developed in Arabia by the 14th century. With the development of worldwide trade routes during the 17th and 18th centuries, caffeinated products spread rapidly from their indigenous environments to other parts of the world. The introduction of caffeine into societies, not unlike the introduction of other drugs such as tobacco, has sometimes provoked moral outrage and attempts to ban use. Failed efforts to suppress the use of caffeine-containing foods, usually in the form of coffee or tea, have been documented worldwide (including Arabia, Turkey, Egypt, England, France, and Prussia). In the late 1700s America protested a British tax on tea resulting in the "Boston Tea Party" in which shipments of tea were thrown into the Boston Harbor. The Continental Congress subsequently passed a resolution against tea consumption, and over the course of a few years coffee became the caffeinated beverage of choice in America. Today coffee is second only to oil as the largest import in the United States.

In the late 1800s, entrepreneurs began selling flavored carbonated beverages with added caffeine. Soft drink consumption has increased steadily over the last century and has become a significant source of caffeine use among individuals of all ages. Over the past decade energy drinks, which typically contain significantly higher concentrations of caffeine than soft drinks, have been growing in popularity in the United States and elsewhere. Some countries presently ban the sale of energy drinks or require health warnings on them due to concerns about negative health effects.

SOURCES OF CAFFEINE

Caffeine occurs naturally in a variety of plant-based products including coffee, tea, cocoa, kola nut, guarana, and maté. In addition to beverages made from these plants, significant

TABLE 22.1 Caffeine content of common foods and medications

Product	Serving size (volume or weight)	Typical caffeine content (mg)	Range (mg)
Coffee			
Brewed/drip	6 oz	100	54–210
Starbucks hot brewed coffee	16 oz	330	
Espresso	1 oz	70	60–95
Starbucks espresso (solo)	1 oz	75	
Instant	6 oz	70	20–130
Decaffeinated	6 oz	4	0–10
Tea			
Brewed	6 oz	40	30–90
Instant	6 oz	30	10–35
Canned or bottled	12 oz	20	8–32
Soft drinks			
Typical caffeinated soft drink	12 oz	40	22–69
Mountain Dew/Diet Mountain Dew	12 oz	55	
Pepsi One	12 oz	55	
Mellow Yellow/Diet Mello Yellow	12 oz	51	
Diet Coke	12 oz	47	
RC Cola	12 oz	43.2	
Diet Sunkist	12 oz	42	
Sunkist	12 oz	41	
Dr. Pepper/Diet Dr. Pepper	12 oz	41	
Mr. Pibb/Diet Mr. Pibb	12 oz	40	
Pepsi-Cola	12 oz	38	
Diet Pepsi	12 oz	36	
Coke Classic	12 oz	35	
Coke Zero	12 oz	35	
Cherry Coke	12 oz	34	
A&W Cream Soda	12 oz	29	
Barq's Root Beer	12 oz	23	
A&W Diet Cream Soda	12 oz	22	
Cocoa/hot chocolate	6 oz	7	2–10
Chocolate milk	6 oz	4	2–7
Chocolate			
Hershey's Chocolate Bar	1.55 oz	9	
Hershey's Special Dark	1.45 oz	18	
Hershey's Baking Chocolate	1.0 oz	30	
Caffeinated water			
Typical amount	16.9 oz	60	60–200
Water Joe	16.9 oz	60	
Buzzwater	16.9 oz	100 or 200	
Energy drinks			
Typical amount	varies	varies	50–505
Wired-X-505	23.5 oz	505	
FIXX	20 oz	500	
Cocaine	8.2 oz	280	
Rockstar	16 oz	160	
Full Throttle	16 oz	144	

Product	Serving size (volume or weight)	Typical caffeine content (mg)	Range (mg)
Red Bull	8.3 oz	80	
Coffee ice cream or yogurt	8 oz (one cup)	50	8–85
Dannon Coffee Yogurt	6 oz	30	
Starbucks Coffee Ice Cream	8 oz	60	
Miscellaneous foods and beverages			
Stay Alert Caffeinated Gum	1 stick	100	
Starbucks bottled Frappuccino	9.5 oz	85	
Extreme Sport Beans Jelly Beans	1 oz	50	
Powerbar Tangerine Powergel	41 g	50	
Jolt Caffeinated Gum	1 stick	33	
Penguin Peppermints	1 mint	7	
Stimulants			
Typical	1 tablet	100 or 200	100–200
Vivarin	1 tablet	200	
NoDoz	1 tablet	100 or 200	
Analgesics (OTC and prescription)			
Typical	2 tablets	64 or 130	64–130
Anacin Advanced Headache	2 tablets	130	
Excedrin Extra Strength	2 tablets	130	
Goody's Headache Powder	1 powder packet	32.5	
Fiorinal	2 tablets	80	
Darvon	1 tablet	32.4	
Weight-loss products/sports nutrition			
Typical	1 or 2 tablets	Varies	50–300
Metabolife Ultra	2 caplets	150	
Dexatrim Max	1 caplet	50	
Leptopril	2 capsules	220	
Stacker 3	1 caplet	254	
Swarm Extreme Energizer	1 capsule	300	

1 fluid oz = 30 mL; 1 oz weight = 28 g; serving sizes are based on commonly consumed portions, typical container sizes, or pharmaceutical instructions. Caffeine values for brand name products were obtained from product labels, or the manufacturer's Web site or customer service department.

amounts of caffeine are found in foods such as coffee ice cream, coffee yogurt, and dark chocolate. Caffeine is added to cola and noncola soft drinks as well as to other common food items such as energy drinks, water, candy bars, mints, and gum. Caffeine is also added to hundreds of prescription and over-the-counter (OTC) medications including stimulants, analgesics, weight-loss supplements, and nutritional supplements. Table 22.1 lists the caffeine content of many common foods and medications.

In the United States, coffee and soft drinks are the major dietary sources of caffeine. The Food and Drug Administration limits the amount of caffeine that can be added to soft drinks to 0.2 mg/ml or 71.5 mg for a 12-oz serving. It is noteworthy that energy drinks often contain significantly higher levels of caffeine than those permitted in soft drinks with levels ranging from 50 to over 500 mg per can or bottle (1). Also, manufacturers are not required to list caffeine as an ingredient in products made with naturally occurring sources of caffeine (e.g., coffee, guarana, kola nut, maté). Products made from some of the less well-recognized sources of caffeine can be a significant hidden source of caffeine. Manufacturers are also not required to provide the amount of caffeine added to beverages and other food products; however, some of the larger soft drink manufacturers have begun to label the amount of caffeine in their products in recent years.

EPIDEMIOLOGY

Estimating actual caffeine exposure in the population is challenging because caffeine is present in a vast number of products, and many consumers are completely unaware of

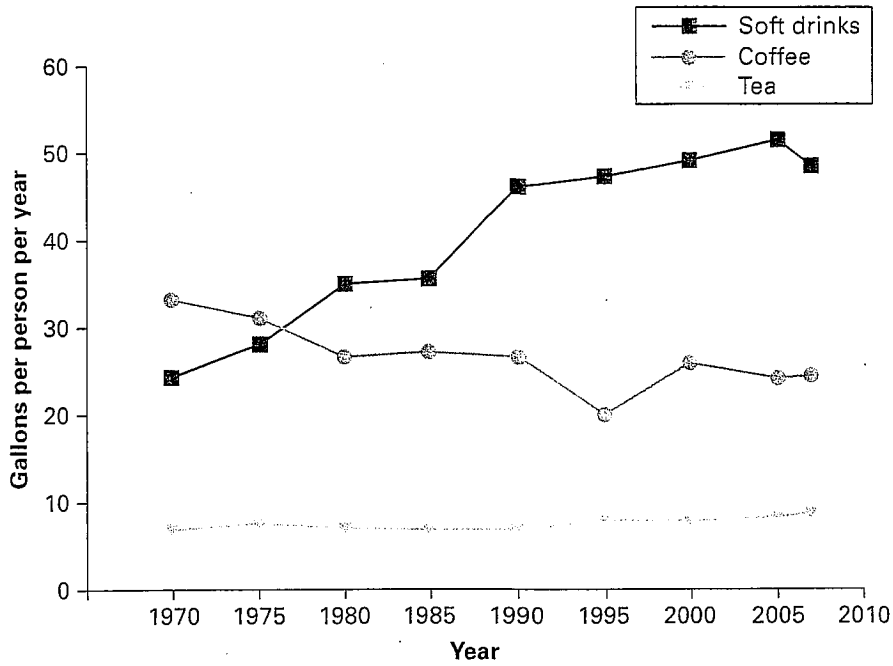

Figure 22.1. Annual per capita consumption of the three major dietary sources of caffeine in the United States. Data from the USDA/Economic Research Service 2009. U.S. Food Supply Data (1970–2007).

whether or not a given product contains caffeine. Furthermore, for many types of caffeinated products both the caffeine concentration and the serving sizes can vary over a wide range. For example, the amount of caffeine in a serving of coffee can range from 17 mg for a small 5-oz cup of instant coffee to 500 mg for a large 20-oz cup of drip coffee.

The most recent large-scale published epidemiologic data on caffeine consumption in the United States was collected more than 10 years ago. Based on the Continuing Survey of Food Intakes by Individuals in 1994 to 1996 and in 1998, it is estimated that 87% of the population in the United States 2 years and older regularly consume caffeine with an average daily consumption of about 193 mg (2). Caffeine use tends to increase with age with the highest consumption observed among adults aged 35 to 64 years (2). Caffeine consumption among adult consumers in the United States is estimated to be about 280 mg with higher daily intakes estimated for some European countries (3). Subgroups that have been identified as being heavy caffeine consumers include psychiatric patients, prisoners, smokers, alcoholics, and individuals with eating disorders. Coffee is the major source of caffeine for adults, followed by soft drinks and tea, whereas soft drinks are the major source of caffeine among children and adolescents (2). More than 50% of adults consume coffee every day, and drink just over three cups per day. Caffeinated soft drinks account for the vast majority of soft drink sales.

Figure 22.1 displays trends in annual per capita consumption of coffee, tea, and soft drinks, the three major sources of caffeine consumption in the United States. Over the nearly four decades shown, use of carbonated soft drinks has more than doubled, while coffee consumption has decreased by about 25%. Tea consumption has increased only slightly over this time period. Since the introduction of Red Bull in the United States in 1997, the energy drink market has grown exponentially, with hundreds of different brands of energy drinks now available to consumers. Sales of energy drinks have increased an average of 55% each year and sales are expected to continue on this trajectory in the coming years (1).

GENETICS

There is evidence that genetic factors account for some of the variability in the use and effects of caffeine (for citations see (4)). Large-scale twin studies have shown that relative to dizygotic twins, monozygotic twins have higher concordance rates for total caffeine consumption, heavy caffeine consumption, coffee and tea intake, caffeine tolerance, caffeine withdrawal, caffeine intoxication, and caffeine-related sleep disturbances with heritabilities ranging between 34% and 77% (5). Findings from twin studies have also suggested that there may be common genetic factors that underlie the use of caffeine, cigarette smoking, and alcohol. One large-scale twin study found that caffeine and nicotine dependence were substantially influenced by genetic factors that appeared to be unique to these licit drugs and distinct from genetic factors found to be common among illicit drugs (6).

Association studies have also been conducted to evaluate how specific gene variations are related to individual differences in the use and effects of caffeine. Because caffeine's primary mechanism of action is adenosine receptor antagonism, one particular gene that has been the focus of attention is the A_{2A} receptor gene (ADORA2A). Another gene of interest is the CYP1A2 gene, which is linked to enzymes responsible for caffeine metabolism. It has been posited that understanding variability in the CYP1A2 gene across individuals could explain variability in caffeine consumption. It has also been pro-

posed as a method of elucidating dose-response associations between actual caffeine consumption and various effects, and health and pregnancy outcomes, by taking differences in caffeine metabolism into account. For example, recent studies have indicated that individuals who carry the CYP1A2 genotype associated with slow caffeine metabolism are at greater risk for coffee-associated hypertension and myocardial infarction (7,8). In another large-scale study, genetic variability in the ADORA2A receptor gene, but not the CYP1A2 gene, was associated with caffeine consumption (9). Variability in the ADORA2A gene has also predicted differential effects of a specific caffeine dose on anxiety (10) and sleep (11).

PHARMACOKINETICS

After oral consumption, caffeine is rapidly and completely absorbed. Caffeine rapidly passes through the blood–brain barrier and enters the brain, which accounts for the quick onset of mood-altering effects (12). Peak caffeine blood concentration (C_{max}) is generally reached in 30 to 45 minutes (13). Caffeine is highly lipid soluble and is rapidly and widely distributed throughout all body tissues and fluids including breast milk and semen. There is no placental barrier to caffeine, and thus the levels of caffeine in the fetus approach the levels of the mother (14). Saliva caffeine concentrations are highly correlated with plasma caffeine concentrations and are often used as a noninvasive alternative to measuring serum levels.

Caffeine metabolism is complex, and more than 25 caffeine metabolites have been identified in humans (15). The primary metabolic pathways involve the cytochrome P-450 liver enzyme system (primarily the CYP1A2 isoenzyme), which carries out the demethylation of caffeine to three pharmacologically active dimethylxanthines: paraxanthine, theophylline, and theobromine (16). These active metabolites need to be considered in understanding the pharmacologic actions of caffeine, especially the primary metabolite paraxanthine. The half-life of caffeine is typically 4 to 6 hours; however, the rate of caffeine metabolism is quite variable across healthy adults and can range from 2 to 12 hours (12). Due to impaired enzyme functioning, caffeine metabolism is significantly slowed among individuals with liver disease (17) as well as women in the second and third trimesters of pregnancy, who show about a threefold increase in the half-life of caffeine (18). Fetuses and newborns lack the liver enzymes needed to metabolize caffeine. Thus, caffeine metabolism in infants prior to 6 months of age is very slow, with a half-life of 80 to 100 hours (18). Tobacco smoking increases the rate of metabolism of caffeine due to stimulation of the CYP1A2 enzyme, with smokers metabolizing caffeine about twice as fast as nonsmokers.

An implication of the central role of cytochrome P-450 liver enzymes in metabolizing caffeine is that other therapeutic drugs may pharmacokinetically interact with caffeine. Inhibition of caffeine metabolism via competition for liver enzymes could lead to caffeine intoxication symptoms that could be misattributed to the effects of the drug. Furthermore, caffeine can impair the metabolism of other drugs, thus interfering with their safety and therapeutic effectiveness. Because the large majority of the population consumes caffeine, knowledge of potential caffeine–drug interactions is desirable when treating various types of psychological and physical conditions. Numerous compounds have been shown to significantly inhibit the metabolism of caffeine including but not limited to oral contraceptives, quinolone antibiotics (e.g., Enoxicin), and some selective serotonin reuptake inhibitors (SSRIs) (e.g., Luvox), reducing the clearance of caffeine by 40% to 80% (15). Some medications used to treat gastroesophageal reflux disease (GERD; e.g., cimetidine) and heart arrhythmias (e.g., propafenone) also interfere with the metabolism of caffeine (15). Caffeine has been shown to interfere with the metabolism of the sleep medication zolpidem, the antipsychotic clozapine, and bronchodilator theophylline (15).

NEUROPHARMACOLOGY

Adenosine

The primary mechanism of action of caffeine is nonselective antagonism at adenosine receptors. Adenosine is an endogenous nucleoside that plays a role in a number of central and peripheral nervous system functions. Although four adenosine receptor subtypes have been identified, A_1 and A_{2A} receptors are the major targets of caffeine (19). A_1 and A_{2A} receptors are both g-protein coupled receptors that produce a variety of downstream cellular effects via multiple mechanisms including inhibition and activation of adenylyl cyclase, respectively, and inhibition and activation of various ion channels (e.g., Ca^{2+}) (14). A_1 receptors are widely expressed in the brain with the highest densities in the hippocampus, cerebellum, cerebral cortex, and areas of the thalamus. A_{2A} receptors tend to be concentrated in dopamine-rich areas of the brain including the striatum, nucleus accumbens, and the olfactory tubercle (14). Adenosine receptors are also colocalized and functionally interact with each other as well as with dopamine receptors and glutamate receptors in various brain regions (19). A detailed analysis of the respective functions of adenosine receptors and their heteromers in physiologic and behavioral processes is presented elsewhere (14,19).

In general, adenosine has inhibitory effects on the CNS. Adenosine inhibits the release of excitatory neurotransmitters, reduces the spontaneous rate of neuron firing, and has anticonvulsant effects (14). There is also evidence that the accumulation of adenosine, triggered by energy depletion, functions as a sleep-promoting factor (20). Adenosine also suppresses motor activity and operant response rates. In the periphery, adenosine causes cerebral vasodilation, constricts bronchial smooth muscle, produces negative inotropic/chronotropic effects on the heart, and inhibits gastric secretions, lipolysis, and renin release (21).

Caffeine, which is structurally similar to adenosine, binds with adenosine receptors and produces effects that are consistent with reversal of the inhibiting effects of adenosine on

the aforementioned systems. For example, in the CNS, caffeine increases spontaneous neuronal firing, increases the turnover or levels of various neurotransmitters (e.g., acetylcholine, norepinephrine, dopamine, serotonin, glutamate, and GABA), has convulsant activity, increased motor activity, and inhibits sleep (20,21). Some of the peripheral nervous system effects of caffeine include cerebral vasoconstriction, relaxation of bronchial smooth muscle, and increased gastric secretions.

Dopamine

Similar to classic stimulants such as amphetamine and cocaine, there is evidence that some of the motor and reinforcing effects of caffeine are mediated by dopaminergic mechanisms. Caffeine antagonizes adenosine at receptors that are colocalized and that functionally interact with dopamine receptors (i.e., adenosine–dopamine heteromers). Functionally, caffeine produces its motor and reinforcing effects in part by releasing the pre- and postsynaptic brakes imposed by antagonistic adenosine–dopamine interactions (19). In animal studies, caffeine produces behavioral effects similar to classic dopaminergically mediated stimulants such as increased locomotor activity, increased rotational behavior, stimulant-like discriminative stimulus effects, and self-injection. Caffeine potentiates the behavioral effects of dopaminergically mediated stimulants on these same behaviors, effects that can be diminished or abolished by the blockade or depletion of dopamine receptors (14,22).

Dopamine release in the shell of the nucleus accumbens appears to be a neuropharmacologic mechanism underlying the abuse potential of many drugs (23). In vivo microdialysis studies demonstrate that caffeine increases dopamine release in the dorsal shell of the nucleus accumbens (24,25).

Other Mechanisms

Caffeine can also inhibit phosphodiesterase activity and mobilize intracellular calcium release (21). However, these effects are generally observed at levels much higher than typical dietary doses. Nevertheless, it remains possible that these non-adenosine mechanisms may mediate some of the effects produced by high doses of caffeine such as those associated with caffeine intoxication. For example, there are preclinical data that suggest that some of the cardiac and respiratory effects of caffeine may be mediated via inhibition of phosphodiesterase activity (21).

PHYSIOLOGIC EFFECTS

Caffeine produces effects on a variety of organ systems as has been reviewed elsewhere (4,12). At moderate dietary doses, caffeine increases blood pressure and tends to have no effect or to reduce heart rate. Caffeine constricts cerebral blood vessels and reduces cerebral blood flow. Caffeine dilates bronchial pathways, although not as effectively as theophylline (12), and increases the rate of respiration. Caffeine stimulates gastric acid secretion (12) and colonic activity. Caffeine produces dose-related thermogenic effects, lipolysis (12), and has been shown to be ergogenic during exercise (26,27). Caffeine increases plasma epinephrine, norepinephrine, rennin, and free fatty acids. Caffeine increases diuresis and the urinary excretion of calcium, magnesium, potassium, sodium, and chlorides. Caffeine also increases adrenocorticotropic hormone (ACTH) and cortisol levels. Caffeine increases insulin levels and reduces insulin sensitivity in healthy individuals, and increases postprandial glucose and insulin responses among patients with type 2 diabetes who are habitual coffee drinkers (28). Not all of the observed physiologic effects of caffeine necessarily have clinical significance (see the section "Caffeine and Health" in this chapter), and the development of tolerance needs to be considered in understanding the physiologic effects of caffeine consumption.

THERAPEUTIC USES

As a mild central nervous stimulant, caffeine is commonly used to increase energy and alertness and ward off fatigue. A number of OTC caffeine preparations are marketed as energy aids (e.g., Vivarin, NoDoz). Studies demonstrate that caffeine can enhance cognitive and motor performance, especially under conditions of fatigue, sleep deprivation, or caffeine withdrawal. Caffeine is also used to enhance athletic performance due to its ergogenic effects (26,27), and has been restricted by some major athletic governing bodies. Caffeine can enhance the analgesic effects of certain medications, and it is currently added to a variety of OTC and prescription analgesics (e.g., Excedrin, Cafergot) used to treat various types of pain including headache. Not surprisingly, caffeine is the most effective treatment for caffeine withdrawal headaches, which are likely caused by rebound cerebral vasodilation in response to acute caffeine abstinence. Likewise, caffeine can prevent postsurgical caffeine withdrawal headaches when administered prophylactically to habitual caffeine consumers (29). As a respiratory stimulant, caffeine is one of the standard treatments for apnea of prematurity in neonates. Because of its lipolytic and thermogenic effects, caffeine is also used to promote weight loss and can be found in many weight-loss products. Caffeine has also been used to treat postprandial hypotension, although its therapeutic effectiveness for this indication is unclear.

CAFFEINE AND HEALTH

The possibility that caffeine may pose health risks is of great interest to the general public and scientific community, and has been the focus of numerous studies and scholarly reviews (30–32). Though associations between caffeine consumption and various health conditions have been found, there is no evidence for nonreversible pathologic consequences of caffeine use (e.g., cancer, congenital malformations). However, there are some groups of individuals who are considered to be at higher risk for caffeine-related problems including pregnant women, children, adolescents, and the elderly (31). Further-

more, individuals with medical problems such as hypertension, diabetes, cardiac problems, urinary incontinence, insomnia, and anxiety may be more vulnerable to the adverse effects of caffeine. As discussed in more detail throughout this chapter, caffeine use can also be associated with several distinct psychiatric syndromes: caffeine intoxication, caffeine withdrawal, caffeine dependence, caffeine-induced sleep disorder, and caffeine-induced anxiety disorder. Recent epidemiologic research also suggests that caffeine and/or coffee consumption may offer some protective effects against specific diseases (31). The associations between caffeine and specific health issues are briefly outlined below.

Negative Health Effects

Research has shown that caffeine can increase blood pressure by 5 to 15 mg Hg systolic and 5 to 10 Hg diastolic for several hours in healthy adults (32). It has been argued that, even after taking the effects of tolerance into account, the hypertensive effects of caffeine represent an important cardiovascular risk factor (33,34). A recent longitudinal genetic association study found that variability in the CYP1A2 gene predicted the later development of hypertension, with those carrying the allele associated with slow metabolism of caffeine having a much greater risk of developing coffee-associated hypertension (7). Caffeine can influence heart rate variability and increase arterial stiffness with peak effects about 60 minutes after ingestion, but the clinical significance of these findings is not clear (35). Both caffeinated and decaffeinated coffees contain lipids that significantly raise serum total and low-density lipoprotein (LDL) cholesterol (31). The highest levels of lipids are delivered from espresso (a component of many popular coffee drinks such as cappuccino and latte), French press, Turkish, and boiled coffee. Instant coffees and those prepared by paper filtration contain much lower levels of these lipids. Epidemiologic studies examining the relationship between coffee consumption and risk of myocardial infarction (MI) on the whole have been equivocal; however a recent analysis suggests that coffee-associated risk of MI is much greater among coffee drinkers who have the CYP1A2 genotype associated with slow caffeine metabolism (8). Some studies suggest that coffee can exacerbate gastroesophageal reflux (GERD); however, it is not clear if it is due specifically to caffeine or other coffee constituents.

Caffeine also increases detrusor instability (i.e., unstable bladder) in patients with complaints of urinary urgency and detrusor instability. Chronic caffeine consumption has been shown to contribute to urinary incontinence in psychogeriatric patients, and caffeine reduction can improve urinary incontinence symptoms (36). Caffeine increases the urinary excretion of calcium. Thus, it has been suggested that caffeine may negatively affect overall calcium balance; however, the amount of increased calcium loss due to caffeine is likely not clinically significant in individuals with adequate calcium intake (32). Associations between high caffeine consumption and bone fractures have been observed in some epidemiologic studies, particularly among women with low calcium intake (37); however, a direct effect of caffeine on the increased likelihood of fractures has not been observed. Caffeine has also been shown to impair glucose metabolism and insulin sensitivity among individuals with type 2 diabetes (28) and among pregnant women with gestational diabetes (38).

The degree to which maternal caffeine consumption affects pregnancy outcomes has been given considerable research attention. Caffeine readily crosses the placental barrier and is distributed to all fetal tissues including the CNS. Fetuses lack the necessary enzyme systems to metabolize caffeine, and caffeine metabolism slows considerably in the later stages of pregnancy allowing for substantial fetal exposure (18). Research suggests that maternal caffeine use increases the likelihood of spontaneous abortion in a roughly dose-dependent fashion (39,40). Associations between high caffeine use and decreased fecundity and reduced fetal growth have also been observed (31,32), including a recent study that showed that reduced fetal growth was predicted by as little as one to two cups of coffee consumption per day (41). Comprehensive scientific reviews of research on caffeine and pregnancy have concluded that reproductive aged women should consume no more than 300 mg of caffeine per day (31,32).

There is no evidence that caffeine has negative effects on cancer risk, fibrocystic breast disease, peptic or duodenal ulcers, or risk of stroke.

Positive Health Effects

Case control and epidemiologic studies have suggested a relationship between caffeine consumption and reduced risk of Parkinson disease (42). Epidemiologic studies have also reported an association between coffee drinking and reduced incidence of chronic liver disease (43), although the potential mechanisms are unclear, and may be unrelated to caffeine. Additionally, epidemiologic studies have reported a protective effect of coffee drinking for risk of developing type 2 diabetes with the effects attributed to coffee constituents other than caffeine (44).

SUBJECTIVE AND DISCRIMINATIVE STIMULUS EFFECTS

Acute doses of caffeine in the typical dietary dose range (i.e., 20 to 200 mg), produce a number of positive subjective effects including increased well-being, happiness, energy, alertness, and sociability (4,45). These effects are qualitatively similar to those produced by other stimulants such as amphetamine and cocaine (46). In habitual caffeine consumers positive subjective effects are most reliably demonstrated when caffeine is administered after a period of caffeine abstinence and thus may in part represent a reversal of withdrawal (47,48). However, positive subjective effects of caffeine have also been demonstrated in caffeine consumers under conditions of minimal caffeine abstinence as well as among light nonhabitual caffeine consumers.

Negative subjective effects typically emerge at higher caffeine doses. Acute doses of caffeine greater than 200 mg are

more likely to produce increased reports of anxiety, jitteriness, tense negative mood, upset stomach, insomnia, and "bad effects." Individual differences in caffeine sensitivity and tolerance seem to play an important role in the likelihood and severity of negative subjective effects. For example, individuals with panic disorder or generalized anxiety disorder tend to be particularly sensitive to the anxiogenic effects of caffeine.

The negative subjective effects of caffeine tend to be relatively mild and short-lived, consistent with its half-life of 4 to 6 hours. However, very high doses of caffeine have been associated with clinically significant distress and psychopathology (e.g., caffeine intoxication), as discussed in the section "Caffeine Intoxication."

Several studies have demonstrated that most individuals can reliably discriminate caffeine (100 to 320 mg) from placebo (4). Some individuals are able to discriminate very low doses of caffeine (e.g., 10 mg) after training (45), which is consistent with findings that low doses of caffeine (e.g., 9 to 12.5 mg) can produce improvements in behavioral performance (49). Subjects in these studies generally report making the discrimination based on the subjective effects of caffeine, with positive subjective effects typically providing the basis for low caffeine dose discrimination and negative subjective effects providing the basis for high dose discrimination.

Drug discrimination studies have demonstrated both similarities and differences between caffeine and other stimulant drugs. For example, both caffeine and *d*-amphetamine produced cocaine-appropriate responding in a cocaine versus placebo discrimination study (50). Other studies showed that caffeine produced dose-related partial generalization to *d*-amphetamine in *d*-amphetamine-trained subjects (46) and that subjects can be trained to reliably discriminate between caffeine and *d*-amphetamine (51). In caffeine-trained subjects methylphenidate and theophylline produced caffeine-appropriate responding (4).

PERFORMANCE

Many studies have examined the effects of caffeine on human performance (for citations see (4)). In general, caffeine at normal dietary doses can restore performance that has been degraded by sleep deprivation, fatigue, prolonged vigilance, or caffeine withdrawal (52,53). Specifically, caffeine improves sustained attention (or vigilance), reaction time, and tapping speed relative to placebo, although results are variable across studies and the effects are often small. The effect of caffeine on memory has also been investigated, but there is little evidence for an association. A number of recent studies using military personnel have demonstrated that caffeine can improve performance relative to placebo on military-type cognitive (e.g., vigilance) and physical tasks (e.g., running times) after periods of prolonged wakefulness (53).

The great majority of studies claiming to demonstrate performance-enhancing effects of caffeine are difficult to interpret because they do not account for the effects of caffeine withdrawal. That is, many studies compare the effects of caffeine versus placebo in regular caffeine consumers who have abstained from caffeine, usually overnight. Under these conditions, improvements in performance after caffeine relative to placebo may reflect restoration of performance deficits caused by withdrawal, rather than a performance-enhancing effect of caffeine per se (47). However, some studies have shown caffeine-related performance enhancements among light nondependent caffeine consumers and nonconsumers. It seems likely that caffeine enhances human performance on some types of tasks (e.g., vigilance), especially among nontolerant individuals. Performance enhancements beyond withdrawal reversal effects are likely to be modest among high-dose habitual caffeine consumers (47).

There is a growing body of research on the effects of caffeine on exercise performance. In general, controlled studies show that relative to placebo, caffeine can enhance performance during endurance exercise (e.g., 30 to 120 minutes) (26,54), can reduce ratings of perceived exhaustion or effort, and can improve speed and/or power output in simulated race conditions. Some studies have also demonstrated a beneficial effect of caffeine during short-term high-intensity exercise and anaerobic resistance training, but these effects are generally more difficult to demonstrate and smaller than effects observed during endurance activities (54). A number of nonindependent mechanisms have been proposed to explain caffeine's ergogenic effects including increased fatty acid oxidation, increased availability of muscle glycogen, mobilization of intracellular calcium, increased muscle contractile force, and direct CNS effects via adenosine antagonism (26). There is also some evidence that caffeine may increase muscle contractile force during endurance exercise (27).

Studies have directly compared the effects of caffeine, modafinil, and *d*-amphetamine on vigilance performance after an extended period of sleep restriction (44 to 64 hours) and showed that the three stimulants were equally effective at restoring vigilance performance, with caffeine having the shortest duration of action and *d*-amphetamine having the longest (55).

CAFFEINE AND SLEEP

It is well documented that caffeine increases wakefulness and inhibits sleep onset. The mechanism of action is hypothesized to be antagonism of endogenous adenosine, which is believed to be a homeostatic sleep factor that mediates sleepiness following prolonged wakefulness (20). Perhaps the most widely accepted therapeutic use of caffeine is to increase wakefulness and alertness, and reverse performance decrements produced by sleep deprivation (56). There is also abundant evidence that caffeine has disruptive effects on planned sleep (i.e., insomnia). Caffeine ingested throughout the day or before bedtime has been shown to interfere with sleep onset, total time slept, sleep quality, and sleep stages (56). Because of caffeine's ability to disrupt sleep, caffeine is used as a challenge agent to study insomnia in healthy volunteers. Caffeine's effects on sleep appear to be determined by a number of factors including dose, the time between caffeine ingestion and attempted sleep, and in-

dividual differences in sensitivity and/or tolerance to caffeine. Caffeine's effects on sleep appear to be dose dependent, with greater amounts of caffeine causing greater sleep difficulties. The closer caffeine is taken to bedtime, the more likely it is to produce disruptive effects. However, 200 mg of caffeine taken early in the morning has been shown to produce small but significant effects on the following night's total sleep time, sleep efficiency, and EEG power spectra (57). Caffeine-induced sleep disturbance is greatest among nonconsumers of caffeine; however, it is not clear whether this difference is due to an absence of acquired tolerance or to a preexisting population difference in sensitivity to caffeine. Genetic factors appear to explain some of the individual differences in sensitivity to the sleep-disruptive effects of caffeine. For example, variation in the ADORA2A gene has been shown to be associated with individual differences in caffeine's effects on sleep, measured both subjectively and objectively (11). Although there is evidence for tolerance to the sleep-disrupting effects of caffeine, tolerance appears to be incomplete, and thus regular caffeine consumers may still be vulnerable to caffeine-related sleep problems. A recent study concluded that the sleep-disruptive effects of caffeine are more pronounced during daytime recovery sleep than nocturnal sleep, perhaps due to an interaction of caffeine pharmacology and circadian rhythms (58).

In addition to caffeine's ability to disrupt sleep, there have been case reports of caffeine causing hypersomnia. Furthermore, acute abstinence after chronic caffeine consumption has been shown to increase daytime sleepiness as well as to increase nighttime sleep duration and quality (59).

The *DSM-IV-TR* includes a diagnosis of caffeine-induced sleep disorder, which is characterized by a prominent sleep disturbance that is etiologically related to caffeine use (60). It is not necessary to meet full criteria for a *DSM-IV-TR* sleep disorder to qualify for a diagnosis of caffeine-induced sleep disorder. Caffeine is most often associated with insomnia; however, the *DSM-IV-TR* also recognizes hypersomnia due to caffeine withdrawal. Caffeine-induced sleep disorder is diagnosed when symptoms of a sleep disturbance (e.g., insomnia) are greater than would be expected during caffeine intoxication or caffeine withdrawal. There are no specific data on the prevalence or incidence of caffeine-induced sleep disorder.

REINFORCEMENT

A number of carefully controlled research studies over the past 20 years provide substantial evidence for the reinforcing effects of caffeine (for citations see (4)). Controlled laboratory studies demonstrate that subjects will choose caffeine over placebo in double-blind choice procedures, as well as perform work or forfeit money in exchange for caffeine. When multiple self-administration opportunities are available within a day, doses as low as 25 mg have been shown to be reinforcing (61). When self-administration is limited to once a day, then doses of 100 and 200 mg are reinforcing, while doses of 400 mg and greater tend to be avoided.

There is quite a bit of individual variability in the reinforcing effects of caffeine. Across studies, the overall incidence of caffeine reinforcement in normal caffeine users is approximately 40%, with a higher incidence (i.e., 80% to 100%) of reinforcement under conditions of repeated caffeine exposure. In choice studies, subjects who choose caffeine tend to report positive subjective effects, whereas those who choose placebo are more likely to report negative subjective effects (e.g., jitteriness) at low to moderate caffeine doses (62).

Caffeine physical dependence potentiates the reinforcing effects of caffeine. For example, caffeine consumers were more than twice as likely to show caffeine reinforcement if they reported caffeine withdrawal symptoms after drinking decaffeinated coffee (63). In studies in which caffeine physical dependence has been experimentally manipulated, subjects are more than twice as likely to choose caffeine over placebo when they are physically dependent (64). There is also evidence that avoidance of caffeine withdrawal determines caffeine consumption to a greater extent than the positive effects of caffeine (64). Caffeine reinforcement also appears to be influenced by task requirements. That is, in a double-blind study subjects chose caffeine over placebo when required to perform a vigilance task, but chose placebo over caffeine when required to engage in relaxation (65).

A series of studies have used a conditioned flavor preference paradigm to provide indirect evidence of caffeine reinforcement (66). In these studies, subjects who were repeatedly exposed to a novel flavored drink paired with caffeine tended to show increased ratings of drink pleasantness, while subjects receiving placebo-paired drinks showed decreased ratings of drink pleasantness (67). Among habitual caffeine consumers, the ability of caffeine to produce increases in flavor liking appears to be primarily determined by the alleviation of withdrawal symptoms (i.e., negative reinforcement) (67). It seems plausible that such conditioned flavor preferences in the natural environment play an important role in the development of consumer preferences for different types of caffeine-containing beverages.

Caffeine reinforcement has also been observed in animals using self-administration, conditioned place preference, and conditioned taste aversion procedures. In contrast to classic abused stimulants such as amphetamine and cocaine, caffeine self-administration is observed in animals under a relatively narrow range of conditions (4).

TOLERANCE

The degree of caffeine tolerance depends on a number of factors including the challenge and maintenance doses, frequency of administration, and individual differences in caffeine elimination. High doses of caffeine (400 to 1200 mg/day) administered throughout the day have been shown to produce "complete" tolerance to some, but not all of the effects of caffeine. However, typical dietary doses of caffeine do not usually produce complete tolerance to caffeine's central and peripheral effects.

Controlled human laboratory studies have demonstrated tolerance to the subjective effects of caffeine. Complete tolerance (i.e., no difference between placebo and caffeine after

prolonged caffeine administration) to subjective effects (e.g., energetic) has been demonstrated after 300 mg t.i.d. for 18 days (62) and 200 mg b.i.d for 14 days (68), but not after lower doses or shorter exposure periods (69). Substantial but incomplete tolerance has been shown to the sleep-disruptive effects of high doses of caffeine (e.g., 400 mg t.i.d. for 7 days) (4).

Some studies have shown complete tolerance to blood pressure and other physiologic effects (plasma norepinephrine and epinephrine and plasma rennin activity) after high doses of caffeine (e.g., 600 to 750 mg/day) (33). However, about half of the subjects fail to show complete tolerance to the hypertensive effects of caffeine even after maintenance dosing with 600 mg/day (70). Doses in the range of typical daily caffeine consumption (i.e., 300 to 400 mg/day) produce only incomplete tolerance to hypertensive and other physiologic effects of caffeine (e.g., cerebral blood flow velocity, EEG) (33,68,69).

PHYSICAL DEPENDENCE AND WITHDRAWAL

The caffeine withdrawal syndrome has been well-characterized. A 2004 comprehensive review of caffeine withdrawal evaluated 57 experimental studies and 9 survey studies to validate individual symptoms of caffeine withdrawal and identify other important parameters of the caffeine withdrawal syndrome (71). That review identified 13 caffeine withdrawal symptoms that were reliably observed across carefully controlled studies (Table 22.2). Headache is a hallmark feature of caffeine withdrawal with approximately 50% of regular caffeine users reporting headache by the end of the first day of abstinence. Such headaches have been described as diffuse, throbbing, gradual in development, and sensitive to movement. Caffeine constricts cerebral blood vessels via antagonism of adenosine. Caffeine abstinence produces rebound cerebral vasodilatation and increased cerebral blood flow, and such vascular changes are a likely mechanism underlying caffeine withdrawal headache (68,72). Other commonly observed caffeine withdrawal symptoms include fatigue, decreased energy/activeness, decreased alertness, drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability, and foggy/not clearheaded. In addition, flu-like symptoms, nausea/vomiting, and muscle pain/stiffness can be present (71). These symptoms can be conceptually clustered into five categories: (a) headache, (b) fatigue or drowsiness, (c) dysphoric mood, depressed mood or irritability, (d) difficulty concentrating, and (e) flu-like somatic symptoms of nausea, vomiting, and muscle pain/stiffness (71), but empirical studies are needed to statistically determine how symptoms cluster together. Changes in EEG, increased cerebral blood flow, and cognitive and behavioral performance deficits have also been observed during acute caffeine abstinence (68,71).

TABLE 22.2 Empirically validated symptoms of caffeine withdrawal

Headache
Tiredness/fatigue
Drowsiness/sleepiness
Irritability
Depressed mood
Difficulty concentrating
Muzzy/foggy/not clearheaded
Flu-like symptoms
Nausea/vomiting
Muscle pain/stiffness
Decreased energy/activeness
Decreased alertness/attentiveness
Decreased contentedness/well-being

Source: Juliano LM, Griffiths RR. A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology (Berl).* 2004;176:1–29.

Withdrawal symptoms typically emerge 12 to 24 hours after the last dose of caffeine and tend to peak within the first 2 days. Symptoms usually persist anywhere from 2 to 9 days (71), although there are reports of caffeine withdrawal headache lasting for up to 3 weeks (71).

The severity of caffeine withdrawal can range from mild to incapacitating. There is variability in withdrawal severity both within and across individuals. The incidence of caffeine withdrawal–related impairment or distress to the point of significantly interfering with normal functioning is about 13%. For example, caffeine withdrawal can produce severe headaches that are described as the worst ever experienced (73). Some individuals experiencing caffeine withdrawal have reported that they cannot continue to perform their normal daily activities such as caring for children or going to work (74).

Although there is wide variability across individuals, in general the likelihood and severity of caffeine withdrawal increases as daily caffeine dose increases (75). The daily caffeine dose necessary to produce withdrawal is surprisingly low, with significant withdrawal symptoms observed in individuals consuming as little as 100 mg caffeine per day—the amount in a small cup of brewed coffee (75,76). Caffeine withdrawal can occur after relatively short-term exposure to daily caffeine. Significant withdrawal symptoms have been observed after just three consecutive days of 300 mg/day caffeine, with more severe withdrawal symptoms manifesting after 7 and 14 consecutive days of caffeine (75). In individuals who normally abstain from caffeine, withdrawal headache has been observed in individuals after just a week of prescribed heavy caffeine consumption (i.e., 600 to 750 mg) (73).

Caffeine withdrawal symptoms are usually alleviated quickly after caffeine re-exposure (i.e., 60 minutes or less). Caffeine withdrawal can be suppressed by caffeine doses well below the usual daily dose (e.g., 25 mg caffeine suppressed withdrawal after daily doses of 300 mg) (75). An implication of these findings is that a substantial decrease in caffeine consumption is necessary to manifest the full caffeine withdrawal syndrome.

Retrospective survey studies have also been conducted to determine the frequency of caffeine withdrawal in the general population. In one population-based random digit dialing survey study, 44% of caffeine users reported having stopped or reduced caffeine use for at least 24 hours in the past year. Of those, over 40% reported experiencing one or more withdrawal symptoms. Interestingly, over 70% of those who stopped or reduced caffeine as part of a permanent quit attempt reported withdrawal symptoms, and 24% reported headache and other symptoms that interfered with performance (77). In another study, 11% of caffeine users who were making an inquiry about participation in a clinical research trial reported that they had "problems or symptoms on stopping caffeine in the past," of which 25% reported that the problems were severe enough to interfere with normal activity (78). The number of individuals who actually experienced a period of caffeine abstinence was not ascertained.

Although most withdrawal research has been with adults, there is evidence that children and adolescents who use caffeine also experience caffeine withdrawal symptoms upon abstinence (79). It is possible that children may be even more susceptible to experiencing withdrawal episodes as they likely have less control over the regular availability of caffeine-containing products. Caffeine withdrawal has also been documented in neonates born to mothers who have had recent caffeine exposure.

The observations that caffeine withdrawal can cause clinically significant distress or functional impairment have resulted in the inclusion of caffeine withdrawal as an *ICD-10* diagnosis (80) and as a proposed diagnosis in *DSM-IV-TR* (60,81). The 1994 *DSM* Work Group included caffeine withdrawal as a proposed diagnosis rather than an official diagnosis to encourage further research on the range and specificity of caffeine withdrawal symptoms (81). Carefully controlled research on caffeine withdrawal has more than doubled since 1994, now providing a sound empirical basis for a diagnosis of caffeine withdrawal (71). The *DSM-IV-TR* criteria are conservative in that it excludes cases in which other withdrawal symptoms occur in the absence of headache. It also excludes symptoms that have been documented in recent studies including dysphoric mood, difficulty concentrating, and irritability, and includes a symptom for which there is little empirical support (i.e., anxiety). To date, only one study has evaluated the incidence of caffeine withdrawal using *DSM-IV-TR* criteria (77). This population-based survey found that 11% of those who had given up or reduced caffeine use in the past year met criteria for caffeine withdrawal. Among individuals who reported trying to stop caffeine use permanently, 24% met criteria for caffeine withdrawal.

Caffeine withdrawal symptoms overlap with various psychological and physical ailments. Caffeine withdrawal should be considered when patients present with headaches, fatigue, mood disturbances, impaired concentration, and flu-like symptoms. Patients are often asked to stop food and fluids before certain blood tests, surgery, or medical procedures (e.g., colonoscopies, fasting blood sugar tests) and may experience adverse effects that could go unrecognized as caffeine withdrawal. Caffeine withdrawal has been identified as a significant cause of postoperative headaches, the risk of which can be reduced if habitual caffeine consumers are administered caffeine on the day of the surgical procedure (29).

A recent study directly compared periods of abstinence from either caffeine or nicotine among habitual users of both drugs and found no differences between the two in the psychosocial manifestations of withdrawal as measured by subjective well-being, social functioning, and drug craving (82).

CAFFEINE INTOXICATION

Caffeine intoxication is currently defined by the *DSM-IV-TR* by a number of symptoms and clinical features that emerge in response to excessive consumption of caffeine (Table 22.3) (60). The most common features of caffeine intoxication include nervousness, restlessness, insomnia, gastrointestinal upset, muscle twitching, tachycardia, and psychomotor agitation. Fever, irritability, tremors, sensory disturbances, tachypnea, and headaches have also been reported in response to excess caffeine use (4).

DSM-IV-TR diagnostic guidelines require that the diagnosis be dependent on recent consumption of at least 250 mg of caffeine, but much higher doses (>500 mg) are usually associated with the syndrome. High-dose intoxicating effects of caffeine are very unpleasant and are not usually sought out by users. Individual differences in sensitivity to caffeine and tolerance likely play a role in vulnerability to caffeine intoxication. Although caffeine intoxication can occur in the context of habitual chronic consumption of high doses of caffeine, it most often occurs after consumption of large doses in infrequent caffeine users, or in regular users who have substantially increased their intake. There are generally no long-lasting consequences of caffeine intoxication, although caffeine can be lethal at very high doses (e.g., 5 to 10 g), and there are documented cases of accidental death and suicide by caffeine overdose, usually in the form of pills (4).

Few studies have assessed the prevalence of caffeine intoxication, and most have evaluated selected populations (e.g., psychiatric inpatients) and used ambiguous criteria. One general population survey found that 7% of respondents met *DSM-IV* criteria for caffeine intoxication (77). The occurrence of individual symptoms of caffeine intoxication appears to be fairly common (e.g., nervousness). For example, a study involving more than 3600 twins found that 29% reported having felt ill or shaky or jittery after consuming caffeinated beverages (83). In a survey of college students, 19% reported experiencing heart palpitations after consuming energy drinks (1).

A recent study evaluated 265 cases of caffeine overuse that were reported to a local area poison center between 2001 and 2004 after ingestion of caffeinated products other than coffee or tea (1). They found that caffeine was in the

TABLE 22.3 Diagnostic criteria for caffeine intoxication (*DSM-IV-TR*)

A) Recent consumption of caffeine, usually in excess of 250 mg (e.g., more than two to three cups of brewed coffee)
B) Five (or more) of the following signs, developing during, or shortly after, caffeine use:
1) Restlessness
2) Nervousness
3) Excitement
4) Insomnia
5) Flushed face
6) Diuresis
7) Gastrointestinal disturbance
8) Muscle twitching
9) Rambling flow of thought and speech
10) Tachycardia or cardiac arrhythmia
11) Periods of inexhaustibility
12) Psychomotor agitation
C) The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D) The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder (e.g., an anxiety disorder).

From American Psychiatric Association. *The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision.* Washington, DC: American Psychiatric Association; 2000, with permission.

form of a medication in 77% of the cases, a caffeine-enhanced beverage in 16% of cases, and a dietary supplement in 14% of cases. Patients were typically young (21 years old on average), half were male, and 12% required hospitalization. Caffeine was implicated in 4656 reports to poison control centers in the United States in 2005, with half warranting treatment in a health care facility (1). Caffeinated gum and energy capsules have also been implicated in published case reports of caffeine intoxication in teenagers requiring medical attention.

It appears that reports of caffeine intoxication may be increasing with the growing popularity of highly caffeinated energy drinks (1). It has been postulated that the potential for caffeine intoxication to occur from consumption of energy drinks may be greater than other dietary sources of caffeine because of the absence of caffeine content labeling and appropriate health warnings, and their appeal and marketing to young and perhaps nontolerant individuals (1). For example, a recent series of case reports based on poison control center data found that a particular energy drink containing 250 mg of caffeine was implicated in a number of reports of caffeine intoxication. The most common symptoms were hypertension, jitteriness, agitation, tremors, nausea, vomiting, and dizziness (84). Consumption of about eight cans of energy drinks (or 640 mg caffeine) was implicated in the cardiac arrest suffered by a 28-year-old male motocross racer (1). There have also been numerous media reports of children becoming sick after consuming energy drinks (1).

CAFFEINE AND ANXIETY

The anxiogenic effects of caffeine are well established (for citations see (4)). Acute doses of caffeine generally greater than 200 mg have been shown to increase anxiety ratings in nonclinical populations, with higher doses sometimes inducing panic attacks (85). Individuals with anxiety disorders tend to be particularly sensitive to the effects of caffeine. Experimental studies have demonstrated that caffeine exacerbates anxiety symptoms in individuals with panic disorder and generalized anxiety disorder to a greater extent than healthy control subjects. Genetic factors can predict variability among individuals to the anxiolytic effects of caffeine. Genetic polymorphisms on the A_{2A} receptor gene (ADORA2A) were shown in two studies to be associated with anxiogenic responses to 150-mg dose of caffeine among low caffeine consumers (10). Furthermore, first-degree relatives of patients with panic disorder show a greater anxiogenic response to a high dose of caffeine (85). It has been suggested that individuals with anxiety disorders may find the stimulus effects of caffeine aversive and therefore may naturally limit their caffeine intake. Laboratory studies have demonstrated that lower baseline anxiety levels predict caffeine consumption using drug choice procedures under double-blind conditions (62). Some correlational studies have found that individuals with anxiety disorders, such as panic disorder, report consuming less caffeine than healthy controls. However, other studies have shown a positive relationship between anxiety disorders or

greater anxiety levels and caffeine use, or no relationship. In light of this mixed data, it seems reasonable to conclude that some but not all highly anxious individuals will limit caffeine, and it is possible that some may fail to recognize the role that caffeine plays in their anxiety.

Abstention from caffeine has been shown to produce improvements in anxiety symptoms among individuals seeking treatment for an anxiety disorder. Interestingly, individuals with high caffeine consumption have been shown to have greater rates of minor tranquilizer use (e.g., benzodiazepines) relative to those with low to moderate caffeine consumption (86), although the mechanism underlying this association has not been established.

The *DSM-IV-TR* includes a diagnosis of caffeine-induced anxiety disorder (60). Caffeine-induced anxiety disorder is characterized by prominent anxiety, panic attacks, obsessions, or compulsions etiologically related to caffeine use. It is not necessary to meet full criteria for a *DSM-IV-TR* anxiety disorder to qualify for a diagnosis of caffeine-induced anxiety disorder. The prevalence and incidence of caffeine-induced anxiety disorder is not known.

CAFFEINE DEPENDENCE

Substance dependence is defined by a cluster of cognitive, behavioral, and physiological symptoms indicating that an individual continues to use a substance despite experiencing significant substance-related problems (60). The *DSM-IV-TR* does not presently include caffeine in its diagnostic schema for substance dependence. In contrast, the World Health Organization's *ICD-10* includes a diagnosis of substance dependence on caffeine, using very similar diagnostic criteria as the *DSM-IV-TR*. The rationale for excluding substance dependence on caffeine during the last major revision of the *DSM* in 1994 was that although it had been established that caffeine produces physical dependence, there was a lack of information pertaining to other features of substance dependence such as the inability to stop caffeine use and continued caffeine use despite knowledge of negative health consequences (81).

Since that time a number of published studies have described adults and adolescents who report problematic caffeine consumption and fulfill *DSM-IV-TR* substance dependence criteria on caffeine (Table 22.4) (74,77,79,87,88). For example, 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 only a restrictive set of four of the seven *DSM-IV* criteria that seemed most appropriate to problematic caffeine use were assessed (use despite harm, desire, or unsuccessful efforts to stop, withdrawal, and tolerance) (74). Using the same four criteria, another study identified adolescents who fulfilled diagnostic criteria for caffeine dependence (79). A study of pregnant women found that 57% of caffeine users fulfilled *DSM-IV* criteria for lifetime substance dependence on caffeine by endorsing three or more of the seven criteria (87).

The one population-based survey to date suggests that when individuals in the general population are surveyed about their caffeine use, a surprisingly large proportion endorse substance dependence criteria. In a random digit dialing 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

TABLE 22.4 Prevalence of endorsement of *DSM-IV* criteria for substance dependence among caffeine users (in %)

	General population		*DSM-IV* defined caffeine dependent individuals		
	Adults[a] (Ref. 77)	Pregnant women[a] (Ref. 87)	Adults[b] (Ref. 74)	Adolescents[b] (Ref. 79)	College students[a] (Ref. 88)
Used despite harm	14	43	94	58	57
Desire or unsuccessful efforts to stop	56	45	81	83	60
Withdrawal	18	77	94	100	73
Tolerance	8	50	75	92	70
Used more than intended	28	45	–	–	83
Give up activities to use	<1	0	–	–	20
Great deal of time with the drug	50	25	–	–	77
Endorsed three or more criteria	30	57	100	100	100

[a] Assessed all seven *DSM-IV* criteria for substance dependence.

[b] Assessed four *DSM-IV* criteria thought to be most pertinent to a meaningful assessment of problematic caffeine use.

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 (77).

As shown in Table 22.4, the rates of endorsement of the individual criteria vary widely across samples and data collection methodologies. The five *DSM-IV-TR* criteria for substance dependence that appear to be most pertinent to a meaningful assessment of problematic caffeine use are: (a) 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; (b) persistent desire or unsuccessful efforts to cut down or control substance use; (c) characteristic withdrawal syndrome or use of the substance to relieve or avoid withdrawal symptoms; (d) 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; and (e) substance is often taken in larger amounts or over a longer period than was intended. The remaining two criteria would not seem to be relevant to a widely available, culturally accepted drug like caffeine: (f) important social, occupational, or recreational activities are given up or reduced because of substance use and (g) a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects. Furthermore, inclusion of the last criterion could trivialize the diagnosis of caffeine dependence (e.g., sipping soft drinks throughout the day).

Individuals meeting criteria for caffeine dependence have shown a wide range of daily caffeine intake and have been consumers of various types of caffeinated products (e.g., coffee, soft drinks, tea, medications). A diagnosis of caffeine dependence has been shown to prospectively predict a greater incidence of caffeine reinforcement (89) and more severe withdrawal (74). Furthermore, among a sample of pregnant women advised by their physician to eliminate all caffeine throughout pregnancy, a caffeine dependence diagnosis predicted greater use of caffeine during pregnancy and a history of daily cigarette smoking (87). In that study, those with a caffeine dependence diagnosis and a family history of alcoholism used potentially problematic amounts of caffeine during pregnancy (i.e., half used more than 300 mg/day). Caffeine dependence has also been shown to be associated with a past history of alcohol abuse or dependence (74).

Available research and case reports suggest that a clinically meaningful caffeine dependence syndrome does exist. Additional research is needed to determine the prevalence of the disorder, the utility and clinical significance of the diagnosis, its relationship with other drug dependencies, and effective treatment strategies. 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. The Composite International Diagnostic Interview–Substance Abuse Module (CIDI-SAM), a well-regarded structured interview focused on substance-use disorders, contains a section for caffeine dependence according to *DSM-IV-TR* and *ICD-10* criteria.

CAFFEINE AND OTHER DRUGS OF DEPENDENCE

Alcohol

Heavy use and clinical dependence on caffeine is associated with heavy use and clinical dependence on alcohol (90). In one study, almost 60% of individuals fulfilling *DSM-IV* diagnostic criteria for substance dependence on caffeine had a history of alcohol abuse or dependence (74). Despite common lore that caffeine reverses the impairing effects of alcohol, controlled research suggests that such effects are generally of small magnitude and highly inconsistent across different types of behavioral and subjective measures. There is suggestive evidence that individuals consuming caffeine with alcohol tend to underestimate their levels of intoxication and impairment and may be more prone to injury (1). The popular practice of combining caffeinated energy drinks and alcohol, presumably to counteract the sedative effects of alcohol, suggests there is a need for research in this area.

Benzodiazepines

Benzodiazepines and benzodiazepine-like drugs (e.g., zolpidem) are widely used in the treatment of anxiety disorders and insomnia. Animal and human studies suggest a mutually antagonistic relationship between caffeine and benzodiazepines. An important clinical implication is that caffeine use should be evaluated when treating anxiety or insomnia with benzodiazepines. One study reported that a greater percentage of heavy caffeine consumers also use benzodiazepine minor tranquilizers; however, in general, rates of caffeine intake are similar among benzodiazepine users and nonusers.

Nicotine and Cigarette Smoking

Epidemiologic studies have shown that cigarette smokers consume more caffeine than nonsmokers (91), a finding that is consistent with the observation that cigarette smoking increases caffeine metabolism. Several studies have shown that cigarette smoking abstinence results in significant increases in caffeine blood levels among heavy caffeine consumers, presumably due to a reversal of smoking-induced increased caffeine metabolism. Although it has been posited that this effect could make smoking cessation attempts more difficult, the clinical significance has not been demonstrated (91). Some human and animal studies have demonstrated that caffeine can increase the reinforcing and discriminative stimulus effects of intravenous nicotine (92). Some studies have failed to show that caffeine administra-

tion reliably increases cigarette smoking or nicotine self-administration (93,94).

Cocaine

There is little epidemiologic data on the co-occurrence of caffeine and cocaine use. One study reported that the prevalence of caffeine use among cocaine abusers is lower than the general population (95). Interestingly, in that same study, cocaine users who consumed caffeine reported using less cocaine than those who do not regularly consume caffeine.

In animal studies caffeine increases the acquisition of cocaine self-administration, reinstates responding previously maintained by cocaine, and potentiates the stimulant and discriminative stimulus effects of cocaine (22). Caffeine was shown to produce cocaine-appropriate responding in a cocaine versus placebo discrimination study (50). The subjective effects of intravenous caffeine have been reported as cocaine-like in one study (96), but not another (97). Intravenous caffeine administration has been shown to produce a significant increase in craving for cocaine in cocaine abusers (96); however, oral administration of caffeine has not produced this effect (98). Although the documented interactions between caffeine and cocaine are interesting, the clinical importance has not been established.

CLINICAL IMPLICATIONS

Given the wide range of symptoms produced by excessive caffeine use and withdrawal, as described throughout this chapter, caffeine use should be routinely assessed during medical and psychiatric evaluations. Caffeine use or intoxication should be assessed in individuals with complaints of anxiety, insomnia, headaches, palpitations, tachycardia, or gastrointestinal disturbance. Caffeine intoxication should be considered in the differential diagnosis of amphetamine or cocaine intoxication, mania, medication-induced side effects, hyperthyroidism, and pheochromocytoma. Likewise, caffeine withdrawal should be considered when patients present with headaches, fatigue, mood disturbances, or difficulty concentrating. Caffeine withdrawal should be considered in the differential diagnosis of migraine or other headache disorders, viral illnesses, and other drug withdrawal states.

Caffeine users who are instructed to refrain from all food and beverages prior to medical procedures may be at risk for experiencing caffeine withdrawal. Caffeine withdrawal has been identified as a cause of postoperative headaches, and caffeine supplements during surgery have been shown to be effective in preventing withdrawal (29).

Caffeine interacts with a number of medications. Caffeine and benzodiazepine-like drugs (e.g., diazepam, alprazolam, triazolam) are mutually antagonistic, and thus caffeine use may interfere with the efficacy of benzodiazepines (4). Caffeine may also interfere with the metabolism of the antipsychotic clozapine as well as the bronchodilator theophylline to an extent that may be clinically significant (15). Case studies have suggested that caffeine withdrawal may be associated with increased serum lithium concentrations and lithium toxicity (15). Numerous compounds have been shown to decrease the rate of elimination of caffeine including oral contraceptive steroids, cimetidine, and fluvoxamine (15).

TREATMENT

Reduction or elimination of caffeine is advised for individuals who have caffeine-related psychopathology or when it is believed that caffeine is causing or exacerbating medical or psychiatric problems, or interfering with medication efficacy. A surprisingly large percentage of caffeine users in the general population (56%) report a desire or unsuccessful efforts to stop or reduce caffeine use (77). Fourteen percent of adults with a lifetime history of caffeine use report stopping caffeine completely, usually due to health concerns or unpleasant side effects (99).

There are no published reports of treatment interventions designed to assist individuals who would like to completely eliminate caffeine. Several reports suggest the efficacy of a structured caffeine reduction regimen (i.e., caffeine fading) for achieving substantial reductions of caffeine intake (4). A study of patients recruited from a urinary continence clinic found that a 4-week reduction program with a consumption goal of <100 mg/day was effective at reducing caffeine intake as well as urinary frequency and urgency outcomes (36).

Given the limited number of treatment strategies that have been evaluated for reducing or eliminating caffeine consumption, a reasonable approach is to adapt validated behavioral techniques used to treat dependence on other drugs (e.g., tobacco dependence). Effective behavior modification strategies include coping response training, self-monitoring, social support, and reinforcement for abstinence. Substance abuse treatment strategies including motivational interviewing and relapse prevention could also be readily applied to the treatment of caffeine dependence. Providing a list of caffeine-containing products may help to increase awareness of sources of caffeine and should facilitate self-monitoring efforts (Table 22.1). Some individuals may not readily accept the idea that caffeine is contributing to their problems (e.g., insomnia, anxiety). Such individuals should be encouraged to engage in a caffeine-free trial. There is some evidence that withdrawal symptoms may thwart quit attempts. Gradually reducing caffeine consumption may help attenuate withdrawal symptoms, although there has been no systematic research to determine the most efficacious reduction schedule. In general, reduction schedules over the course of 3 to 4 weeks have been shown to be effective. No data about the probability of relapse is currently available, although relapse after caffeine reduction has been reported (4). Table 22.5 lists practical guidelines for reducing or ceasing caffeine use.

TABLE 22.5 Guidelines for reducing or eliminating caffeine

1) *Education*
Patients should be educated about potential sources of caffeine. It may be useful to provide patients with a list of common caffeinated products (see Table 22.1). Some individuals may not be aware that caffeine is present in noncola beverages such as lemon-lime soft drinks and products made with guarana, maté, or kola nut.

2) *Self-monitoring*
Caffeine use should be self-monitored using a food diary for 1–2 weeks to determine a baseline level. If a self-monitoring period is not feasible, treatment providers can determine a rough estimate of total caffeine consumption via self-report. Self-monitoring should also be continued during the caffeine reduction phase of treatment.

3) *Calculate total daily caffeine consumption (mg)*
Calculate daily caffeine exposure in milligrams, taking into account the caffeine content of specific products, the serving sizes, and the number of servings.

4) *Determine a caffeine modification goal*
Decide on a caffeine modification goal with the patient. Some individuals may be interested in completely eliminating caffeine, whereas others may want to reduce their caffeine consumption. Individuals who would like to continue to consume some amount of caffeine, but who want to avoid experiencing withdrawal symptoms if they omit caffeine for a day, should be advised to consume no more than 50 mg/day.

5) *Generate a gradual reduction schedule*
A gradual reduction schedule should help to prevent or alleviate caffeine withdrawal symptoms. A reasonable decrease would be 10–25% of the baseline dose every few days until the caffeine moderation or cessation goal is achieved. Patients should identify a noncaffeinated substitute for their usual caffeine-containing beverage. Caffeinated beverages can either be omitted to achieve the desire amount or can be mixed with decaffeinated beverages.

6) *Employ behavior modification techniques*
Patients may benefit from behavior modification techniques shown to be effective in the treatment of dependence on other substances (e.g., nicotine). Such strategies may include self-monitoring, coping response training, reinforcement for abstinence, identifying barriers to change, social support, and reframing withdrawal as a temporary inconvenience.

7) *Follow-up*
Schedule a follow-up contact with the patient to check on the patient's progress.

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