03 - 20.3 Caffeine Related Disorders

20.3 Caffeine-Related Disorders

of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1268. Vergés A, Jackson KM, Bucholz KK, Grant JD, Trull TJ, Wood PK, Sher KJ. Deconstructing the age-prevalence curve of alcohol dependence: Why “maturing out” is only a small piece of the puzzle. J Abnormal Psychol. 2012;121:511. 20.3 Caffeine-Related Disorders Caffeine is the most widely consumed psychoactive substance in the world. Caffeine is found in more than 60 species of plants and belongs to the methylxanthine class of alkaloids, which also includes theobromine (found in chocolate) and theophylline (often used in the treatment of asthma). In the United States, 87 percent of children and adults consume foods and beverages containing caffeine. Caffeine affects various neurobiological and physiological systems and produces significant psychological effects. Caffeine is not associated with any life-threatening illnesses, but its use can result in psychiatric symptoms and disorders. The habitual use of caffeine and its widely accepted integration into daily customs can lead to an underestimation of the role that caffeine may play in one’s daily life and can make the recognition of caffeine-associated disorders particularly challenging. Hence, it is important for the clinician to be familiar with caffeine, its effects, and problems that can be associated with its use. Caffeine use is associated with five disorders: caffeine use disorder, caffeine intoxication, caffeine withdrawal, caffeine-induced anxiety disorder, and caffeineinduced sleep disorder. EPIDEMIOLOGY Caffeine is contained in drinks, foods, prescription medicines, and over-the-counter medicines (Table 20.3-1). An adult in the United States consumes about 200 mg of caffeine per day on average, although 20 to 30 percent of all adults consume more than 500 mg per day. The per capita use of coffee in the United States is 10.2 pounds per year. A cup of coffee generally contains 100 to 150 mg of caffeine; tea contains about one third as much. Many over-the-counter medications contain one third to one half as much caffeine as a cup of coffee, and some migraine medications and over-the-counter stimulants contain more caffeine than a cup of coffee. Cocoa, chocolate, and soft drinks contain significant amounts of caffeine, enough to cause some symptoms of caffeine intoxication in small children when they ingest a candy bar and a 12-ounce cola drink. Table 20.3-1 Common Sources of Caffeine and Representative Decaffeinated Products

Caffeine consumption also varies by age. The average daily caffeine consumption of caffeine consumers of all ages is 2.79 mg/kg of body weight in the United States. A substantial amount of caffeine is consumed even by young children (i.e., more than 1 mg/kg for children between the ages of 1 and 5 years). Worldwide, estimates place the average daily per capita caffeine consumption at about 70 mg. Up to 85 percent of adults consume caffeine in any given year. COMORBIDITY Persons with caffeine-related disorders are more likely to have additional substancerelated disorders than are those without diagnoses of caffeine-related disorders. About two thirds of those who consume large amounts of caffeine daily also use sedative and hypnotic drugs. ETIOLOGY After exposure to caffeine, continued caffeine consumption can be influenced by several different factors, such as the pharmacological effects of caffeine, caffeine's reinforcing effects, genetic predispositions to caffeine use, and personal attributes of the consumer.

Neuropharmacology Caffeine, a methylxanthine, is more potent than another commonly used methylxanthine, theophylline (Primatene). The half-life of caffeine in the human body is 3 to 10 hours, and the time of peak concentration is 30 to 60 minutes. Caffeine readily crosses the blood–brain barrier. Caffeine acts primarily as an antagonist of the adenosine receptors. Adenosine receptors activate an inhibitory G protein (Gi) and, thus, inhibit the formation of the second-messenger cyclic adenosine monophosphate (cAMP). Caffeine intake, therefore, results in an increase in intraneuronal cAMP concentrations in neurons with adenosine receptors. Three cups of coffee are estimated to deliver so much caffeine to the brain that about 50 percent of the adenosine receptors are occupied by caffeine. Several experiments indicate that caffeine, especially at high doses or concentrations, can affect dopamine and noradrenergic neurons. Specifically, dopamine activity may be enhanced by caffeine, a hypothesis that could explain clinical reports associating caffeine intake with an exacerbation of psychotic symptoms in patients with schizophrenia. Activation of noradrenergic neurons has been hypothesized to be involved in the mediation of some symptoms of caffeine withdrawal. Subjective Effects and Reinforcement Single low to moderate doses of caffeine (i.e., 20 to 200 mg) can produce a profile of subjective effects in humans that is generally identified as pleasurable. Thus, studies have shown that such doses of caffeine result in increased ratings on measures such as well-being, energy and concentration, and motivation to work. In addition, these doses of caffeine produce decreases in ratings of feeling sleepy or tired. Doses of caffeine in the range of 300 to 800 mg (the equivalent of several cups of brewed coffee ingested at once) produce effects that are often rated as being unpleasant, such as anxiety and nervousness. Although animal studies have generally found it difficult to demonstrate that caffeine functions as a reinforcer, well-controlled studies in humans have shown that people choose caffeine over placebo when given the choice under controlled experimental conditions. In habitual users, the reinforcing effects of caffeine are potentiated by the ability to suppress low-grade withdrawal symptoms after overnight abstinence. Thus, the profile of caffeine's subjective effects and its ability to function as a reinforcer contribute to the regular use of caffeine. Genetics and Caffeine Use Some genetic predisposition may exist to continued coffee use after exposure to coffee. Investigations comparing coffee or caffeine use in monozygotic and dizygotic twins have shown higher concordance rates for monozygotic twins for total caffeine consumption, heavy use, caffeine tolerance, caffeine withdrawal, and caffeine intoxication, with heritabilities ranging between 35 and 77 percent. Multivariate structural equation modeling of caffeine use, cigarette smoking, and alcohol use suggests that a common genetic factor—polysubstance use—underlies use of these three substances. Age, Sex, and Race The relationship between long-term chronic caffeine use and demographical features, such as age, sex,

and race, has not been widely studied. Some evidence suggests that middle-aged people may use more caffeine, although caffeine use in adolescents is not uncommon. No known evidence indicates that caffeine use differs between men and women, and no data specifically address caffeine use for different races. Some evidence suggests that, for both children and adults in the United States, whites consume more caffeine than blacks.

Special Populations Cigarette smokers consume more caffeine than nonsmokers. This observation may reflect a common genetic vulnerability to caffeine use and cigarette smoking. It may also be related to increased rates of caffeine elimination in cigarette smokers. Preclinical and clinical studies indicate that regular caffeine use can potentiate the reinforcing effects of nicotine. Heavy use and clinical dependence on alcohol is associated with heavy use and clinical dependence on caffeine as well. Individuals with anxiety disorders tend to report lower levels of caffeine use, although one study showed that a greater proportion of heavy caffeine consumers also use benzodiazepines. Several studies have also shown high daily amounts of caffeine use in psychiatric in-patients. For example, several studies have found that such patients consume the equivalent of an average of five or more cups of brewed coffee each day. Finally, high daily caffeine consumption has also been noted in prisoners. Personality Although attempts have been made to link preferential use of caffeine to particular personality types, results from these studies do not suggest that any particular personality type is especially linked to caffeine use. Effects on Cerebral Blood Flow Most studies have found that caffeine results in global cerebral vasoconstriction, with a resultant decrease in cerebral blood flow (CBF), although this effect may not occur in persons over 65 years of age. According to one recent study, tolerance does not develop to these vasoconstrictive effects, and the CBF shows a rebound increase after withdrawal from caffeine. Some clinicians believe that caffeine use can cause a similar constriction in the coronary arteries and produce angina in the absence of atherosclerosis. DIAGNOSIS The diagnosis of caffeine intoxication or other caffeine-related disorders depends primarily on a comprehensive history of a patient’s intake of caffeine-containing products. The history should cover whether a patient has experienced any symptoms of caffeine withdrawal during periods when caffeine consumption was either stopped or severely reduced. The differential diagnosis for caffeine-related disorders should include the following psychiatric diagnoses: generalized anxiety disorder, panic disorder with or without agoraphobia, bipolar II disorder, attention-deficit/hyperactivity disorder (ADHD), and sleep disorders. The differential diagnosis should include the abuse of caffeine-containing over-the-counter medications, anabolic steroids, and other stimulants, such as amphetamines and cocaine. A urine sample may be needed to screen for these substances. The differential diagnosis should also include hyperthyroidism and pheochromocytoma. Caffeine Intoxication The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

diagnostic criteria for caffeine intoxication includes the recent consumption of caffeine, usually in excess of 250 mg. The annual incidence of caffeine intoxication is an estimated 10 percent, although some clinicians and investigators suspect that the actual incidence is much higher. The common symptoms associated with caffeine intoxication include anxiety, psychomotor agitation, restlessness, irritability, and psychophysiological complaints such as muscle twitching, flushed face, nausea, diuresis, gastrointestinal distress, excessive perspiration, tingling in the fingers and toes, and insomnia. Consumption of more than 1 g of caffeine can produce rambling speech, confused thinking, cardiac arrhythmias, inexhaustibleness, marked agitation, tinnitus, and mild visual hallucinations (light flashes). Consumption of more than 10 g of caffeine can cause

generalized tonic–clonic seizures, respiratory failure, and death. Ms. B, a 30-year-old, went for consultation due to “anxiety attacks.” The attacks occurred mid- to late afternoon, when Ms. B became restless, nervous, and easily excited and sometimes was noticed to be flushed, sweating, and, according to coworkers, “talking a mile a minute.” In response to questioning, Ms. B admitted to consuming six to seven cups of coffee each day before the time the attacks usually occurred. Caffeine Withdrawal The appearance of withdrawal symptoms reflects the tolerance and physiological dependence that develop with continued caffeine use. Several epidemiological studies have reported symptoms of caffeine withdrawal in 50 to 75 percent of all caffeine users studied. The most common symptoms are headache and fatigue; other symptoms include anxiety, irritability, mild depressive symptoms, impaired psychomotor performance, nausea, vomiting, craving for caffeine, and muscle pain and stiffness. The number and severity of the withdrawal symptoms are correlated with the amount of caffeine ingested and the abruptness of the withdrawal. Caffeine withdrawal symptoms have their onset 12 to 24 hours after the last dose; the symptoms peak in 24 to 48 hours and resolve within 1 week. The induction of caffeine withdrawal can sometimes be iatrogenic. Physicians often ask their patients to discontinue caffeine intake before certain medical procedures, such as endoscopy, colonoscopy, and cardiac catheterization. In addition, physicians often recommend that patients with anxiety symptoms, cardiac arrhythmias, esophagitis, hiatal hernias, fibrocystic disease of the breast, and insomnia stop caffeine intake. Some persons simply decide that it would be good for them to stop using caffeine-containing products. In all these situations, caffeine users should taper the use of caffeinecontaining products over a 7- to 14-day period rather than stop abruptly. Mr. F was a 43-year-old attorney who was brought for a psychiatric consultation by

his wife. Mr. F had been complaining of fatigue, loss of motivation, sleepiness, headache, nausea, and difficulty concentrating. His symptoms occurred mostly over the weekends. He withdrew from weekend social activities due to his symptoms, which worried Mrs. F because he seems fine during the week. Mr. F is in good health with no recent history of medical disorders. Mr. F worked in a very busy law practice, many times working 60-hour weeks, and barely sees his family during the week. At work he is often anxious, restless, and constantly busy. He worries about his job so much that he has difficulty sleeping on weeknights. He denies any marital or family problems, other than those caused by his not wanting to do anything over the weekend. At work, Mr. F regularly consumes approximately 4 to 5 cups of coffee per day. He cut out coffee on the weekends because he felt that it may be contributing to his anxiety and sleeplessness. Caffeine-Induced Anxiety Disorder The anxiety related to caffeine use can resemble that of generalized anxiety disorder. Patients with the disorder may be perceived as “wired,” overly talkative, and irritable; they may complain of not sleeping well and of having energy to burn. Caffeine can induce and exacerbate panic attacks in persons with a panic disorder, and although a causative association between caffeine and a panic disorder has not yet been demonstrated, patients with panic disorder should avoid caffeine. Mr. B was a 28-year-old single African American male graduate student who was in good health and had no history of previous psychiatric evaluation or treatment. He took no medications, did not smoke or consume alcohol, and had no current or past history of illicit drug use. His chief complaint was that he had begun feeling mounting “anxiety” when working in the laboratory where he was pursuing his graduate studies. His work had been progressive well, he felt his relationship with his advisor was good and supportive, and he could not identify any problems with staff or peers that might explain his anxiety. He had been working long hours, but found the work interesting and had recently had his first paper accepted for publication. Despite these successes, he reported feeling a

“crescendoing anxiety” as his day would progress. He noted that by the afternoon he would be experiencing palpitations, bursts of his heart racing, tremors in his hands, and an overall feeling of “being on the edge.” He also noted a nervous energy in the afternoons. These experiences were occurring daily and seemed confined to the laboratory (although he admitted he was in the laboratory every day of the week). When reviewing Mr. B’s caffeine intake, it was found that he was consuming excessive amounts of coffee. Staff made a large urn of caffeinated coffee each morning, and Mr. B routinely started with a large mug of coffee. Over the course of

the morning he would consume three to four mugs of coffee (the equivalent of about six or eight 6-oz cups of coffee), and continued this level of use throughout the afternoon. He occasionally had a single can of a caffeinated soft drink, and used no other forms of caffeine on a regular basis. Mr. B estimated that he drank a total of six to eight or more mugs of coffee per day (which was estimated to be at least 1,200 mg of caffeine per day). Once pointed out to him, he realized that this level of caffeine consumption was considerably higher than at any other time in his life. He admitted he liked the taste of coffee and felt a burst of energy in the morning when he drank coffee that helped him start his day. Mr. B and his physician developed a plan to decrease his caffeine use by tapering off caffeine. Mr. B was successful in decreasing his caffeine use and had good resolution of his anxiety symptoms once his daily caffeine use had markedly decreased. (Courtesy of Laura M. Juliano, Ph.D., and Roland R. Griffiths, Ph.D.) Caffeine-Induced Sleep Disorder Caffeine is associated with delay in falling asleep, inability to remain asleep, and early morning awakening. Caffeine Use Disorder A diagnosis of caffeine use disorder can be given in some people with problematic caffeine consumption. It is included in Section III of DSM-5, which is reserved for conditions that require further research. No studies have examined the course and prognosis for patients with a diagnosis of caffeine use disorder. Subjects with caffeine use disorder have reported continued use of caffeine despite repeated efforts to discontinue their caffeine use. Ms. G was a 35-year-old married, white homemaker with three children, aged 8, 6, and 2. She took no prescription medications, took a multivitamin and vitamins C and E on a daily basis, did not smoke, and had no history of psychiatric problems. She drank moderate amounts of alcohol on the weekends, had smoked marijuana in college but had not used it since, and had no other history of illicit drug use. She had started consuming caffeinated beverages while in college, and her current beverage of choice was caffeinated diet cola. Ms. G had her first soft drink early in the morning, shortly after getting out of bed, and she jokingly called it her “morning hit.” She spaced out her bottles of soft drinks over the course of the day, with her last bottle at dinnertime. She typically drank four to five 20-oz bottles of caffeinated diet cola each day. She and her husband had argued about her caffeinated soft drink use in the past, and her husband had believed she should not drink caffeinated soft drinks while pregnant. However, she had continued to do so during each of her pregnancies.

Despite a desire to stop drinking caffeinated soft drinks, she was unable to do so. She described having a strong desire to drink caffeinated soft drinks, and if she resisted this desire, she found that she could not think of anything else. She drank caffeinated soft drinks in her car, which had a manual transmission, and noted that she fumbled while shifting and holding the soft drink and spilled it in the car. She also noted that her teeth had become yellowed, and she suspected this was related to her tendency to swish soft drink in her mouth before swallowing it. When asked to describe a time when she stopped using soft drinks, she reported that she had run out of it on the day one of her children was to have a birthday party, and she did not have time to leave her home

to buy more. In the early afternoon of that day, a few hours before the scheduled start of the party, she felt extreme lethargy, a severe headache, irritability, and craving for a soft drink. She called her husband and told him she planned to cancel the party. She then went to the grocery store to buy soft drinks, and after drinking two bottles, she felt well enough to host the party. Although initially expressing interest in decreasing or stopping her caffeinated soft drink use, Ms. G did not attend scheduled follow-up appointments after her first evaluation. When finally contacted at home, she reported she had only sought help initially at her husband's request, and she had decided to try to cut down on her caffeine use on her own. (Courtesy of Eric Stain, M.D.) Caffeine-Related Disorder Not Elsewhere Classified This category is used for caffeine-related disorders that do not meet the criteria for caffeine use disorder, caffeine intoxication, caffeine withdrawal, caffeine-induced anxiety disorder, or caffeine-induced sleep disorder. CLINICAL FEATURES Signs and Symptoms After the ingestion of 50 to 100 mg of caffeine, common symptoms include increased alertness, a mild sense of well-being, and a sense of improved verbal and motor performance. Caffeine ingestion is also associated with diuresis, cardiac muscle stimulation, increased intestinal peristalsis, increased gastric acid secretion, and (usually mildly) increased blood pressure. Caffeine Use and Nonpsychiatric Illnesses Despite numerous studies examining the relationship between caffeine use and physical illness, significant health risk from nonreversible pathological consequences of caffeine use, such as cancer, heart disease, and human reproduction, has not been conclusively demonstrated. Nonetheless, caffeine use is often considered to be contraindicated for various conditions, including generalized anxiety disorder, panic disorder, primary insomnia, gastroesophageal reflux, and pregnancy. In addition, the modest ability of

caffeine to increase blood pressure and the documented cholesterol-elevating compounds of unfiltered coffee have raised the issue of the relationship of caffeine and coffee use to cardiovascular disease. Finally, there may be a mild association between higher daily caffeine use in women and delayed conception and slightly lower birth weight. Studies, however, have not found such associations, and effects, when found, are usually with relatively high daily dosages of caffeine (e.g., the equivalent of five cups of brewed coffee per day). For a woman who is considering pregnancy, especially if there is some difficulty in conceiving, it may be useful to counsel the elimination of caffeine use. Similarly, for a woman who becomes pregnant and has moderate to high daily caffeine consumption, a discussion about decreasing her daily caffeine use may be warranted. TREATMENT Analgesics, such as aspirin, almost always can control the headaches and muscle aches that may accompany caffeine withdrawal. Rarely do patients require benzodiazepines to relieve withdrawal symptoms. If benzodiazepines are used for this purpose, they should be used in small dosages for a brief time, about 7 to 10 days at the longest. The first step in reducing or eliminating caffeine use is to have patients determine their daily consumption of caffeine. This can best be accomplished by having the patient keep a daily food diary. The patient must recognize all sources of caffeine in the diet, including forms of caffeine (e.g., beverages, medications), and accurately record the amount consumed. After several days of keeping such a diary, the clinician can meet with the patient, review the diary, and determine the average daily caffeine dose in milligrams. The patient and clinician should then decide on a fading schedule for caffeine consumption. Such a schedule could involve a decrease in increments of 10 percent every few days. Because caffeine is typically consumed in beverage form, the patient can use a substitution procedure in which a decaffeinated beverage is gradually used in place of the caffeinated beverage. The diary should be maintained during this time, so that the patient's progress can be monitored. The fading should be individualized for each patient, so that the rate of decrease in caffeine consumption minimizes withdrawal symptoms. The patient should probably

avoid stopping all caffeine use abruptly, because withdrawal symptoms are likely to develop with sudden discontinuation of all caffeine use. REFERENCES Bhorkar AA, Dandekar MP, Nakhate KT, Subhedar NK, Kokare DM. Involvement of the central melanocortin system in the effects of caffeine on anxiety-like behavior in mice. Life Sci . 2014;95(2):72–80. Butt MS, Sultan MT. Coffee and its consumption: Benefits and risks. Crit Rev Food Sci Nutr. 2011;51:363. Jonjev ZS, Bala G. High-energy drinks may provoke aortic dissection. Coll Antropol. 2013;37:227. Juliano LM, Griffiths RR. Caffeine-related disorders. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:1296. Kennedy DO, Haskell CF. Cerebral blood flow and behavioural effects of caffeine in habitual and non-habitual consumers of

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