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

Chapter 6

# Caffeine: Pharmacology and Clinical Effects

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Caffeine, which is a member of the methylxanthine class of alkaloids, is the most widely used mood-altering drug in the world. More than 60 species of caffeine-containing plants have been identified. The most widely consumed are coffee, tea, cola nut, cocao pod, guarana, and maté (Gilbert, 1984).

## DRUGS IN THE CLASS

Caffeine is the common name for 1,3,7-trimethylxanthine (Figure 1). The structurally related dimethylxanthines, theophylline and theobromine, also are found in a variety of plants. Caffeine is a weakly basic alkaloid. The free base is a bitter white powder that is moderately soluble in water (21.7 mg/ml) (Budavari, O'Neil et al., 1996).

Clinically available pharmaceutical preparations of caffeine include caffeine anhydrous, caffeine sodium benzoate, and citrated caffeine.

**Common Sources of Caffeine.** Table 1 shows the range of caffeine content in common foods and medications, as well as estimated "typical" caffeine content of these products. Of the three major dietary sources of caffeine, servings of tea and soft drinks usually contain about one-half to one-third the amount of caffeine in a serving of coffee.

A significant problem in estimating caffeine exposure occurs because of the wide differences in the amount of caffeine delivered in common foods, as well as significant differences in common serving sizes (cf. Table 1). For example, the amount of caffeine in a serving of coffee may vary over a 10-fold range, from as little as 20 mg for a small 5-ounce cup of instant coffee to 300 mg for a large 12-ounce cup of strong drip coffee. A similar 10-fold variation may occur with soft drinks, with a small glass of one of the weaker cola drinks containing as little as 12 mg of caffeine, in con-

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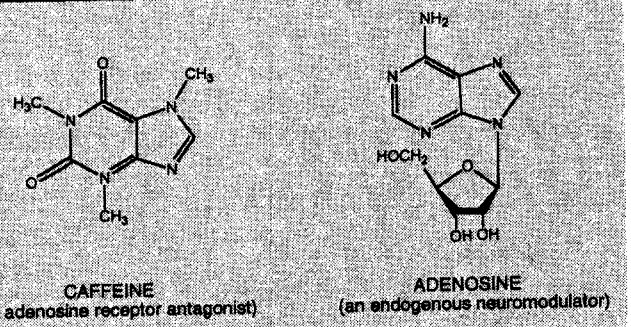
**FIGURE 1. The Chemical Structure of Caffeine**




The chemical structures of caffeine (1,3,7-trimethylxanthine) and adenosine. Adenosine is an endogenous neuromodulator that has structural similarities to caffeine. Most of the physiological effects of caffeine, including the CNS stimulant effects, probably are mediated through adenosine receptor antagonism.

trast to about 120 mg from a 20-ounce bottle of one of the stronger colas.

Although most people are aware that coffee, tea, and most cola beverages contain caffeine, there are several sources of caffeine about which there is less awareness. In the United States, about 70% of all soft drinks consumed contain caffeine (Beverage Digest Company, 1999). A number of non-cola drinks (such as root beer, orange soda, cream soda, and lemon-lime drinks) contain caffeine in amounts similar to those in the cola drinks. Some, but not all, coffee ice creams and yogurts deliver a significant dose of caffeine. Although chocolate milk, cocoa, and milk chocolate candy also contain caffeine, the dose delivered in a usual serving generally is below the threshold for readily detectable mood and behavioral effects (<10 mg). The one exception is that a serving of dark or bitter chocolate candy may contain about 30 mg of caffeine.

Popular over-the-counter (OTC) medications containing caffeine include the stimulants NoDoz® (100 and 200 mg/tablet) and Vivarin® (200 mg/tablet); the analgesics Excedrin® (130 mg/2 tablets), Anacin® (64 mg/2 tablets), and Midol Menstrual® (120 mg/2 tablets); and the weight-loss supplements Metabolife 365® (80 mg/2 tablets) and Diet Fuel® (200mg/3 capsules).

**History.** Cultivation of tea in China, coffee in Ethiopia, and cocao pod in South America date back to time immemorial (Hattox, 1985; Weinberg & Bealer, 2001). Recorded use of tea dates back at least 2,000 years in China (Hara, Luo et al., 1995). About 600 years ago, the use of coffee spread from Ethiopia to Yemen (Hattox, 1985), and about 500 years ago, the use of cocao spread from Mexico to Spain (Weinberg & Bealer, 2001). With the development of world trade in the 17th and 18th centuries, the use of caffeinated foods spread rapidly from their points of geographic origin, despite unsuccessful attempts to restrict or eliminate the use of these caffeine-containing foods, based on economic, religious, medical, or political grounds (Austin, 1979; Pendergrast, 1999; Weinberg & Bealer, 2001).

Although difficult to imagine in the context of the present culture, in which caffeine products are widely and freely used, the ancient spread of caffeinated foods and the substantial economic and social effects they engendered have many parallels in the contemporary growth of the international trade in cocaine. Numerous failed efforts to eliminate the use of caffeine-containing foods have been documented worldwide (in Arabia, Turkey, England, France, and Prussia, among others). In America, the protest of a British tax on tea became a symbolic focal point for revolution, resulting in the famous "Boston tea party," during which containers of tea were thrown into the Boston harbor in 1773. In the aftermath, the Continental Congress passed a resolution against tea consumption and, over the course of a few years, America was transformed from a predominantly tea-drinking society to one in which coffee was the caffeinated beverage of choice (Pendergrast, 1999).

Coffee has become a major agricultural import into the United States, second only after oil in the total value of imported goods (Gilbert, 1984). In addition to the wide availability of coffee and tea, the last 100 years have seen the development of flavored carbonated beverages ("soft drinks") as a commercially successful alternative for the delivery of caffeine (Pendergrast, 1993).

**Epidemiology.** Today, consumption of caffeine is almost universal, with only alcohol consumption coming close in popularity (Gilbert, 1984). Dietary survey studies in North America indicate that weekly or more frequent consumption of caffeine-containing foods occurs in 80% to 90% of children and adults (Gilbert, 1984; Hughes & Oliveto, 1997). Figure 2 depicts recent trends in annual per capita consumption of the three major sources of dietary caffeine in the United States: coffee, tea, and soft drinks. Over the 31 years shown, consumption of carbonated soft drinks has more than doubled, increasing from 24 to 49 gallons per capita, while coffee consumption decreased by 25%, from

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**TABLE 1. Typical Caffeine Content of Common Foods and Medications**

| Substance | Serving Size (volume or weight) | Caffeine Content (range) | Caffeine Content (typical) |
|---|---|---|---|
| Coffee | | | |
| Brewed/Drip | 6 oz | 77-150 mg | 100 mg |
| Instant | 6 oz | 20-130 mg | 70 mg |
| Espresso | 1 oz | 30-50 mg | 40 mg |
| Decaffeinated | 6 oz | 2-9 mg | 4 mg |
| Tea | | | |
| Brewed | 6 oz | 30-90 mg | 40 mg |
| Instant | 6 oz | 10-35 mg | 30 mg |
| Canned or Bottled | 12 oz | 8-32 mg | 20 mg |
| Caffeinated Soft Drinks | 12 oz | 22-71 mg | 40 mg |
| Caffeinated Water | 16.9 oz | 50-125 mg | 100 mg |
| Cocoa/Hot Chocolate | 6 oz | 2-10 mg | 7 mg |
| Chocolate Milk | 6 oz | 2-7 mg | 4 mg |
| Coffee Ice Cream or Yogurt | 1 cup (8 oz) | 8-85 mg | 50 mg |
| Chocolate Bar | | | |
| Milk Chocolate | 1.5 oz | 2-10 mg | 10 mg |
| Dark Chocolate | 1.5 oz | 5-35 mg | 30 mg |
| Caffeinated Gum | 1 stick | 50 mg | 50 mg |
| Caffeine-Containing OTC Products | | | |
| Analgesics | 2 tablets | 64-130 mg | 64 or 130 mg |
| Stimulants | 1 tablet | 75-350 mg | 100 or 200 mg |
| Weight-loss Products | 2-3 tablets | 80-200 mg | 80-200 mg |
| Sports Nutrition | 2 tablets | 200 mg | 200 mg |

1 fluid oz = 30 ml; 1 oz weight = 28 g. Serving sizes are based on commonly consumed portions, typical container sizes, or pharmaceutical instructions.

SOURCES: Data are from Barone & Roberts (1996), Carriollo & Benitez (2000), Amurol Confections Company (personal communication) and the web sites for the National Soft Drink Association (2001), National Coffee Association (2001), Center for Science and the Public Interest (2001), Hershey Foods (2001), Lindt & Sprüngli AG (2001), and Twinlab Corporation (2001).

33 to 26 gallons per person. Tea consumption increased only modestly over this time period. A survey of the general population showed that the prevalence of weekly use of coffee, soft drinks, and tea was 62%, 47%, and 24%, respectively (Hughes & Oliveto, 1997). Among those who had ever used caffeine, 14% had stopped caffeine use altogether, citing concern about health and unpleasant side effects.

Mean daily intake of caffeine for adult consumers in the United States has been estimated to be about 280 mg, with higher intakes estimated for consumers in the United Kingdom and Denmark (Barone & Roberts, 1996).

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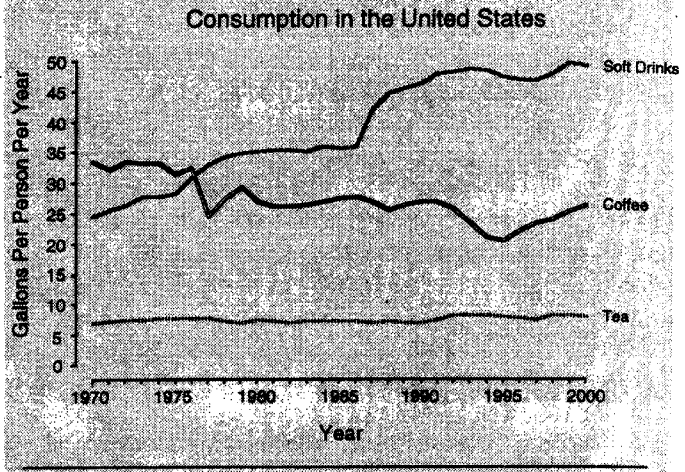
**Therapeutic Uses.** As a mild central nervous system (CNS) stimulant, caffeine is widely used to restore behavior that has been degraded by fatigue (Penetar, McCann et al., 1994; Patat, Rosenzweig et al., 2000). Caffeine also is commonly used in the treatment of pain of various origins (cf. Sawynok, 1995; James, 1997). Not surprisingly, caffeine alone is the most effective treatment for caffeine withdrawal headache (Dreisbach & Pfeiffer, 1943; Griffiths & Woodson, 1988a), with prophylactic caffeine administration recognized as an effective treatment for post-surgical withdrawal headaches (Fennelly, Galletly et al., 1991; Nikolajsen, Larsen et al., 1994; Hampl, Schneider et al., 1995). Caffeine also is used in the treatment of post-dural puncture headache following lumbar puncture or spinal anesthesia, although its efficacy may be due in part to suppression of caffeine withdrawal (James, 1997; Yucel, Ozyalcin et al., 1999). Caffeine in combination with ergotamine is used in treatment of migraine headache (Sawynok, 1995). Finally, because evidence suggests that caffeine functions as an analgesic adjuvant (Laska, Sunshine et al., 1984), it is combined with commonly used analgesics such as aspirin and acetaminophen in a wide range of OTC and prescription analgesic products.

Administered intravenously or orally, caffeine is efficacious as a respiratory stimulant in treating apnea in neonates and infants (James, 1997; Tobias, 2000). Intravenous caffeine has been administered prior to electroconvulsive therapy (ECT) for the treatment of severe depression and other serious psychiatric disorders (James, 1997). Although caffeine has been shown to lengthen the duration of seizures, the therapeutic merits of caffeine augmentation of ECT are unclear (Rosenquist, McCall et al., 1994; Kelsey & Grossberg, 1995). Because caffeine is known to have both lipolytic and thermogenic effects, it sometimes is used for weight loss. Modest effects of caffeine-ephedrine combinations on weight loss appear to be greater than the effects of either drug alone (James, 1997). Caffeine has been used to prevent postprandial reductions in blood pressure in elderly persons (Hesseltine, el-Jabri et al., 1991), although studies have questioned the clinical relevance of this effect (Lipsitz, Jansen et al., 1994). Because caffeine is ergogenic and has been shown to increase speed and/or power output in simulated race conditions, it often is used to facilitate athletic performance (Graham, 2001).

## ABSORPTION AND METABOLISM

**Routes of Administration.** By far the most common route of administration of caffeine is oral. Caffeine sometimes is administered intravenously in the treatment of post-surgical headache, neonatal apnea, and to enhance electroconvulsive therapy. Caffeine in combination with ergotamine also sometimes is administered rectally via suppository (Caferot®) for the treatment of migraine headaches. Topical administration of caffeine has been used in neonates (Amato, Isenschmid et al., 1991).

**FIGURE 2. Annual Per Capita Consumption in the U.S. of the Three Major Dietary Sources of Caffeine**




SOURCE: U.S. Department of Agriculture, 2002.

Annual per capita consumption in the U.S. of the three major dietary sources of caffeine: coffee, tea, and soft drinks (that is, flavored carbonated beverages).

**Absorption and Distribution.** Caffeine is rapidly and completely absorbed after oral administration, with peak levels reached in 30 to 45 minutes (Mumford, Benowitz et al., 1996; Liguori, Hughes et al., 1997b). Caffeine absorption from soft drinks containing sugar and from chocolate may be somewhat slower, with peak levels attained at 60 to 120 minutes (Marks & Kelly, 1973; Mumford, Benowitz et al., 1996; Liguori, Hughes et al., 1997b). Caffeine is readily distributed throughout the body, with concentrations in blood correlating strongly with those in saliva, breast milk, amniotic fluid, fetal tissue, semen, and the brain (James, 1997). Binding to plasma proteins is estimated to range between 10% and 35% (Denaro & Benowitz, 1991). Caffeine concentrations in saliva, which often exceed 75% of plasma concentrations (Cook, Tallent et al., 1976; Zylber-

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Katz, Granit et al., 1984) are used as a noninvasive alternative to serum monitoring.

**Metabolism.** Caffeine metabolism is complex, with more than 25 metabolites identified in humans (Carrillo & Benitez, 2000). The primary metabolic pathways involve the P-450 liver enzyme system, which is responsible for the demethylation of caffeine to three biologically active dimethylxanthines: paraxanthine, theobromine, and theophylline, which account for 80%, 10%, and 4% of caffeine metabolism, respectively (Denaro & Benowitz, 1991). The large amounts of paraxanthine, coupled with the demonstration of similar sympathomimetic effects of paraxanthine and caffeine (Benowitz, Jacob et al., 1995), suggest that paraxanthine needs to be considered in understanding the clinical pharmacology of caffeine. Substantial differences between species in primary metabolic pathways and in rates of elimination underscore the need for caution when generalizing findings from animal studies to humans (Bonati, Latini et al., 1985).

**Individual Differences in Caffeine Elimination.** On average, caffeine half-life is four to six hours; however, there are wide individual differences in rates of caffeine elimination, with half-lives varying more than 10-fold in healthy subjects (Denaro & Benowitz, 1991). An important implication of the central role of P450 in metabolizing caffeine is that drugs or conditions that affect this metabolic system also significantly alter caffeine elimination. Caffeine's half-life is prolonged by liver disease (Denaro & Benowitz, 1991). Although caffeine half-life does not differ between younger and older adults (Blanchard & Sawers, 1983), caffeine half-life is markedly increased in premature and full-term newborns (in whom the half-life is 80 to 100 hours) because liver enzyme capacity is not completely developed until about six months of age (Aranda, Cook et al., 1979; Parsons & Neims, 1981). Cigarette smoking, which induces liver enzymes, decreases caffeine half-life by as much as 50% (Parsons & Neims, 1978; May, Jarboe et al., 1982).

Numerous compounds have been shown to inhibit caffeine metabolism, including high doses of caffeine itself, oral contraceptive steroids, cimetidine, some quinoline antibiotics, fluvoxamine, and mexiletine (Denaro, Brown et al., 1990; Carrillo & Benitez, 2000). Caffeine inhibits the metabolism of the antipsychotic clozapine and the bronchodilator theophylline to an extent that might be clinically significant (Carrillo & Benitez, 2000; Hagg, Spigset et al., 2000). Caffeine half-life increases markedly toward the end of pregnancy (Aldridge, Bailey et al., 1981).

## MECHANISMS OF ACTION

**Molecular Sites of Action.** Three primary sites of action for caffeine have been proposed: mobilization of calcium, inhibition of phosphodiesterase activity, and blockade of adenosine receptors (Daly, 1993). There are data suggesting that some of the cardiac and respiratory effects of caffeine may be mediated by inhibition of phosphodiesterase (Daly, 1993; Howell, 1993; Howell & Landrum, 1997). However, intracellular calcium release and inhibition of phosphodiesterase generally occur at caffeine concentrations considerably above those attained during usual human caffeine consumption. In contrast, adenosine antagonism occurs at physiologically relevant concentrations. These observations have led increasingly to the conclusion that antagonism of adenosine receptors is the primary cellular mechanism underlying most of the physiological effects of caffeine, including its centrally mediated mood- and performance-stimulating effects (Daly, 1993; Fredholm, Bättig et al., 1999).

**Competitive Antagonism of Adenosine Receptors.** Caffeine, which is structurally related to adenosine (Figure 1), is a competitive antagonist at $A_1$ and $A_{2A}$ receptors, which are tonically activated at basal adenosine concentrations (Fredholm, Bättig et al., 1999). Thus, caffeine produces a range of central and peripheral effects that are opposite those of adenosine. For example, in the central nervous system, adenosine decreases spontaneous electrical activity, inhibits neurotransmitter release, has anticonvulsant activity, and depresses locomotor activity and operant response rates. In the periphery, adenosine constricts bronchial smooth muscle, produces negative inotropic/chronotropic effects on the heart, and inhibits lipolysis, renin release, and gastric secretions. All of these effects are opposite those that are produced by caffeine (Daly, 1993; Garrett & Griffiths, 1997). Moreover, the behavioral stimulant effects of caffeine in rodents and non-human primates correlate with caffeine's ability to antagonize adenosine receptors (Snyder, Katims et al., 1981; Howell, Coffin et al., 1997). These stimulant effects are abolished in $A_{2A}$ receptor knock-out mice (El Yacoubi, Ledent et al., 2000), suggesting that adenosine receptor antagonism plays a critical role in the stimulant effects of caffeine.

**Effects on Neurotransmitters.** Preclinical studies have shown that caffeine affects turnover or levels of a range of neurotransmitters in the central nervous system; such neurotransmitters include norepinephrine, dopamine, serotonin, acetylcholine, GABA, and glutamate (Shi, Nikodijevic

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et al., 1993; Daly, 1993). A probable mechanism for some of these effects is that caffeine blocks basal levels of adenosine at $A_1$ receptors, which tonically inhibit neurotransmitter release (Daly, 1993). The release of norepinephrine, in particular, has been suggested as a mechanism underlying caffeine's stimulant effects (Daly, 1993), and some data suggest that the discriminative effects of caffeine are mediated in part by an alpha adrenergic mechanism (Holtzman, 1986).

**Dopaminergic Effects.** Considerable evidence suggests that some of the behavioral effects of caffeine are mediated by dopaminergic mechanisms. It is well established that caffeine enhances dopaminergic activity by competitive antagonism of $A_{2A}$, and possibly $A_1$, receptors that are co-localized and functionally interact with dopamine receptors (Fredholm, Bättig et al., 1999). As a competitive antagonist at adenosine receptors, caffeine is believed to produce its stimulant behavioral effects by removing the negative modulatory effects of adenosine from dopamine receptors, thus stimulating dopaminergic activity. Evidence for this mechanism is particularly compelling for blockade of $A_{2A}$ receptors in the striatum (Fredholm, Bättig et al., 1999).

Consistent with the *in vitro* data, preclinical behavioral studies show that caffeine produces behavioral effects similar to classic dopaminergically mediated stimulants such as cocaine and amphetamine, including increased locomotor activity, increased rotational behavior in 6-hydroxydopamine lesioned rats, stimulant-like discriminative stimulus effects, and self-injection. Moreover, caffeine potentiates the effects of dopaminergically mediated drugs on locomotor activity, rotational behavior, drug discrimination, and self-injection. Finally, some of caffeine's effects on these behaviors can be blocked by dopamine receptor antagonists (Garrett & Griffiths, 1997; Fredholm, Bättig et al., 1999; Powell, Koppelman et al., 1999; Green & Schenk, 2002).

## EFFECTS ON MAJOR ORGAN SYSTEMS

**Cardiovascular.** At moderate dietary dose levels, caffeine produces increases in blood pressure and tends to have no effect on or to reduce heart rate in humans (Rush, Sullivan et al., 1995; James, 1997). Although the magnitude of caffeine-induced blood pressure increases is small, some recent studies suggest that it may be clinically significant in individuals with borderline hypertension (James, 1997; Nurminen, Niittynen et al., 1999; Hartley, Sung et al., 2000; Lovallo, al'Absi et al., 2000). Coffee has been shown to contain lipids that significantly raise total and LDL cholesterol levels in humans. Decaffeination does not remove these lipids. Although paper-filtered and instant coffee contain low levels of the lipids, high levels are delivered in espresso, French press, mocha, Turkish, and boiled coffee (Urgert & Katan, 1997).

**Gastrointestinal.** Caffeine stimulates gastric acid secretion (Cohen & Booth, 1975), although the exacerbation of gastroesophageal reflux by coffee probably is due to coffee constituents other than caffeine (Wendl, Pfeiffer et al., 1994). Caffeine is a colonic stimulant, with caffeinated coffee producing colonic motor activity stimulation similar to that produced by a meal (Rao, Welcher et al., 1998).

**Renal and Urinary.** Caffeine is a diuretic, increasing urine volume 30% or more for several hours after ingestion (Wemple, Lamb et al., 1997). Caffeine also has been shown to increase detrusor pressure on the bladder in patients with complaints of urinary urgency and confirmed detrusor instability (Creighton & Stanton, 1990). Chronic caffeine consumption has been shown to contribute to urinary incontinence in psychogeriatric patients (James, Sawczuk et al., 1989). Lithium toxicity may occur after caffeine withdrawal due to decreased renal clearance of lithium (Carrillo & Benitez, 2000).

**Respiratory.** Like theophylline, caffeine is a bronchodilator at high doses (Becker, Simons et al., 1984; Duffy & Phillips, 1991). Caffeine also is a respiratory stimulant (Pianosi, Grondin et al., 1994), a characteristic that has been used therapeutically in the treatment of apnea in neonates and infants (James, 1997; Tobias, 2000).

**Musculoskeletal.** Caffeine is ergogenic in most exercise situations, with activity mediated by various mechanisms, including effects on muscle contractility (Tarnopolsky & Cupido, 2000).

**Hormonal.** Caffeine increases plasma epinephrine, norepinephrine, renin, and free fatty acids, particularly in nontolerant individuals (Patwardhan, Desmond et al., 1980; Robertson, Wade et al., 1981; Benowitz, Jacob et al., 1995). Caffeine also has been shown to increase ACTH and cortisol (Lovallo, al'Absi et al., 1996; Lin, Uhde et al., 1997; al'Absi, Lovallo et al., 1998).

**Reproductive.** Although the physiological mechanism is not clear, recent studies and a meta-analysis of previous studies suggest that maternal caffeine use increases the rate of spontaneous abortion (James, 1997; Fernandes, Sabharwal et al., 1998; Klebanoff, Levine et al., 1999; Cnattingius, Signorello et al., 2000; Wen, Shu et al., 2001).

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## BEHAVIORAL EFFECTS IN ANIMALS

**Stimulant Motor Activity.** Acute caffeine produces biphasic effects on spontaneous motor activity in rodents, with moderate doses (for example, 10 to 30 mg/kg) increasing, and higher doses decreasing, overall activity. A similar inverted U-shaped function is shown on rotational behavior in rodents (Garrett & Holtzman, 1994, 1996; Fredholm, Bättig et al., 1999). Caffeine potentiates the stimulatory effects of psychomotor stimulants on motor activity and rotational behavior (Garrett & Griffiths, 1997; Gasior, Jaszyna et al., 2000).

**Drug Discrimination.** Drug discrimination procedures in animals provide information analogous to subjective effect measures in humans. In the discrimination paradigm, animals typically are trained to make one response after administration of drug (such as caffeine) and another response after administration of vehicle. The extent to which a novel drug occasions drug-appropriate responding (that is, generalization) provides a measure of the similarity between the training stimulus and the test stimulus. As with motor activity, the discriminative dose effects of caffeine are biphasic. Stimulant drugs such as cocaine and *d*-amphetamine occasion responding in animals trained to low and moderate doses of caffeine (10 to 30 mg/kg) (Holtzman, 1986; Mumford & Holtzman, 1991).

Although caffeine does not usually occasion drug-appropriate responding in animals trained with other behavioral stimulants alone, caffeine potentiates the discriminative effects of subthreshold doses of the training drug in cocaine and amphetamine-trained rats (Garrett & Griffiths, 1997). The discriminative stimulus effects of high caffeine doses appear to be qualitatively different than the discriminative stimulus effects of low caffeine training doses, with only theophylline occasioning drug-appropriate responding (Mumford & Holtzman, 1991).

**Reinforcement.** The reinforcing efficacy of a drug refers to the relative effectiveness in establishing or maintaining drug self-administration behavior. Intravenous drug self-injection in laboratory animals is often regarded as providing the most direct and unequivocal assessment of a drug's reinforcing effect. With this procedure, animals are given access to a lever, responding on which results in a drug injection. The ability of the injection to reinforce behavior is assessed by examining the establishment or maintenance of responding. Eight of 10 studies that have examined caffeine self-injection have demonstrated that caffeine can function as a reinforcer (cf. Griffiths & Mumford, 1995; Fredholm, Bättig et al., 1999). Most of these studies demonstrated caffeine self-injection in all animals; however, some studies showed that only a subset of animals (25% to 33%) self-injected caffeine. A sporadic pattern of caffeine self-injection, which is characterized by periods of relatively high rates of intake alternating irregularly with periods of low intake, has been reported in three studies with nonhuman primates which examined self-injection over an extended period of consecutive days (Deneau, Yanigita et al., 1969; Griffiths, Brady et al., 1979; Griffiths & Mumford, 1995). These intravenous self-injection studies show that caffeine can function as a reinforcer under some conditions. However, the inconsistent results across animals and studies contrast with the results reported with the classic abused stimulants (such as amphetamine and cocaine), which have more consistently been shown to maintain intravenous self-injection across a wide range of species and conditions (Griffiths, Brady et al., 1979).

The variation in results with caffeine is analogous to that which has been reported in self-injection studies with nicotine: nicotine has not reliably maintained self-injection across animals and studies (Goldberg & Henningfield, 1988; Dworkin, Vrana et al., 1993).

Conditioned place preference procedures provide an indirect approach to assessing the reinforcing effects of drugs. With this procedure, animals initially are administered a drug when confined in a distinctive compartment. During subsequent testing, when animals may move between compartments, the relative time spent in the drug-paired compartment provides an indirect measure of reinforcing effect. Studies in rats have shown that low doses of caffeine produce conditioned place preference, while higher doses produce clear place avoidance (Brockwell, Eikelboom et al., 1991; Patkina & Zvartau, 1998; Bedingfield, King et al., 1998). These biphasic dose effects of caffeine are similar to the biphasic effects on other preclinical and clinical measures. Similar to the self-injection data, a direct comparison of place preference between caffeine and cocaine suggests that cocaine has greater reinforcing effects (Patkina & Zvartau, 1998).

As with preclinical data on locomotor and discriminative performance, there is evidence from studies of drug reinforcement that caffeine increases the effects of dopaminergically mediated stimulants. Low doses of caffeine and cocaine produced additive effects on measures of conditioned place preference (Bedingfield, King et al., 1998). Intravenous self-injection studies show that caffeine

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increases low rates of cocaine self-injection, enhances the rate of acquisition of cocaine self-injection, and reinstates previous cocaine self-administration behavior (Comer & Carroll, 1996; Fredholm, Bättig et al., 1999; Schenk & Partridge, 1999; Kuzmin, Johansson et al., 1999, 2000). Whether such caffeine-induced enhancements reflect interactions with cocaine reinforcement *per se* is unclear (Kuzmin, Johansson et al., 2000).

**Tolerance.** Tolerance refers to an acquired change in responsiveness of an individual as a result of exposure to drug, such that an increased dose of drug is necessary to produce the same degree of response, or that less effect is produced by the same dose of drug. Seventeen studies have demonstrated the development of caffeine tolerance across different species (such as mice, rats, and monkeys) and a wide range of experimental measures (for example, locomotor activity, schedule-controlled responding, reinforcement thresholds for electrical brain stimulation, caffeine-induced seizure thresholds, and discriminative responding in caffeine-trained animals) (cf. Griffiths & Mumford, 1996; Fredholm, Bättig et al., 1999; Powell, Iuvone et al., 2001).

Caffeine tolerance has been most widely studied with regard to its locomotor stimulant effect in rats. Studies have shown that such tolerance is rapid, usually insurmountable, and exhibits cross-tolerance to other methylxanthines, but not to other nonmethylxanthine psychomotor stimulants such as *d*-amphetamine and methylphenidate (Holtzman, 1983; Finn & Holtzman, 1987, 1988; Holtzman & Finn, 1988).

Tolerance to other effects of caffeine (such as the discriminative stimulus effects) may develop more slowly, suggesting that different mechanisms may be operative for different behaviors (Holtzman & Finn, 1988). Although changes in various neurotransmitter receptors have been demonstrated following chronic caffeine administration, the neurochemical mechanism(s) underlying caffeine tolerance remain unclear (Shi, Nikodijevic et al., 1993; Holtzman, Mante et al., 1991; Johansson, Georgiev et al., 1997; Fredholm, Bättig et al., 1999; Powell, Iuvone et al., 2001).

**Physical Dependence.** Physical dependence is manifested by time-limited biochemical, physiological and behavioral disruptions (that is, a withdrawal syndrome) on termination of chronic or repeated drug administration. Of the 11 reports of caffeine withdrawal in laboratory animals (mice, rats, cats, and monkeys) (cf. Griffiths & Mumford, 1996; Fredholm, Bättig et al., 1999), most have documented substantial behavioral disruptions following cessation of chronic caffeine dosing (for example, 50% to 80% reductions in spontaneous locomotor activity, or 20% to 50% reductions in operant responding). Similar to human studies, the severity of withdrawal in laboratory animals is a function of the caffeine maintenance dose, with maximal withdrawal effects occurring on the first or second day of caffeine withdrawal (Holtzman, 1983; Finn & Holtzman, 1986). It has been speculated—and there is some evidence to support the notion—that increased functional tissue sensitivity to endogenous adenosine is the mechanism underlying some caffeine withdrawal effects (von Borstel, Wurtman et al., 1983; Hirsh, 1984; Ahlijanian & Takemori, 1986).

## EFFECTS ON HUMAN PERFORMANCE

A large number of studies have examined the effects of caffeine on human performance. The most consistent generality to emerge is that caffeine reliably reduces decrements in performances on a variety of tasks when those decrements are the result of reduced alertness (for example, under conditions of sleep deprivation, fatigue, or prolonged vigilance) (cf. Weiss & Laties, 1962; James, 1997; van der Stelt & Snel, 1998). Results of most studies of caffeine on performance have been quite inconsistent.

Typically, studies have compared the effects of caffeine and placebo on performance of subjects who abstained from caffeine, usually overnight. Although the results are variable (James, 1997; van der Stelt & Snel, 1998), authors have reported that, compared to placebo, caffeine may improve reaction time, tapping speed, vigilance, attention, and psychomotor performance (Rogers & Dernoncourt, 1998). Likewise, a growing literature on the effects of caffeine on exercise performance suggests that, relative to placebo, caffeine can increase endurance for long-term (30 to 60 minutes) exercise and can improve speed and/or power output in simulated race conditions (Spriet, 1995; Graham, 2001).

A dilemma in interpreting the effects of caffeine on performance is that almost all of these studies have been confounded by caffeine withdrawal. Thus, improvements in performance after caffeine relative to placebo may simply reflect a restoration of deficits caused by withdrawal (James, 1997; Rogers & Dernoncourt, 1998; Rogers, 2000). Although some investigators recently have attempted to address this issue (Warburton, 1995; Smith, 1998), an unequivocal study should involve biologically verified caffeine abstinence for at least a week before testing (James, 1997).

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The only study to include such a condition showed performance decrements during acute abstinence, but failed to demonstrate performance benefits of caffeine (James, 1998). Based on the preclinical literature, which clearly documents the behavioral stimulant effects of caffeine, it seems quite likely that caffeine will be shown to enhance human performance on some types of tasks in non-tolerant individuals. However, at present it is not clear to what extent performance enhancement commonly perceived and reported by regular caffeine consumers after their first morning dose of caffeine is due to true improvement over caffeine-free baseline levels, compared to a caffeine-induced restoration of performance that has been degraded by caffeine withdrawal after overnight abstinence.

## SUBJECTIVE EFFECTS IN HUMANS

"Subjective effects" refer to drug-induced changes in an individual's experiences or feelings that cannot be measured directly by an observer. Subjective effects most often are assessed via self-report instruments that are given after double-blind administration of drug. Many human laboratory studies on caffeine have included questionnaires pertaining to caffeine's subjective effects, and so a substantial amount of data has been acquired across a number of caffeine vehicles (such as capsules, coffee, tea, soft drinks, and other beverages). The qualitative subjective effects of caffeine are dose-dependent, with low dietary doses producing mostly positive effects (such as increased feelings of well-being and energetic arousal) and higher doses leading to predominantly "dysphoric" effects (Griffiths & Mumford, 1995).

**Positive Subjective Effects.** Human laboratory studies have demonstrated that single low to moderate doses of caffeine can produce a number of positive subjective effects. Table 2 lists the various types of positive subjective effects that have been reported in 10 double-blind placebo-controlled studies with caffeine. Caffeine has been shown to result in ratings that indicate increased well-being, happiness, energetic arousal, alertness, and sociability. Although caffeine-induced positive effects have not been observed consistently across all experimental studies (James, 1997), factors that increase the likelihood of positive effects have been identified (Griffiths & Mumford, 1995). First, the positive subjective effects of caffeine most often are demonstrated at low doses, or doses in the range of typical dietary consumption (for example, 20 to 200 mg). Although there appear to be wide individual differences in sensitivity to caffeine, it is clear that the dysphoric/anxiogenic subjective effects of caffeine emerge at higher doses (Chait & Griffiths, 1983; Griffiths & Woodson, 1988b). Second, most studies that have demonstrated positive subjective effects of caffeine have had participants abstain from caffeine prior to testing (often through overnight abstinence). Third, individuals or populations in which caffeine functions as a reinforcer (as demonstrated by caffeine chosen over placebo in blind choice tests) tend to report greater positive effects from caffeine (Griffiths & Mumford, 1995). Although physical dependence and withdrawal may augment the perceived pleasurable effects of caffeine, positive mood effects have been demonstrated in non-habitual users and those maintained on a caffeine-free diet, as well as under conditions of minimal deprivation (Silverman & Griffiths, 1992; Mumford, Evans et al., 1994; Silverman, Mumford et al., 1994; James, 1998).

The overall profile of positive subjective effects of low to moderate doses of caffeine is qualitatively similar to those produced by *d*-amphetamine and cocaine (including increases in energy, alertness, and sociability). Unlike *d*-amphetamine and cocaine, caffeine is more likely to produce dysphoria/anxiety with increased dose (Chait & Griffiths, 1983; Chait & Johanson, 1988).

**TABLE 2. Positive Subjective Effects of Caffeine After Low to Intermediate Doses (18 to 178 mg)**

- Increased sense of wellbeing
- Increased energy/active/vigor
- Increased alertness/clear headedness
- Improved concentration
- Increased self-confidence
- Increased motivation for work
- Increased desire to talk/sociability
- Decreased sleepiness
- Decreased muzzy; not clear-headed.

NOTE: Subjective dimensions significantly affected in double-blind placebo controlled studies: cf. Leathwood & Pollet, 1983; Lieberman, Wurtman et al., 1987; Griffiths, Evans et al., 1990a; Silverman & Griffiths, 1992; Mumford, Evans et al., 1994; Silverman, Mumford & Griffiths, 1994; Robelin & Rogers, 1998; Liguori, Grass & Hughes, 1999; Smit & Rogers, 2000; Watson, Lunt et al., 2000.

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**Negative Subjective Effects.** In general, acute doses of caffeine greater than 200 mg are more likely to be associated with negative subjective effects, such as increases in anxiety, nervousness, jitteriness, upset stomach, and "bad effects" (Goldstein, Kaizer et al., 1969; Evans & Griffiths, 1991; Griffiths & Mumford, 1995; Liguori, Grass et al., 1999). Individual differences in sensitivity and tolerance seem to play an important role in the likelihood and severity of negative subjective effects. Individuals with panic disorder and generalized anxiety disorder, as well as nonclinical populations with higher anxiety sensitivity, tend to be particularly sensitive to the anxiogenic effects of caffeine at high doses (Boulenger, Uhde et al., 1984; Bruce, Scott et al., 1992; Charney, Heninger et al., 1985; Telch, Silverman et al., 1996). Although high-dose subjective effects of caffeine show some overlap with the subjective effects of *d*-amphetamine, caffeine produces greater negative effects (such as anxiety) and fewer positive effects (such as positive mood) (Chait & Griffiths, 1983; Chait & Johanson, 1988). In most cases, the negative subjective effects of caffeine are relatively mild and short-lived. However, acute and/or chronic use of caffeine, especially in very high doses, can cause distress and discrete psychopathology, as discussed below.

## DISCRIMINATIVE STIMULUS EFFECTS

In the drug discrimination paradigm, subjects are trained to respond differentially after administration of different drugs that are given under double-blind conditions. In the typical two-response drug-versus-placebo procedure, subjects are reinforced (usually with money) for making one response (for example, a correct verbal or written drug identification response: "I received Drug A") after double-blind administration of one drug condition on one day, and an alternative response (for example: "I received Drug B") after the other drug condition on another day. A testing phase often is instituted after discrimination training in order to determine how individuals respond to various doses of the drug or another drug (that is, was the test drug "like" or "unlike" the training dose?). In addition, subjects often are asked to report subjective effects as well as the basis on which they made the discrimination. Although the measurement of subjective effects and discriminative stimulus effects are methodologically independent operations, which theoretically could provide totally independent data, research across a range of compounds, including caffeine, has demonstrated an impressive covariation between these measures (cf. Griffiths & Mumford, 1996).

More than 80% of subjects acquired a caffeine versus placebo discrimination in the seven discrimination studies published to date (cf. Griffiths & Mumford, 1996). Doses at which the initial discrimination was acquired have ranged between 100 and 320 mg. Once acquired, the discrimination performance has been very stable over sessions.

Very low caffeine doses (<20 mg) produce discriminative and performance effects. Studies that have explicitly trained discrimination of progressively lower caffeine doses have shown that caffeine doses as low as 1.8 to 10 mg can be reliably discriminated by some subjects (Griffiths, Evans et al., 1990a; Silverman & Griffiths, 1992; Mumford, Evans et al., 1994). In those studies, 70% of subjects detected 56 mg or less, while about 35% detected 18 mg or less. Studies documenting that caffeine can produce reliable discriminative effects at very low doses are consistent with a recent study showing that 12.5 mg of caffeine produced significant increases in behavioral performance (Smit & Rogers, 2000).

**Discriminative Effects of Caffeine Relative to Other Stimulant Drugs.** Several drug discrimination studies demonstrate the similarities and differences between caffeine and other stimulant drugs. In one study, both caffeine and *d*-amphetamine produced dose-related increases in drug-appropriate responding in drug abusing subjects who were trained to discriminate cocaine from placebo (Oliveto, McCance-Katz et al., 1998). These findings are consistent with a previous study (Rush, Sullivan et al., 1995) of drug abusers, which showed that intravenous caffeine produced dose-related increases in the frequency of stimulant identifications (that is, like cocaine or *d*-amphetamine) on a Pharmacological Class Identification questionnaire. However, another study failed to show this effect (Garrett & Griffiths, 2001).

Other discrimination studies (Oliveto, Bickel et al., 1992, 1993) showed that the stimulants methylphenidate and theophylline tended to produce caffeine-appropriate responding in subjects trained to discriminate caffeine from placebo; in contrast, the sedative drugs triazolam and buspirone produced predominantly placebo-appropriate responding. Another study concluded that 100 and 300 mg caffeine produced dose-related partial generalization to *d*-amphetamine in subjects trained in a *d*-amphetamine ver-

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sus placebo discrimination (Chait & Johanson, 1988). Despite these documented similarities in the discriminative effects of caffeine and other stimulants, one study has shown that subjects can be trained to discriminate reliably between caffeine and *d*-amphetamine (Heishman, Taylor et al., 1992).

## REINFORCING EFFECTS

Drug reinforcement is defined by the ability of a drug to maintain drug self-administration or choice behavior. The circumstantial evidence for caffeine as a reinforcer is compelling: it is the most widely self-administered mood-altering drug in the world. Historically, repeated efforts to restrict or eliminate consumption of caffeinated foods have been completely unsuccessful. As reviewed in detail elsewhere (Griffiths & Mumford, 1995), nine blinded studies provide unequivocal evidence of the reinforcing effects of caffeine (Griffiths, Bigelow et al., 1986a, 1986b, 1989; Griffiths & Woodson, 1988b; Hughes, Higgins et al., 1991; Hughes, Hunt et al., 1992; Hughes, Oliveto et al., 1992a; Oliveto, Hughes et al., 1992; Silverman, Mumford et al., 1994).

The present section updates that review based on an additional eight recent studies that provide information about the reinforcing effects of caffeine (Evans, Critchfield et al., 1994; Mitchell, de Wit et al., 1995; Hughes, Oliveto et al., 1995; Hale, Hughes et al., 1995; Liguori, Hughes et al., 1997c; Liguori & Hughes, 1997; Schuh & Griffiths, 1997; Garrett & Griffiths, 1998). These studies demonstrated caffeine reinforcement under double-blind conditions with various subject populations (moderate and heavy adult and adolescent caffeine users; individuals with and without histories of alcohol or drug abuse), using a variety of different methodological approaches (variations on both choice and *ad libitum* self-administration procedures), when caffeine was available in different vehicles (coffee, soft drinks, or capsules), when subjects did and did not have immediate past histories of chronic caffeine exposure, and in the context of different behavioral requirements after drug ingestion (vigilance versus relaxation activities).

**Incidence of Reinforcement.** The overall incidence of caffeine reinforcement in normal caffeine users is 40% (50 of 125 subjects, based on the seven publications that provide this information) (cf. Griffiths & Woodson, 1988b; Hughes, Oliveto et al., 1993; Evans, Critchfield et al., 1994; Silverman, Mumford et al., 1994; Hale, Hughes et al., 1995; Liguori, Hughes et al., 1997c; Liguori & Hughes, 1997). A substantially higher incidence of caffeine reinforcement in normal subjects (82% and 100%) has been demonstrated in studies that involved repeated exposure to the caffeine and placebo test conditions before reinforcement testing (Evans, Critchfield et al., 1994), or that involved repeated exposure plus the requirement that subjects engage in a vigilance task after drug administration (Silverman, Mumford et al., 1994). Subjects with histories of heavy caffeine use and abuse of alcohol or other drugs have shown a higher incidence of caffeine reinforcement (100% of 20 subjects) (Griffiths, Bigelow et al., 1986a, 1986b, 1989), compared to normal subjects (40%).

**Subjective Effects Covary With Caffeine Reinforcement.** Studies repeatedly have demonstrated that qualitative ratings of subjective effects have covaried with measures of reinforcement or choice (Griffiths & Mumford, 1995). An example is provided from a choice study (Evans & Griffiths, 1992), which assessed the subjective effects of placebo and caffeine on forced-exposure days preceding choice days. When the subjective effect data were retrospectively categorized into caffeine choosers and nonchoosers, a face-valid profile of changes in subjective effects emerged: (1) choosers showed "positive" subjective effects of caffeine relative to placebo (for example, increased alertness, contentedness, energy, and liking); (2) nonchoosers showed "negative" effects of caffeine relative to placebo (for example, increased anxiety, mood disturbance, or jitteriness); and (3) choosers showed "negative" effects of placebo (for example, increased headache and fatigue).

**Effects of Dose on Reinforcement.** Caffeine reinforcement appears to be an inverted U-shaped function of dose. Doses as low as 25 mg per cup of coffee and 33 mg per serving of soft drink have been shown to function as reinforcers when subjects could repeatedly self-administer those doses within a day (Hughes, Hunt et al., 1992; Hughes, Oliveto et al., 1995; Liguori, Hughes et al., 1997c). Doses above 50 or 100 mg tend to decrease choice or self-administration (Griffiths, Bigelow et al., 1986b; Griffiths & Woodson, 1988b; Stern, Chait et al., 1989; Hughes, Hunt et al., 1992), with relatively high doses of caffeine (for example, 400 or 600 mg) producing significant caffeine avoidance (Griffiths & Woodson, 1988b).

**Physical Dependence Potentiates Reinforcement.** It is clear that avoidance of abstinence-associated withdrawal symptoms plays a central role in the reinforcing effects of caffeine among regular caffeine consumers. This relationship has been shown in retrospective questionnaire studies (Goldstein & Kaizer, 1969) and in experimental studies that have used indirect (Yeomans, Spetch et al., 1998; Yeomans,

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Jackson et al., 2000) and direct (Griffiths, Bigelow et al., 1986a; Hughes, Oliveto et al., 1993; Schuh & Griffiths, 1997; Liguori & Hughes, 1997; Garrett & Griffiths, 1998) behavioral measures of caffeine reinforcement. For example, Hughes and colleagues (1993) showed that moderate caffeine consumers who reported caffeine withdrawal symptoms (headache, drowsiness) after drinking decaffeinated coffee were more than twice as likely to show caffeine reinforcement. In studies that prospectively manipulated caffeine physical dependence, subjects chose caffeine more than twice as often when they were physically dependent than when they were not physically dependent (Griffiths, Bigelow et al., 1986a; Garrett & Griffiths, 1998).

**Caffeine and Conditioned Flavor Preference.** In addition to the studies providing direct behavioral assessments of caffeine reinforcement, a series of recent studies by Rogers and colleagues used a conditioned flavor preference paradigm to provide indirect indicators of caffeine reinforcement. In the studies, moderate consumers of caffeine were repeatedly exposed over days to a novel flavored drink paired with either caffeine or placebo. Relative to subjects who received the placebo-paired drink, subjects who received the caffeine-paired drink rated the drink as more pleasant (Richardson, Rogers et al., 1996; Yeomans, Spetch et al., 1998) or more preferred (Rogers, Richardson et al., 1995). Analysis of data over days showed that subjects who received the caffeine-paired drink significantly increased ratings of pleasantness, while subjects receiving placebo-paired drinks showed significantly decreased ratings of pleasantness (Yeomans, Spetch et al., 1998; Yeomans, Jackson et al., 2000). In the natural environment, the development of such conditioned flavor preferences over many days of self-administration seems likely to play an important role in development of strong consumer preferences for specific types or even brands of caffeine-containing beverages.

## CAFFEINE TOLERANCE

"Tolerance" refers to an acquired decrease in responsiveness to a drug as the result of drug exposure. Tolerance to caffeine can be expected to vary with caffeine dose, dose frequency, number of doses, and the individual's elimination rate (Shi, Benowitz et al., 1993). As in the animal laboratory, development of tolerance to caffeine in humans has been clearly demonstrated; however, quantitative parametric information is quite fragmentary (cf. Griffiths & Mumford, 1996; Fredholm, Bättig et al., 1999). As described below, several studies have shown that, when very high doses of caffeine (750 to 1200 mg/day throughout the day) are administered daily, "complete" tolerance (that is, caffeine effects no longer are different from baseline or placebo) can occur on some, but not all, measures. It should be noted, however, that at lower doses (similar to those usually consumed in the natural environment), complete tolerance does not occur.

Tolerance to the subjective effects of caffeine was clearly demonstrated in a study in which two groups of subjects received either caffeine (300 mg TID) or placebo (TID) for 18 consecutive days (Evans & Griffiths, 1992). During the last 14 days of chronic dosing, the caffeine and placebo groups did not differ meaningfully on ratings of mood and subjective effects. Moreover, after chronic dosing, caffeine (300 mg BID) produced significant subjective effects (including increases in ratings of tension-anxiety, jittery/nervous/shaky, active/stimulated/energetic, and strength of drug effect) in the chronic placebo group but not in the chronic caffeine group, suggesting the development of "complete" tolerance at these high doses.

Two studies provided some experimental evidence for caffeine tolerance to sleep disruption by demonstrating decreases in caffeine-induced disruption of objective measures of sleep after caffeine dosing of 250 mg BID for two days (Zwyghuizen-Doorenbos, Roehrs et al., 1990) or 400 mg TID for seven days (Bonnet & Arand, 1992). By day 7 in the latter study, a number of sleep measures no longer were different from baseline, suggesting the development of complete tolerance. However, the authors point out that sleep efficiency remained below 90%, suggesting some continuing sleep disruption even after seven days of caffeine consumption.

In addition to the three studies that demonstrated tolerance to centrally mediated caffeine effects, there is good evidence that repeated daily caffeine administration produces decreased responsiveness to physiological effects of caffeine, including diuresis, parotid gland salivation, increased metabolic rate (oxygen consumption), increased blood pressure, increased plasma norepinephrine and epinephrine, and increased plasma renin activity (cf. Griffiths & Mumford, 1996). Several studies (Robertson, Wade et al., 1981; Ammon, Bieck et al., 1983; Denaro, Brown et al., 1991) have demonstrated complete tolerance to blood pressure and other cardiovascular and physiological responses with repeated daily caffeine administration (for example, tolerance to 250 mg TID in one to four days; Robertson, Wade et al., 1981). Despite substantial tolerance development to

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cardiovascular effects at very high doses, caffeine as usually consumed is considered a risk factor in hypertension-prone individuals (Green, Kirby et al., 1996; Nurminen, Niittynen et al., 1999).

## CAFFEINE INTOXICATION

The potential for caffeine intoxication to cause clinically significant distress is reflected by its inclusion as a diagnosis in the *DSM-IV* of the American Psychiatric Association (1994) and the *ICD-10* of the World Health Organization (1992a, 1992b).

Caffeine intoxication long has been recognized as a discrete syndrome associated with excessive caffeine use. In fact, reports of caffeine intoxication can be found in the medical literature dating back to the 1800s (cf. Strain & Griffiths, 1997). "Caffeinism" is an older term that has been used to describe the toxic effects of caffeine that result from acute or chronic use (Greden, 1981; *DSM-IIIR*, APA, 1987).

**Diagnostic Criteria for Intoxication.** Caffeine intoxication currently is defined by a number of symptoms and clinical features that emerge in response to recent consumption of caffeine. As listed in Table 3, common features of caffeine intoxication include nervousness (anxiety), restlessness, insomnia, gastrointestinal upset, tremors, tachycardia, and psychomotor agitation. In addition, there have been reports of patients with caffeine intoxication experiencing fever, irritability, tremors, sensory disturbances, tachypnea, and headaches (cf. Strain & Griffiths, 1997).

There have been no studies comparing the relative importance of the various *DSM-IV* criteria to the diagnosis of caffeine intoxication. However, in a study of general hospital patients, the symptoms most often associated with caffeine use were diuresis, insomnia, withdrawal headache, diarrhea, anxiety, tachycardia, and tremulousness (Victor, Lubsesky et al., 1981). Unlike many other drugs of dependence, but similar to nicotine, the high-dose intoxicating effects of caffeine are not usually sought out by users. High-dose caffeine toxicity very rarely is fatal. However, caffeine can be lethal at very high doses (for example, 5 to 10 g) and there is documentation of suicide by caffeine overdose (Serafin, 1996; Bryant, 1981).

Although *DSM-IV* diagnostic guidelines (Table 3) suggest that diagnosis should depend on the recent daily consumption of at least 250 mg of caffeine, the equivalent of just two and a half cups of brewed coffee, intoxication usually involves much higher doses (>500 mg) (Greden & Pomerleau, 1995). However, differences iin individual sensitivity and tolerance are likely to influence the dose response. For example, an individual with high sensitivity and little tolerance might show signs and symptoms of caffeine intoxication in response to doses of caffeine much lower than those of a regular user.

**TABLE 3. DSM Criteria for Caffeine Intoxication**

A. Recent consumption of caffeine, usually in excess of 250 mg (for example, more than 2 to 3 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).

SOURCE: American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)*. Washington, DC: American Psychiatric Press.

Little is known about who may be most vulnerable to caffeine intoxication. Because caffeine intoxication is directly related to excess caffeine ingestion, any individual who consumes caffeine in large excess of his or her typical consumption may be at risk. Subgroups that have been identified as consuming large amounts of caffeine relative to the general population include psychiatric patients, prisoners, smokers, alcoholics, and individuals with eating

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disorders (cf. Strain & Griffiths, 1997). It has been noted that caffeine intoxication can occur in someone who has been using caffeine for many years without apparent problems (Greden & Pomerleau, 1995).

Treatment providers should be familiar with the signs and symptoms of caffeine intoxication. Such intoxication should be ruled out in the differential diagnosis of psychiatric disorders such as panic disorder, generalized anxiety disorder, sleep disorder, mania, and other substance abuse and substance withdrawal. Because many features of caffeine intoxication overlap with those of other medical and psychiatric disorders, identifying recent ingestion of excess caffeine is critical in diagnosing caffeine intoxication. Serum or saliva assays can be used to verify caffeine use.

**Management of Intoxication.** Caffeine intoxication usually resolves rapidly (consistent with caffeine's half-life of four to six hours) and appears to have no long-lasting consequences. Treatment may consist of short-term management and support of the patient for the time that it takes symptoms to resolve spontaneously. The patient who frequently consumes excessive amounts of caffeine and experiences repeated episodes of caffeine intoxication may benefit from education and behavior modification strategies (see the section on Clinical Implications and Treatment).

Very few studies have examined the incidence and prevalence of caffeine intoxication in the general population. Although many users may experience the negative effects of caffeine on occasion, caffeine intoxication serious enough to come to clinical attention is considered relatively rare (Strain & Griffiths, 2000). A random digit telephone survey found that 7% of current caffeine users met *DSM-IV* criteria for caffeine intoxication by reporting use of more than 250 mg, five or more symptoms, and symptoms that interfered with their functioning at work, school, or home (Hughes, Oliveto et al., 1998). Prior studies that have used ambiguous criteria and have focused on special populations (such as psychiatric patients or college students) have reported caffeine intoxication rates ranging from 2% to 19% (see Strain & Griffiths, 1997).

## ANXIETY AND CAFFEINE

Acute doses of caffeine (generally, >200 mg) have been shown to increase anxiety ratings in non-clinical populations (Goldstein, Kaizer et al., 1969; Chait & Griffiths, 1983; Stern, Chait et al., 1989; Nickell & Uhde, 1994/1995). Higher doses have been shown to induce unequivocal panic attacks in some normal subjects (Uhde, 1990; Nickell & Uhde, 1994/1995; Telch, Silverman et al., 1996; Lin, Uhde et al., 1997). Individuals who score higher on baseline measures of anxiety are less likely to choose caffeine over placebo in blind choice procedures (Evans & Griffiths, 1992; Griffiths & Woodson, 1988b).

Individuals with anxiety disorders appear to be particularly sensitive to the effects of caffeine. When individuals with panic disorder are asked about their responses to caffeine, they report greater anxiety than do respondents in matched control groups (Boulenger, Uhde et al., 1984; Lee, Cameron et al., 1985). Experimental studies have demonstrated that caffeine exacerbates anxiety symptoms in individuals with generalized anxiety disorder (Bruce, Scott et al., 1992) and panic disorder (Beck & Berisford, 1992; Charney, Heninger et al., 1985; Newman, Stein et al., 1992) to a greater extent than in healthy control subjects. Surveys have found that individuals with anxiety disorders tend to report lower levels of caffeine consumption relative to controls (Lee, Cameron et al., 1985; Lee, Flegel et al., 1988; Uhde, 1990; Rihs, Müller et al., 1996).

**Caffeine-Induced Anxiety Disorder.** Caffeine-induced anxiety disorder is a diagnosis included in the *DSM-IV* (APA, 1994). This disorder is characterized by prominent anxiety, panic attacks, or obsessions or compulsions that are related etiologically to caffeine use. Although the symptoms of caffeine-induced anxiety disorder may meet full criteria for a *DSM* anxiety disorder (such as panic disorder or generalized anxiety disorder), one need not meet all diagnostic criteria in order to qualify for a diagnosis of caffeine-induced anxiety disorder. There is no research examining this disorder, although studies have examined the relationship between caffeine and anxiety (as reviewed above). Clinical features of caffeine-induced anxiety have been described (Greden, 1974; Uhde, 1990). The diagnosis requires that the anxiety symptoms comprising the disorder must be caused by caffeine and be greater than what would be expected during caffeine intoxication or withdrawal. Because diagnosing caffeine-induced anxiety disorder depends on demonstrating that caffeine is linked to the anxiety symptoms, a trial of caffeine abstinence (and subsequent symptom remission) may be used to confirm the diagnosis. Although highly anxious individuals tend to be more likely to limit their caffeine use, not all individuals with anxiety problems naturally avoid caffeine, and some may fail to recognize the role that caffeine is playing in their anxiety symptoms. For example, Bruce and Lader (1989) found that instructions to cease caffeine use for one week led to

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significant improvements in more than half of individuals who presented for treatment at an anxiety disorders clinic and some required no further treatment.

## SLEEP AND CAFFEINE

It is widely accepted that caffeine affects sleep. Numerous studies have shown that caffeine increases wakefulness and reduces decrements in performance under conditions of sleep deprivation (Snel, 1993; Wright, Badia et al., 1997; Reyner & Horne, 2000; Patat, Rosenzweig et al., 2000). Because of its ability to cause insomnia, sleep researchers have used caffeine as a challenge agent in order to study insomnia in healthy volunteers (Okuma, Matsuoka et al, 1982; Alford, Bhatti et al., 1996). Caffeine's effects on sleep appear to be determined by a variety of factors, including dose, the time between caffeine ingestion and attempted sleep, and individual differences in sensitivity and/or tolerance to caffeine (Snel, 1993).

The effects of caffeine on sleep are dose-dependent, with higher doses showing greater disruption on a number of sleep quality measures (Karacan, Thornby et al., 1976; Alford, Bhatti et al., 1996; Hindmarch, Rigney et al., 2000). Caffeine administered immediately prior to bedtime or throughout the day has been shown to delay sleep onset, reduce total sleep time, alter the normal stages of sleep, and decrease the reported quality of sleep (cf. Snel, 1993; Alford, Bhatti et al., 1996; Hindmarch, Rigney et al., 2000). There is less evidence to suggest that caffeine taken early in the day negatively affects nighttime sleep (Snel, 1993). However, a recent study found that caffeine (200 mg) taken at 7:10 in the morning produced small but significant effects on the following night's total sleep time, sleep efficiency, and electroencephalography (EEG) power spectra (Landolt, Werth et al., 1995).

Caffeine-induced sleep disturbance is greatest among individuals who are not regular caffeine users (Colton, Gosselin et al., 1968; Snel, 1993). It is not clear whether this difference is due to acquired pharmacologic tolerance or to a preexisting population difference in sensitivity to caffeine (Goldstein, 1964; Goldstein, Warren et al., 1965; Snel, 1993). Although there is evidence for some tolerance to the sleep-disrupting effects of caffeine (Bonnet & Arand, 1992; Zwyghuizen-Doorenbol, Roehrs et al., 1990), complete tolerance may not occur and thus habitual caffeine consumers remain vulnerable to caffeine-induced sleep problems (Goldstein, 1964; Goldstein, Warren et al., 1965).

In addition to caffeine's well-documented ability to disrupt sleep, a few studies have shown that caffeine withdrawal after acute abstinence from chronic caffeine can increase sleep duration and quality (Goldstein, Warren et al., 1965; James, 1998).

**Caffeine-Induced Sleep Disorder.** Caffeine-induced sleep disorder is a diagnosis included in the *DSM-IV* (APA, 1994). The disorder is characterized by a prominent disturbance of sleep that is related etiologically to caffeine use. Caffeine use most often is associated with insomnia; however, cases of caffeine causing excessive sleepiness also have been reported (Regestein, 1989). Like caffeine-induced anxiety disorder, caffeine-induced sleep disorder is diagnosed when symptoms of a sleep disturbance are greater than would be expected during caffeine intoxication or caffeine withdrawal.

There is little information about the incidence or prevalence of caffeine-induced sleep disorder. As discussed earlier, it appears that sleep disturbances due to caffeine are more likely to occur in individuals who are not regular caffeine consumers; nevertheless, complete tolerance to the effects of caffeine on sleep probably does not occur even among heavy caffeine users. Such heavy users may be vulnerable to, but relatively unaware of, the disruptive effects of caffeine on sleep because the pattern develops slowly. In elderly persons, occult caffeine consumption in the form of caffeine-containing analgesic medications may lead to sleep problems (Brown, Salive et al., 1995). Because diagnosing caffeine-induced sleep disorder depends on demonstrating that caffeine is linked to the sleep disturbance, a trial of caffeine abstinence (and subsequent symptom remission) may be used to confirm the diagnosis.

## CAFFEINE WITHDRAWAL

The caffeine withdrawal syndrome has been well-characterized in humans. Fifty-three case reports and experimental studies previously were reviewed by Griffiths & Mumford (1995). This chapter updates their review by incorporating an additional 31 recent studies that provide information about caffeine withdrawal (Bruce, Scott et al., 1991; Weber, Ereth et al., 1993; Strain, Mumford et al., 1994; Lane, 1994; Nikolajsen, Larsen et al., 1994; Brauer, Buican et al., 1994; Höfer & Bättig, 1994a, 1994b; Reeves, Struve et al., 1995; Mitchell, de Wit et al., 1995; Streufert, Pogash et al., 1995; Hampl, Schneider et al., 1995; Richardson, Rogers et al., 1995; Lader, Cardwell et al., 1996; Comer, Haney et

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al., 1997; Weber, Klindworth et al., 1997; Hamill & Levin, 1997; Couturier, Laman et al., 1997; Goldstein & Wallace, 1997; Schuh & Griffiths, 1997; Lane, 1997; Phillips-Bute & Lane, 1998; Lane & Phillips-Bute, 1998; James, 1998; Hughes, Oliveto et al., 1998; Bernstein, Carroll et al., 1998b; Garrett & Griffiths, 1998; Dews, Curtis et al., 1999; Evans & Griffiths, 1999; Jones, Herning et al., 2000; Watson, Lunt et al., 2000). Although most research on withdrawal has been performed with adults, there is evidence that children also experience withdrawal effects during caffeine abstinence (Bernstein, Carroll et al., 1998; Goldstein & Wallace, 1997; Hale, Hughes et al., 1995).

**Signs and Symptoms.** The most commonly reported withdrawal symptom is headache, often described as being gradual in development and diffuse, and sometimes as throbbing and severe (Griffiths & Woodson, 1988a; Strain, Mumford et al., 1994; Lader, Cardwell et al., 1996). Other symptoms, in roughly descending order of prominence, are fatigue (fatigue, lethargy, sluggishness); sleepiness/drowsiness (sleepy, drowsy, yawning); difficulty concentrating (muzzy); work difficulty (decreased motivation for tasks/work); irritability (irritable, cross, miserable, decreased well-being/contentedness); depression (depressed mood); anxiety (anxious, nervous); influenza-like symptoms (nausea/vomiting, muscle aches/stiffness, hot and cold spells, heavy feelings in arms or legs).

In addition to these symptoms, caffeine withdrawal may produce impairment in psychomotor, vigilance, and cognitive performance, increases in cerebral blood flow, and changes in quantitative EEG activity. The observation that withdrawal symptoms such as fatigue or drowsiness can occur in absence of a headache indicates that such symptoms are not merely an epiphenomenon of headache (Griffiths & Woodson, 1988a; Griffiths, Evans et al., 1990b; Streufert, Pogash et al., 1995; Garrett & Griffiths, 1998; Phillips-Bute & Lane, 1998; Jones, Herning et al., 2000).

**Dosing Parameters.** *Caffeine Maintenance Dose*: The incidence (Goldstein & Kaizer, 1969; Goldstein, Kaizer et al., 1969; Galletly, Fennelly et al., 1989; Fennelly, Galletly et al., 1991; Weber, Ereth et al., 1993; Nikolajsen, Larsen et al., 1994) and severity (cf. Griffiths & Woodson, 1988a; Lader, Cardwell et al., 1996) of caffeine withdrawal are an increasing function of daily self-reported caffeine dose. However, this relationship between caffeine dose and withdrawal appears to be relatively weak because it has not been consistently demonstrated across studies (Verhoeff & Millar, 1990; Hughes, Oliveto et al., 1993; Höfer & Bättig, 1994a), and some studies have shown no or only very mild withdrawal after stopping high doses of caffeine (Griffiths, Bigelow et al., 1986a; Strain, Mumford et al., 1994).

The only study to manipulate caffeine maintenance dose experimentally found that withdrawal severity increased progressively across three caffeine maintenance doses (100, 300, and 600 mg/day), with significantly greater withdrawal demonstrated at 600 mg/day than at 100 mg/day (Evans & Griffiths, 1999). This study and a previous study (Griffiths, Evans et al., 1990b) also demonstrated that significant caffeine withdrawal occurred after abstinence from a dose as low as 100 mg/day, which is the caffeine equivalent of one cup of brewed coffee or two to three 12-ounce servings of a caffeinated soft drink.

*Duration of Exposure*: Caffeine withdrawal has been shown to occur after relatively short-term exposure to daily caffeine (Dreisbach & Pfeiffer, 1943; Griffiths, Bigelow et al., 1986a; Evans & Griffiths, 1999). One study showed that significant withdrawal occurred after only three consecutive days of 300 mg/day caffeine, with somewhat greater severity shown after 7 and 14 consecutive days of exposure (Evans & Griffiths, 1999). Another study showed that caffeine withdrawal headache occurred in three individuals who normally abstained from caffeinated beverages, but were given 600 to 750 mg/day caffeine for six or seven days (Dreisbach & Pfeiffer, 1943).

*Within-Day Frequency of Exposure*: One study showed that the range and severity of caffeine withdrawal symptoms did not differ when 300 mg of caffeine was taken as a single dose in the morning, versus 100 mg taken at three time points across the day (Evans & Griffiths, 1999). Thus, although caffeine is eliminated relatively quickly, its mean half-life of four to six hours apparently is long enough to maintain significant caffeine exposure even under a once-a-day dosing regimen.

*Caffeine Suppression of Withdrawal*: Even low doses of caffeine are capable of suppressing caffeine withdrawal. One study showed that when individuals were maintained on 300 mg caffeine/day and tested with a range of lower doses (200, 100, 50, 25, and 0 mg/day), a substantial reduction in caffeine dose (100 mg/day or less) was necessary for the manifestation of caffeine withdrawal (Evans & Griffiths, 1999). Interestingly, even a mere 25 mg/day was sufficient to suppress significant caffeine withdrawal headache. The observation that low doses of caffeine suppress withdrawal is consistent with a recent study, which found that 12.5 mg of caffeine produced performance enhance-

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ment in a group of caffeine users who had been abstinent overnight, but not in a group that consumed very low levels of caffeine (Smit & Rogers, 2000). One implication of these findings is that a substantial percentage reduction in caffeine consumption is necessary to elicit the full caffeine withdrawal syndrome.

**Incidence of Withdrawal.** Blind experimental studies in healthy normal caffeine users who abstained for 24 hours indicate that the incidence of headache is about 50% (ranging from 30% to 86%) (Dreisbach & Pfeiffer, 1943; Griffiths, Evans et al., 1990b; van Dusseldorp & Katan, 1990; Silverman, Evans et al., 1992; Hughes, Oliveto et al., 1993; Lader, Cardwell et al., 1996; Höfer & Battig, 1994a; James, 1998). A similar incidence of headache has been reported in studies of subjects specifically selected for reporting problems with caffeine use or withdrawal (Strain, Mumford et al., 1994; Dews, Curtis et al., 1999). Not surprisingly, when all withdrawal symptoms are considered, the incidence of caffeine withdrawal is higher (ranging from 39% to 100%) (Griffiths, Evans et al., 1990b; Hughes, Oliveto et al., 1993; Strain, Mumford et al., 1994; Lader, Cardwell et al., 1996; Dews, Curtis et al., 1999).

Retrospective studies have been conducted to determine the frequency of caffeine withdrawal in the general population. In a population-based random digit dial telephone survey (Hughes, Oliveto et al., 1998), 44% of caffeine users reported having stopped or reduced caffeine use for at least 24 hours in the preceding year. Of those, 41% reported that they experienced at least one *DSM-IV* defined caffeine withdrawal symptom. Among individuals who stopped caffeine use in an attempt at permanent abstinence, at least 71% reported experiencing *DSM-IV* symptoms, and 24% reported having headache plus other symptoms that interfered with performance. The percentage of those endorsing individual symptoms is shown in Figure 3.

In another study that surveyed callers about participation in a clinical research trial, only 11% of caffeine users endorsed that they had problems or symptoms on stopping caffeine in the past, with 25% of this group reporting that the symptoms were severe enough to interfere with normal activity (Dews, Curtis et al., 1999). However, the number of individuals who actually abstained from caffeine was not determined, nor was it determined whether significant underreporting of symptoms occurred because of the desire to participate in a research trial.

Such studies may underestimate the true rate of caffeine withdrawal. Many caffeine consumers may be unaware of their physical dependence on caffeine because their frequent habitual consumption precludes a period of sustained abstinence. Moreover, it has been demonstrated that as little as 25 mg of caffeine is sufficient to suppress withdrawal (Evans & Griffiths, 1999). Thus, even small amounts of caffeine that are unknowingly consumed on their reported "caffeine-free" days may result in underestimates of the occurrence of withdrawal. Finally, caffeine withdrawal symptoms (headache, nausea, muscle aches) may be attributed incorrectly to other causes or ailments (viral infection).

**Severity of Withdrawal.** When signs or symptoms of caffeine withdrawal occur, their severity can vary from mild to extreme. At its worst, caffeine withdrawal repeatedly has been shown to produce clinically significant distress or impairment in daily functioning and, on rare occasions, to be totally incapacitating (Kingdon, 1833; Bridge, 1893; Dreisbach & Pfeiffer, 1943; Goldstein & Kaizer, 1969; Cobbs, 1982; Greden, Victor et al., 1980; Rainey, 1985; Griffiths, Evans et al., 1990b; Silverman, Evans et al., 1992; Strain, Mumford et al., 1994; Lader, Cardwell et al., 1996). For example, in a double-blind caffeine-withdrawal evaluation (Strain, Mumford et al., 1994), 73% of individuals who met criteria for *DSM-IV* substance dependence on caffeine reported functional impairment in normal activities during an experimental withdrawal phase. Examples of functional impairment included missed work, costly mistakes at work, inability to care for children, and inability to complete schoolwork.

The proportion of regular caffeine users who are at risk for severe functional impairment during caffeine withdrawal is difficult to estimate. One blind study (Dreisbach & Pfeiffer, 1943) conducted in a relatively unselected group of graduate and medical students reported "headache as extreme in severity as the subjects had ever experienced" upon blind withdrawal of caffeine. This extreme headache occurred in 55% of 38 trials in 22 subjects. Another study (Silverman, Evans et al., 1992) tested 62 individuals from the general community with mean caffeine intake of 235 mg/day. The study involved double-blind caffeine abstinence under conditions that obscured that the purpose of the study was to investigate caffeine. During withdrawal, 52% reported moderate to severe headache, and 8% to 11% showed abnormally high scores on standardized depression, anxiety, and fatigue scales. This incidence of moderate to severe caffeine-withdrawal headache is similar to that reported in other studies of healthy subjects (Lader, Cardwell et al., 1996; Couturier, Laman et al., 1997). In the double-

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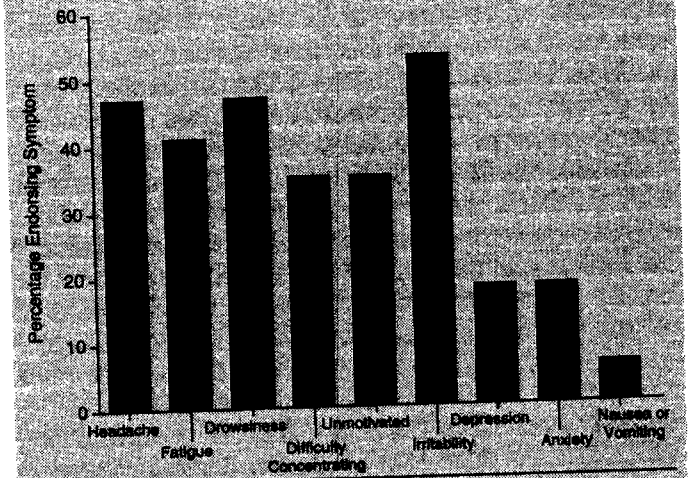
**FIGURE 3. Withdrawal Symptoms Endorsed by Individuals Who Tried to Stop Caffeine Use Permanently**




Data are from a general population survey (Hughes, Oliveto et al., 1998). Bars show percentage of individuals endorsing the symptoms.

blind study by Lader and colleagues, 45% of subjects with a mean caffeine intake of 360 mg/day experienced a "diffuse, throbbing headache." Twenty-eight percent of those reporting headache also reported nausea and sickness.

Another study (Dews, Curtis et al., 1999) evaluated the incidence of functional impairment during abrupt caffeine withdrawal in a group of 18 subjects who reported mild or severe problems or symptoms when previously stopping caffeine. The study found that 33% of subjects spontaneously reported caffeine withdrawal symptoms, while 22% showed substantial decreases in their ratings of daily functioning (in work and leisure activities). However, the authors note that none of the subjects reported "incapacitating" symptoms. Although totally incapacitating symptoms of caffeine withdrawal (such as complete inability to work or going to bed because of symptoms misattributed to illness) have been documented (Bridge, 1893; Silverman, Evans et al., 1992; Strain, Mumford et al., 1994), the rate appears low and thus may be undetected with a sample size of only 18 subjects. The authors also commented that the frequency and severity of caffeine withdrawal symptoms are lower than reported in previous studies. Possible reasons for this discrepancy include: (1) caffeine withdrawal symptoms were not assessed directly, but rather were inferred from spontaneous written comments in a "remarks" section of the questionnaire that asked about daily functioning; (2) subjects completed all questionnaires outside of the laboratory under unmonitored and unstructured conditions, reporting to the laboratory only at weekly intervals; (3) subjects consumed relatively low doses of caffeine immediately prior to abstinence (mean=231 mg/day); and (4) biological verification of caffeine abstinence was questionable (sample collection was not observed, data were reported only on the first morning of abstinence, and the lower limits of caffeine detection in the assay would have been unable to detect use of a small dose of caffeine sufficient caffeine to significantly suppress caffeine withdrawal).

**Individual Differences**. There are substantial differences within and across individuals with regard to the incidence and/or severity of caffeine withdrawal. As discussed above, only about 50% of regular caffeine consumers report headache after any single episode of caffeine abstinence. One study that examined repeated abstinence trials clearly documented differences within and across subjects: one subject never showed caffeine withdrawal headache, some subjects showed consistent headaches, while others reported headaches on some trials but not other trials (Griffiths, Evans et al., 1990b). A second study, which analyzed the effects of repeated abstinence trials, found that at least 36% of subjects who showed statistically significant elevations in headache failed to report this effect consistently across repeated trials (Hughes, Oliveto et al., 1993). Little is known about the determinants of these differences.

**Time Course of Withdrawal**. The caffeine withdrawal syndrome follows an orderly time course, as shown in Figure 4. Onset usually occurs 12 to 24 hours after the last dose of caffeine, although onset as late as 36 hours has been documented (cf. Griffiths & Woodson, 1988a; Griffiths, Evans et al., 1990b). Peak withdrawal intensity generally occurs 20 to 48 hours after the last dose (Griffiths & Woodson, 1988a; Griffiths, Evans et al., 1990b; Höfer & Bättig, 1994a). The duration of withdrawal usually is described as ranging between two and seven days (Griffiths, Bigelow et al., 1986a; Griffiths, Evans et al., 1990b; van Dusseldorp & Katan, 1990; Evans & Griffiths, 1992; Höfer & Bättig, 1994a), although longer durations have been reported (Griffiths, Bigelow et al., 1986a; Griffiths, Evans et al., 1990b; Richardson, Rogers et al., 1995).

**Diagnostic Criteria for Withdrawal**. The potential for caffeine withdrawal to cause clinically significant distress

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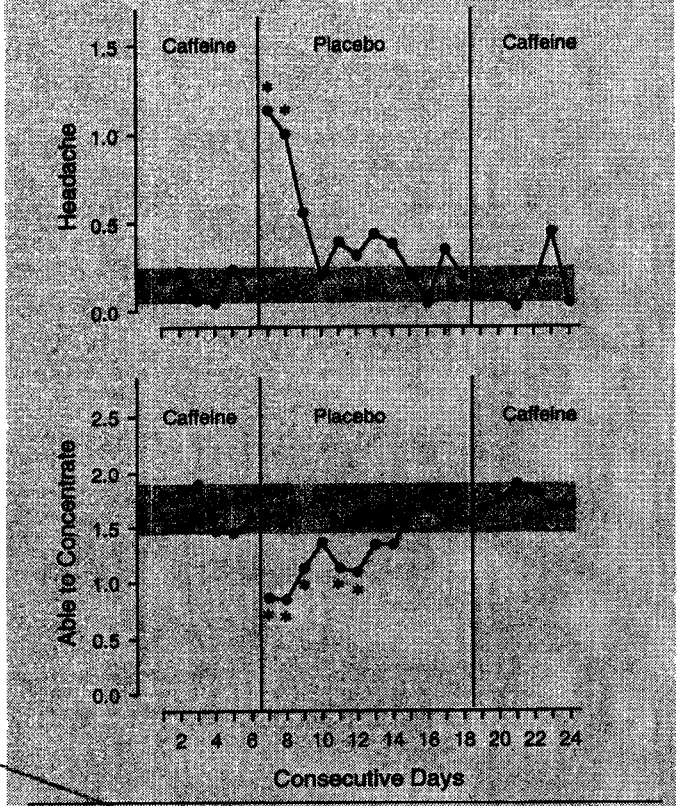
or impairment in function is reflected in its inclusion as an official diagnosis in the *ICD-10* (WHO, 1992a, 1992b) and as a proposed diagnosis in the *DSM-IV* (APA, 1994). (The 1994 DSM Work Group included caffeine withdrawal as a proposed diagnosis rather than an official diagnosis to encourage further research on the range and specificity of caffeine withdrawal symptoms [Hughes, 1994].) As reviewed above, the research literature on caffeine withdrawal has almost doubled since 1994, and now provides a sound empirical basis for a diagnosis of caffeine withdrawal.

As described in Table 4, the proposed criteria for a *DSM-IV* research diagnosis of caffeine withdrawal require the presence of headache and one or more of the following: marked fatigue or drowsiness, marked anxiety or depression, nausea or vomiting.

These criteria are very conservative because they exclude cases in which withdrawal headache is not accompanied by other symptoms and cases in which symptoms are experienced without headache. They also exclude several withdrawal symptoms that have been documented repeatedly in recent studies: difficulty concentrating, irritability, and work difficulty (such as decreased motivation for tasks/work).

The only study to evaluate the incidence of caffeine withdrawal using the criteria for the *DSM-IV* research diagnosis was a random-digit telephone survey of the general population (Hughes, Oliveto et al., 1998). That study found that 11% of those who had given up or reduced caffeine use in the past year met criteria for caffeine withdrawal. Notably, among the subgroup of individuals who reported trying to stop caffeine use permanently, 24% met criteria for the diagnosis (see Figure 3 for withdrawal symptoms).

**FIGURE 4. Withdrawal Time-Course**




Effects of double-blind substitution of placebo capsules for caffeine capsules (100 mg/day). Asterisks show which placebo days are significantly different from the initial caffeine period. Data are from Griffiths, Evans et al. (1990b).

## CAFFEINE DEPENDENCE

In the terminology of the *DSM-IV*, "substance dependence" is characterized by a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of a substance despite significant substance-related problems (APA, 1994). The clinical diagnosis of substance dependence encompasses several features, which may or may not include physical dependence (as evidenced by withdrawal). The *ICD-10* recognizes a diagnosis of substance dependence due to caffeine (WHO, 1992a, 1992b). Despite the fact that the *DSM-IV* uses very similar criteria for making a diagnosis of substance dependence, caffeine dependence is not presently included in *DSM-IV* and it is explicitly stated that "a diagnosis of substance dependence can be applied to every class of substance except caffeine." The rationale for excluding caffeine dependence from the *DSM-IV* was that, although caffeine withdrawal had been documented, there was no available database pertaining to other important features of substance dependence, such as inability to stop use and continued use despite harm (Hughes, Oliveto et al., 1992b; Hughes, 1994).

More recently, three studies have identified adults and adolescents who report problematic caffeine consumption and fulfill the *DSM-IV* criteria for substance dependence on caffeine. In one study (Strain, Mumford et al., 1994), 16 of 99 individuals who self-identified as having psychological or physical dependence on caffeine met the *DSM-IV*

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**TABLE 4. Proposed DSM Criteria for Caffeine Withdrawal**

A. Prolonged daily use of caffeine.

B. Abrupt cessation of caffeine use, or reduction in the amount of caffeine used, closely followed headache and one (or more) of the following symptoms:

(1) Marked fatigue or drowsiness
(2) Marked anxiety or depression
(3) Nausea or vomiting.

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 the direct physiological effects of a general medical condition (*e.g.*, migraine, viral illness) and are not better accounted for by another medical disorder.

SOURCE: American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)*. Washington, DC: American Psychiatric Press.

criteria for substance dependence on caffeine when four of the seven *DSM-IV* criteria that seemed most applicable to caffeine were assessed. Criteria used for making the diagnosis and rates of endorsement were: withdrawal (94%), use continued despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by caffeine use (94%), persistent desire or unsuccessful efforts to cut down or control caffeine use (81%), and tolerance (75%). Median daily caffeine intake of those fulfilling a caffeine dependence diagnosis was 357 mg, with a range of 129 to 2,548. The preferred vehicle was almost equally divided between soft drinks and coffee. Interestingly, although there were few concurrent psychiatric disorders in this population, 57% had a past diagnosis of alcohol abuse or dependence.

Using the same four *DSM-IV* criteria, another study identified adolescents who met diagnostic criteria for caffeine dependence (Bernstein, Carroll et al., 2002; Oberstar, Bernstein et al., 2002). The third study was a random-digit dial telephone survey of the general population in which all seven *DSM-IV* substance dependence criteria were assessed (Hughes, Oliveto et al., 1998). Thirty percent of 162 caffeine users (222 mg/day) fulfilled diagnostic criteria for caffeine dependence by endorsing three or more of the seven criteria. When the restrictive set of four criteria (described above) were used, only 9% were considered caffeine dependent. The most commonly reported symptom (56%) was persistent desire or unsuccessful efforts to reduce or control caffeine use (see Figure 5).

The *DSM-IV* diagnostic studies by Strain and colleagues and Bernstein and colleagues can be considered a series of case reports documenting that caffeine can produce a substance dependence disorder. The study by Hughes and colleagues suggests that the prevalence of the disorder in the general population is not trivial. The validity of the diagnosis is suggested by two studies that prospectively demonstrated that the severity of caffeine withdrawal (Strain, Mumford et al., 1994) and the incidence of caffeine reinforcement (Liguori & Hughes, 1997) was greater in individuals who fulfilled diagnostic criteria for caffeine dependence. However, the clinical and research utility of the diagnosis remains to be determined.

Clearly, additional research is needed to characterize more fully the prevalence of the disorder, the extent of clinically significant distress experienced, the prognosis if the disorder is untreated, and the relationship of the disorder to problems with other abused substances. For research purposes, a section for the diagnosis of caffeine dependence according to *DSM-IV* or *ICD-10* criteria is now available on the Composite International Diagnostic Interview—Substance Abuse Module (CIDI-SAM), which is a reliable and valid structured interview focused on substance use disorders (Cottler, Robins et al., 1989; Compton, Cottler et al., 1996).

## HERITABILITY OF CAFFEINE USE PROBLEMS

Genetic factors have been shown to account for individual variability in the use and effects of caffeine. Several twin studies comparing monozygotic and dizygotic twins found that the heritability of coffee consumption ranged from 36% to 51% (cf. Swan, Carmelli et al., 1996; Kendler & Prescott, 1999). A study of male twins also showed heritability of heavy coffee use (>5 cups/day) to be 51% (Swan, Carmelli et al., 1997). A recent detailed analysis of caffeine use in female twins found that total caffeine consumption, heavy use (> 625 mg/day), caffeine tolerance, caffeine withdrawal, and caffeine intoxication also had a greater co-occurrence

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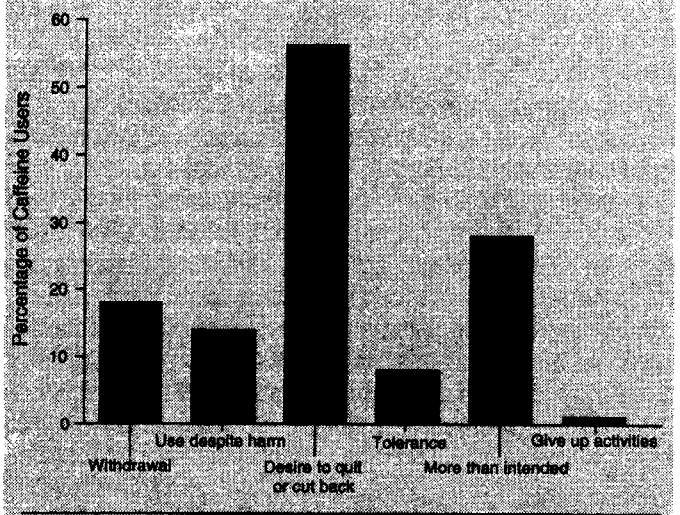
in monozygotic twins than dizygotic twins, with heritabilities between 35% and 77% (Kendler & Prescott, 1999).

Interestingly, three additional twin studies using multivariate structural equation modeling of caffeine use, cigarette smoking, and alcohol use concluded that a common genetic factor (polysubstance use) underlies the use of these three substances, with 28% to 41% of the heritable effects of caffeine use (or heavy use) shared with alcohol and smoking (Swan, Carmelli et al., 1996, 1997; Hettema, Corey et al., 1999). The conclusion that a common factor underlies joint use of caffeine, cigarettes, and alcohol is consistent with findings of a study by Kozlowski, Henningfield et al., (1993) on the co-occurrence of substance use among drug abusers. They found that severity of alcoholism was directly related to use of caffeine and cigarettes, and they concluded that dependence on caffeine, nicotine, and alcohol may be governed by the same factors.

These results in humans are consistent with previous research with inbred mice demonstrating genetic differences in responses to caffeine (Seale, Johnson et al., 1985; Logan, Seale et al., 1986). As a whole, these data on the genetics of use vulnerability underscore the fact that caffeine use problems have an underlying biological basis, part of which is shared with other commonly abused substances.

**FIGURE 5. DSM-IV Dependence Criteria Endorsed in a Survey of the General Population**




DSM-IV criteria for Substance Dependence endorsed by caffeine users in a survey of the general population. One of the criteria (a great deal of time spent in activities necessary to use the substance) is omitted because it is not clinically meaningful with caffeine. Data are from Hughes, Oliveto et al. (1998).

## ASSOCIATIONS WITH OTHER DRUGS OF DEPENDENCE

In addition to the twin studies and the population-based study suggesting that common factors underlie the use of caffeine, nicotine, and alcohol, a substantial body of research also documents associations between caffeine use and individual drugs of dependence.

**Nicotine and Cigarette Smoking**. Epidemiologic studies have shown that cigarette smokers consume more caffeine than do nonsmokers (Istvan & Matarazzo, 1984; Swanson, Lee et al., 1994). This finding is consistent with the observation previously discussed, that cigarette smoking increases the rate of caffeine elimination (Parson & Neims, 1978; May, Jarboe et al., 1982). Although coffee drinking and cigarette smoking also tend to covary temporally within individuals (Emurian, Nellis et al., 1982; Lane, 1996), caffeine administration does not reliably increase cigarette smoking (Chait & Griffiths, 1983), suggesting that the coffee-smoking interaction is not controlled by the pharmacologic effects of caffeine alone. A recent series of preclinical studies showed that chronic exposure to caffeine facilitated acquisition of nicotine self-administration and produced alterations in brain dopaminergic activity consistent with caffeine enhancing the reinforcing effects of nicotine (Shoaib, Swanner et al., 1999; Gasior, Jaszyna et al., 2000; Tanda & Goldberg, 2000).

Several studies have shown that abstinence from cigarette smoking can produce substantial increases in blood levels of caffeine in heavy consumers of caffeine, presumably as the result of reversal of cigarette-smoking induced caffeine metabolism (Brown, Jacob et al., 1988; Benowitz, Hall et al., 1989). Although it has been speculated that such an effect might make smoking cessation attempts more difficult, the clinical significance has not been demonstrated (Oliveto, Hughes et al., 1991; Hughes & Oliveto, 1993; Swanson, Lee et al., 1994).

**Alcohol**. Heavy use and clinical dependence on alcohol is associated with heavy use and clinical dependence on caffeine (Istvan & Matsarazzo, 1984; Kozlowski, Henningfield et al., 1993; Hughes, Oliveto et al., 2000). One study reported substantial increases in caffeine consumption following alcohol detoxification in alcoholics (Aubin, Laureaux et al., 1999). A study of individuals who

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met the *DSM-IV* diagnostic criteria for substance dependence on caffeine found that almost 60% had a past diagnosis of alcohol abuse or dependence (Strain, Mumford et al., 1994).

It is common clinical lore that caffeine can reverse the impairing effects of alcohol. There has been some speculation that a mechanism underlying such an effect is caffeine antagonism of adenosine-mediated alcohol effects (cf. Fredholm, Bättig et al., 1999). Although some animal and human studies show that caffeine can reduce alcohol sedation and impairment, a number of studies contradict that finding (Rush, Higgins et al., 1993; Hasenfratz, Buzzini et al., 1994; White, 1994; Liguori & Robinson, 2001). The available data suggest that such interactive effects generally are incomplete and inconsistent across different types of behavioral and subjective measures.

**Benzodiazepines.** Benzodiazepines are used widely in the treatment of anxiety, panic, and insomnia. Both animal and human studies suggest a mutually antagonistic relationship between caffeine and benzodiazepines (cf. White, 1994). Although it is possible that this interaction occurs at the benzodiazepine receptor, the lack of uniform antagonism across measures suggests that the effect is functional in nature (Roache & Griffiths, 1987; Oliveto, Bickel et al., 1997; White, 1994). Interestingly, although individuals with anxiety disorders tend to report lower levels of caffeine consumption than do controls (Lee, Cameron et al., 1985; Lee, Flegel et al., 1988; Uhde, 1990; Rihs, Müller et al., 1996), one study reported that a greater proportion of heavy caffeine consumers also use benzodiazepine tranquilizers (Greden, Procter et al., 1981). An important clinical implication is that the role of caffeine should be carefully evaluated in the treatment of anxiety, panic, or insomnia with benzodiazepines.

**Cocaine.** Cocaine users report using more caffeine than do caffeine consumers in the general population; however, the prevalence of caffeine use among cocaine users is lower (Budney, Higgins et al., 1993). Interestingly, caffeine-using cocaine users reported using cocaine less frequently than did cocaine users who did not use caffeine regularly (Budney, Higgins et al., 1993). Preclinical studies show that caffeine increases acquisition of cocaine self-administration, reinstates self-administration behavior previously maintained by cocaine, and potentiates the stimulant and discriminative stimulus effects of cocaine (cf. Garrett & Griffiths, 1997).

In human experimental studies, oral caffeine increases drug-appropriate responding in individuals trained to discriminate cocaine (Oliveto, McCance-Katz et al., 1998). Intravenous caffeine administration produced a significant increase in craving for cocaine in cocaine abusers (Rush, Sullivan et al., 1995); however, a study involving oral administration of caffeine in coffee showed no such effect (Liguori, Hughes et al., 1997a). The subjective effects of intravenous caffeine were identified as cocaine-like in one study (Rush, Sullivan et al., 1995), but not another (Garrett & Griffiths, 2001). Overall, although intriguing interactions between caffeine and cocaine effects have been documented, the clinical significance remains to be determined.

## CLINICAL IMPLICATIONS AND TREATMENT

**Differential Diagnosis.** Given the wide range of symptoms produced by caffeine use, intoxication, and withdrawal, caffeine use should be assessed routinely as part of a patient's medical and psychiatric history.

Caffeine use or intoxication can mimic or exacerbate symptoms of a variety of medical and psychiatric conditions, such as generalized anxiety disorder, panic disorder, mania, amphetamine or cocaine intoxication, primary insomnia, medication-induced side effects, arrhythmia, gastroesophageal reflux, hyperthyroidism, and pheochromocytoma. Caffeine use should be considered in the diagnosis of patients presenting with common symptoms such as anxiety, insomnia, panic attacks, palpitations, tachycardia, or gastrointestinal disturbance. Likewise, caffeine withdrawal can completely mimic or exacerbate migraine and other headache disorders, viral illnesses, and other drug withdrawal states such as amphetamine or cocaine withdrawal. Caffeine withdrawal should be evaluated in individuals presenting with headaches, fatigue, mood disturbances, or impaired concentration.

**Medication Interactions.** Benzodiazepine-like drugs, including diazepam, alprazolam, triazolam, and zolpidem, are widely used in the treatment of anxiety, panic, and insomnia. Because animal and human studies suggest a mutually antagonistic relationship between caffeine and benzodiazepines (White, 1994), the role of caffeine should be carefully evaluated when using benzodiazepines to treat patients with anxiety, panic, or insomnia.

Caffeine inhibits the metabolism of the antipsychotic clozapine to an extent that might be clinically significant.

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Because caffeine and theophylline mutually inhibit each other's metabolism, caffeine consumption during theophylline therapy should be monitored.

Finally, lithium toxicity may occur after caffeine withdrawal due to decreased renal clearance of lithium (cf. Carrillo & Benitez, 2000).

**Short-Term Abstinence for Medical Procedures.** Patients often are asked to stop food and fluids before certain blood tests, surgeries, or procedures such as endoscopies, colonoscopies, and cardiac catherizations. Whether patients scheduled to undergo such procedures could be allowed caffeine supplements to avoid the symptoms of withdrawal should be considered. Caffeine withdrawal has been identified as a significant cause of postoperative headaches, the risk of which can be reduced if regular caffeine users are given caffeine on the day of the surgical procedure (Galletly, Fennelly et al., 1989; Fennelly, Galletly et al., 1991; Weber, Ereth et al., 1993; Nikolajsen, Larsen et al., 1994; Weber, Klindworth et al., 1997).

**Medically Indicated Long-Term Abstinence.** The majority of habitual caffeine consumers experience no clinically significant problems as a result of their caffeine use. Long-term reduction or elimination of caffeine intake should be advised for patients who have a caffeine-related clinical diagnosis (such as caffeine intoxication, caffeine-induced anxiety disorder, caffeine-induced sleep disorder, caffeine withdrawal, or caffeine dependence) or when it is suspected that caffeine is mimicking or exacerbating psychiatric or medical conditions or interfering with the efficacy of medications (as with benzodiazepines or clozapine). Long-term caffeine reduction or abstinence also may be recommended to pregnant women.

**Strategies for Reduction or Elimination of Caffeine.** There have been few evaluations of strategies to reduce or eliminate caffeine use. A scheduled caffeine reduction program is believed to help attenuate withdrawal symptoms, although there is no systematic research to determine the most efficacious reduction schedule. Indeed, there have been very few evaluations of strategies to reduce or eliminate caffeine use.

Several studies with heavy caffeine consumers demonstrated the efficacy of a structured caffeine reduction treatment program ("caffeine fading") in achieving substantial reductions in consumption (Foxx & Rubinoff, 1979; Bernard, Dennehy et al., 1981; James, Stirling et al., 1985; James, Paull et al., 1988). One of these studies found that a four-week structured caffeine fading schedule was more effective than self-guided reduction (James, Stirling et al., 1985). However, little is known about the long-term efficacy of these procedures (James, Paull et al., 1988). There are no reports on treatment interventions for individuals who would like to eliminate caffeine completely.

In the absence of empirically validated treatments for problematic caffeine use, a reasonable approach would be to use behavior modification strategies that are effective in treating other drugs of dependence (such as education, behavioral substitution, coping suggestions, self-monitoring, and reinforcement for abstinence). Many individuals may not be knowledgeable about sources of caffeine in their diets, so education and history-taking are likely to be important components of treatment. It has been suggested that a caffeine-free trial should be recommended to individuals who are resistant to the idea that caffeine is contributing to their problems (Greden & Walters, 1992).

The clinician should anticipate that withdrawal symptoms may thwart quit attempts. One rationale for the caffeine fading approach is that withdrawal symptoms may be avoided or attenuated. No data about the probability of relapse are available, although relapse after caffeine reduction has been reported (Greden & Pomerleau, 1995; James, Paull et al., 1988). Practical guidelines for reducing or eliminating caffeine use include the following:

- Educate the patient about sources of caffeine. For example, some individuals may not be aware that caffeine is present in non-cola soft drinks or OTC analgesics.
- Have the patient self-monitor caffeine consumption, using a food diary, for one week.
- Identify all sources of caffeine and calculate the total caffeine consumption in mg.
- Present caffeine cessation as a temporary trial to patients who are resistant to treatment or who appear to have a caffeine-related disorder, but do not believe that caffeine is the cause of their complaints.
- Generate a graded reduction ("fading") schedule with the patient. A reasonable decrease would be 10% to 25% of the usual dose every couple of days.
- Help the patient identify a non-caffeinated substitute for their usual caffeine-containing beverage. If the patient is a coffee drinker, have him or her begin by mixing decaffeinated and caffeinated coffee, then progressively increase the percentage of decaffeinated coffee until the

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desired level is achieved. If the patient consumes soft drinks, ask him or her to alternate between caffeinated and caffeine-free soft drinks, or to mix the two until the caffeinated soft drink is reduced or eliminated.

- Discuss the possibility of relapse with the patient. Discuss triggers (antecedent conditions) for caffeine use and offer suggestions for coping with situations that pose a high risk of relapse.
- Suggest that the patient continue to self-monitor his or her caffeine consumption.

## ADDICTION LIABILITY

Given that caffeine is the most widely used mood-altering drug in the world, that some users report difficulty quitting, and that abrupt abstinence can produce clinically significant functional impairment, it is not surprising that it is periodically labeled as a drug of abuse or addiction (Gilbert, 1973; Austin, 1979). Objections to considering caffeine to be a classic drug of addiction include the observations that caffeine is used by most people in our society, that it has subtle psychological effects that are socially acceptable, that the harmful effects of excess use are largely transient, and that overuse of any food substance can be harmful. However, definitions of what constitutes a drug of addiction can be controversial, as indicated by the debate as to whether nicotine should be considered a drug of addiction (Robinson & Prichard, 1992a, 1992b; West, 1992).

**Psychiatric Approach.** One approach to considering whether it is meaningful to consider caffeine a drug of addiction is to evaluate the effects of caffeine from a psychiatric perspective. A number of studies have shown that some individuals fulfill criteria (of the *ICD-10* and *DSM-IV*) for a psychiatric diagnosis of substance dependence on caffeine by endorsing diagnostic items including withdrawal, continued use despite persistent or recurrent physical or psychological problems that are likely to have been caused or exacerbated by caffeine use, and persistent desire or unsuccessful efforts to cut down or control caffeine use.

Although the World Health Organization (*ICD-10*) recognizes the diagnosis of substance dependence on caffeine, the American Psychiatric Association (*DSM-IV*) currently explicitly excludes caffeine because of an insufficient database documenting clinical features of caffeine dependence (Hughes, Oliveto et al., 1992b; Hughes, 1994). However, a recent population-based survey study showed that a substantial portion of caffeine users (9% or more) may fulfill *DSM-IV* criteria for substance dependence on caffeine, with more than half reporting desire or unsuccessful efforts to stop caffeine use (Hughes, Oliveto et al., 1998).

**Reinforcement/Adverse Effects Analysis.** Another approach is to consider a reinforcement/adverse effects analysis (cf. Griffiths, Lamb et al., 1985). This model is useful in explaining societal perceptions of the relative abuse liability of a range of psychotropic drugs. In this framework, drugs of abuse or addiction have two defining characteristics: They have reinforcing effects, and their use leads to adverse effects (that is, they have the capacity to harm the individual or society). The relative abuse potential of a drug can be considered to be a multiplicative function of the degree of reinforcing effect and the degree of adverse effect.

With regard to reinforcing effects, the animal and human studies reviewed in this chapter demonstrate that caffeine can function as a reinforcer under certain conditions. Studies in which laboratory animals learn to self-inject caffeine indicate that, like nicotine, caffeine functions as a reinforcer under a more limited range of conditions than classic psychomotor stimulant drugs of abuse such as cocaine. In humans, self-administration and choice studies clearly demonstrate modest reinforcing effects of low and moderate doses of caffeine and suggest that such effects may be potentiated by physical dependence on caffeine.

With regard to adverse effects, a balanced discussion is beyond the scope of this chapter and has been the focus of several scholarly books (Spiller, 1984; James, 1991, 1997; Garattini, 1993). The adverse health effects of caffeine use reviewed in this chapter include caffeine intoxication, caffeine withdrawal, caffeine-induced sleep disorder, and caffeine-induced anxiety disorder. Medical and psychiatric conditions for which caffeine use often is thought to be contraindicated include generalized anxiety disorder, panic disorder, primary insomnia, gastroesophageal reflux, and pregnancy. In addition, the modest pressor effects of caffeine and the potent cholesterol-raising components of unfiltered coffee have raised concerns about the role of caffeine and coffee in cardiovascular disease (cf. James, 1997). Importantly, however, and in contrast to many classic drugs of abuse, significant health risk from nonreversible patho-

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logical consequences of caffeine use (including cancer, heart disease, and reproductive disorders) has not been demonstrated conclusively.

This reinforcement/adverse effects analysis indicates that caffeine does indeed have the two defining characteristics of drugs of abuse. However, the modest reinforcing effects and modest adverse effects documented to date suggest that caffeine has a low abuse liability relative to classic drugs of abuse. This analysis also predicts that if future research were to demonstrate conclusively that life-threatening health risks are associated with caffeine, societal perceptions of the abuse liability of caffeine would be increased substantially, as has been the case with nicotine over the past few decades.

*ACKNOWLEDGMENT: Preparation of this chapter was supported, in part, by U.S. Public Health Service grants R01 DA03890 and R01 DA01147 from the National Institute on Drug Abuse.*

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**Published by the American Society of Addiction Medicine, Inc.**
**4601 North Park Avenue, Suite 101**
**Chevy Chase, Maryland 20815**
**U.S.A.**
**Telephone 301/656-3920**
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*Principles of Addiction Medicine* is a publication of the American Society of Addiction Medicine (ASAM). ASAM is a national medical specialty society of physicians who are concerned about alcoholism and other drug dependencies, and who care for persons affected by those illnesses. For information about ASAM's programs, policies and publications, contact the American Society of Addiction Medicine, 4601 North Park Ave., Suite 101, Chevy Chase, MD 20815.

First Edition 1994
Second Edition 1998
Third Edition 2003

Library of Congress Cataloging in Publication Data:

Principles of addiction medicine / edited by
Allan W. Graham, Terry K. Schultz, Michael F. Mayo-Smith, Richard K. Ries,
Bonnie B. Wilford — 3rd ed.
p.cm.
Includes bibliographical references and index.
ISBN 1-880425-08-4
1. Substance abuse. 2. Substance abuse—treatment.
3. Substance abuse—diagnosis. 4. Addiction medicine
I. Graham, Allan W. II. Schultz, Terry K.
III. Mayo-Smith, Michael F. IV. Ries, Richard K.
V. Wilford, Bonnie B.
[DNLM: 1. Substance abuse. WM 270 S941]
RC564._____ 2003
ISBN 1-880425-08-4

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Printed in the United States of America.

**ISBN: 1-880425-08-4**