Psychopharmacology (2004) 176: 1–29
DOI 10.1007/s00213-004-2000-x

REVIEW

Laura M. Juliano · Roland R. Griffiths

A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features

Received: 9 March 2004 / Accepted: 24 July 2004 / Published online: 21 September 2004

Abstract *Rationale:* Although reports of caffeine withdrawal in the medical literature date back more than 170 years, the most rigorous experimental investigations of the phenomenon have been conducted only recently. *Objectives:* The purpose of this paper is to provide a comprehensive review and analysis of the literature regarding human caffeine withdrawal to empirically validate specific symptoms and signs, and to appraise important features of the syndrome. *Methods:* A literature search identified 57 experimental and 9 survey studies on caffeine withdrawal that met inclusion criteria. The methodological features of each study were examined to assess the validity of the effects. *Results:* Of 49 symptom categories identified, the following 10 fulfilled validity criteria: headache, fatigue, decreased energy/activeness, decreased alertness, drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability, and foggy/not clearheaded. In addition, flu-like symptoms, nausea/vomiting, and muscle pain/stiffness were judged likely to represent valid symptom categories. In experimental studies, the incidence of headache was 50% and the incidence of clinically significant distress or functional impairment was 13%. Typically, onset of symptoms occurred 12–24 h after abstinence, with peak intensity at 20–51 h, and for a duration of 2–9 days. In general, the incidence or severity of symptoms increased with increases in daily dose; abstinence from doses as low as 100 mg/day produced symptoms. Research is reviewed indicating that expectancies are not a prime determinant of caffeine withdrawal and that avoidance of withdrawal symptoms plays a central role in habitual caffeine consumption. *Conclusions:* The caffeine-withdrawal syndrome has been well characterized and there is sufficient empirical evidence to warrant inclusion of caffeine withdrawal as a disorder in the DSM and revision of diagnostic criteria in the ICD.

Keywords Caffeine · Abstinence · Cessation · Deprivation · Withdrawal · Headache · Physical dependence · DSM · ICD · Humans

L. M. Juliano
Department of Psychology, American University,
4400 Massachusetts Avenue,
Washington, DC, 20016, USA

R. R. Griffiths (✉)
Department of Psychiatry and Behavioral Sciences, Department of Neuroscience, Johns Hopkins University School of Medicine,
5510 Nathan Shock Drive,
Baltimore, MD, 21224-6823, USA
e-mail: rgriff@jhmi.edu
Tel.: +1-410-5500034
Fax: +1-410-5500030

Introduction

Caffeine is the most widely used behaviorally active drug in the world (Gilbert 1984). In North America, 80–90% of adults report regular use of caffeine (Gilbert 1984; Hughes and Oliveto 1997). Mean daily intake of caffeine among caffeine consumers in the United States is about 280 mg, with higher intakes estimated in some European countries (Gilbert 1984; Barone and Roberts 1996). In the United States, coffee and soft drinks are the most common sources of caffeine, with almost half of caffeine consumers ingesting caffeine from multiple sources, including tea (Hughes and Oliveto 1997).

After oral ingestion, caffeine is rapidly and completely absorbed, with peak blood levels generally reached in 30–45 min (Denaro and Benowitz 1991; Mumford et al. 1996; Liguori et al. 1997a), and is quickly eliminated, with a typical half-life of 4–6 h (Denaro and Benowitz 1991). The primary mechanism of action of caffeine is competitive antagonism at A_1 and A_{2A} adenosine receptors (Fredholm et al. 1999). Caffeine produces a variety of physiological effects, including effects on the cerebral vascular system, blood pressure, respiratory functioning, gastric and colonic activity, urine volume, and exercise performance (James 1997). Low to moderate doses of caffeine (20–200 mg) produce reports of increased well-being, happiness, energy, alertness, and sociability,

whereas higher doses are more likely to produce reports of anxiety, jitteriness, and upset stomach (Griffiths et al. 2003). Chronic administration of caffeine results in tolerance to a number of its physiological, subjective, and behavioral effects (Griffiths and Mumford 1996). Caffeine has been shown to function as a reinforcer in humans (e.g. Hughes et al. 1991; Evans et al. 1994), and some individuals become clinically dependent on caffeine as indicated by being unable to quit and continuing use despite having medical problems made worse by caffeine (Strain et al. 1994; Hughes et al. 1998).

Regular use of caffeine also produces physical dependence, evidenced as time-limited withdrawal symptoms upon the termination or reduction of one's usual caffeine dose. Physical dependence on caffeine has been documented in both pre-clinical and clinical research, and the biological basis has been hypothesized to be increased functional sensitivity to endogenous adenosine (Griffiths and Mumford 1996). Symptoms of caffeine withdrawal have been described in the medical literature for more than 170 years. In 1988, the first comprehensive review of clinical reports and experimental studies on caffeine withdrawal was published (Griffiths and Woodson 1988), which provided evidence for caffeine withdrawal as a discrete clinical syndrome. Since that time, the research literature on caffeine withdrawal has increased substantially. For example, of 48 blind caffeine-withdrawal studies identified for this review, only five were published before 1988.

The present review was inspired by this emergent research literature, which has not been comprehensively reviewed, as well as by the practical need to develop empirically based diagnostic criteria for caffeine withdrawal. In 1994, a tentative research diagnosis of caffeine withdrawal was proposed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) to encourage research on diagnostic criteria and the utility of the diagnosis (American Psychiatric Association 1994). Only one-quarter of the blind studies identified for this review were available to the DSM-IV Work Group (Hughes 1994). The review also addresses the previous suggestions (Rubin and Smith 1999; Dews et al. 2002) that caffeine withdrawal is not clinically significant and is primarily determined by expectancies.

Methods for searching and categorizing the literature

Search strategy and inclusion criteria

The following strategies were used to identify possible studies for this review: (1) PubMed (1950–2004) and PsycInfo (1872–2004) searches were conducted with the keywords "caffeine" in conjunction with "withdrawal," "dependence," "deprivation," or "abstinence"; (2) the authors searched their personal journal article collections on caffeine withdrawal; and (3) relevant references cited in papers obtained through the first two strategies and major reviews of caffeine and caffeine withdrawal (Griffiths and Woodson 1988; Fredholm et al. 1999; Nehlig 1999; Griffiths et al. 2003) were examined to identify additional relevant papers. To be included, experimental studies had to require a caffeine abstinence period of 12 h or greater because withdrawal onset generally occurs after 12 h of abstinence (Griffiths and Woodson 1988).

Excluded studies

Although possibly relevant to caffeine withdrawal, several types of studies were excluded from detailed summarization and analysis (Tables 1, 2, 3, 4): (1) several studies were excluded because they were not clearly interpretable (Horst et al. 1934; Mackenzie et al. 1981; Ammon et al. 1983; Smith 1996; Reeves et al. 1999; Watson et al. 2000); (2) a series of carefully conducted studies comparing placebo and caffeine conditions after overnight abstinence were not presented in a way that was clearly interpretable as caffeine-withdrawal effects (Yeomans et al. 2000a,b, 2001); (3) several studies that purported to demonstrate caffeine effects after a period of abstinence (e.g., Lieberman et al. 1987; Brice and Smith 2002) were excluded, although some of these studies acknowledged that the effects may represent a reversal of caffeine withdrawal (e.g., Bruce et al. 1986; Hindmarch et al. 1998; Kenemans et al. 1999; Smit and Rogers 2000); (4) studies exploring caffeine-withdrawal headache following surgical anesthesia were excluded because of the possible confounding effects of anesthesia (Galletly et al. 1989; Fennelly et al. 1991; Weber et al. 1993; Nikolajsen et al. 1994; Hampl et al. 1995); (5) case studies of neonatal caffeine withdrawal were excluded (McGowan et al. 1988; Thomas 1988); and (6) a survey study purporting to assess the prevalence of caffeine-withdrawal headache was excluded because the methods were ambiguous and it was not clear whether the subjects ever experienced periods of caffeine abstinence (Sjaastad and Bakketeig 2004).

Categorization of withdrawal studies

The inclusion strategy resulted in the identification of 42 double-blind experiments (Table 1), 15 non-blind and single-blind experiments (Table 2), and 9 survey studies (Table 3). Table 4 provides a summary of the individual withdrawal symptoms that are documented in Tables 1, 2, and 3 (for completeness, Appendix A shows which of the experimental studies in Tables 1 and 2 failed to document each of the evaluated symptoms and signs). In constructing Table 4, all symptoms documented in Tables 1, 2, and 3 were first catalogued, and then phenomenologically similar descriptors were combined (e.g., drowsiness, sleepy, drowsy/sleepy/tired, sedated, feel half awake, and decreased wakefulness were combined in a single category called "drowsiness/sleepiness"). Categories and descriptors for each category are presented below. It is recognized that the resulting 49 symptom categories may not represent fully independent constructs. In the absence of empirical

Table 1 Summary of double-blind experimental studies of caffeine withdrawal[a]

Reference	Design	Withdrawal signs and symptoms[b,c]
1. Goldstein (1964) [experiments c and d]	*N* = approximately 16 heavy coffee drinkers (5 or more cups/day), 25 moderate drinkers (2–4 cups/day), and 37 light drinkers (0–1 cups/day); within-subjects design; subjects abstained from coffee after lunch and received 150-mg caffeine or placebo in decaffeinated coffee at bedtime over four consecutive nights, with both treatments given twice; abstinence not biologically verified	In heavy coffee drinkers morning headache occurred significantly more frequently after placebo (25% of trials) than after caffeine (3% of trials); in moderate drinkers the frequency of headache was non-significantly higher after placebo (12% of trials) than after caffeine (7% of trials); in light drinkers the frequency of headache was <1% after both caffeine and placebo
2. Goldstein et al. (1969)	*N*=38 female daily coffee drinkers (5 or more cups/day) and 18 female coffee abstainers; within subjects and across group design; subjects abstained from caffeine after dinner and received placebo, 150-mg or 300-mg caffeine in decaffeinated coffee the following morning (about 0900 hours); treatments were repeated three times; abstinence not biologically verified	Compared with coffee abstainers, coffee users were less alert, active/energetic, and content, and more sleepy, irritable, and nervous after caffeine abstinence; among coffee users placebo produced increased ratings of headache, lazy/sluggish, irritable, sleepy, and decreased ratings of talkative, contentedness, and energy/active compared with caffeine; caffeine generally produced a dose-related suppression of withdrawal symptoms in the coffee users
3. Robertson et al. (1981)	*N*=18 adults who were not habitual caffeine consumers were caffeine abstinent for 3 weeks preceding the study; within subjects and across group design; approximately half the subjects received 750 mg caffeine/day in flavored drinks for 7 days, followed by substitution of placebo flavored drinks for 4 days; abstinence was biologically verified	Substitution of placebo did not result in detectable effects on blood pressure, urinary norepinephrine, or urinary epinephrine
4. Griffiths et al. (1986)	*N*=7 males who were heavy coffee drinkers (mean 12 cups/day); within-subjects design; after approximately 10 consecutive days of ad libitum coffee consumption (mean 1.25-g/day caffeine for the last 5 days), subjects were switched to decaffeinated coffee for at least 10 days; abstinence not biologically verified but study was conducted in a residential laboratory	Compared with caffeinated coffee consumption, decaffeinated coffee substitution resulted in increased subject ratings of headache, sleepy, lazy, fatigue (POMS) and decreased alert, active, vigor (POMS), and friendliness (POMS); observation of subjects' behavior also showed significant withdrawal based on a composite withdrawal score; cigarette smoking decreased during decaffeinated coffee consumption; 100% of subjects reported withdrawal headache
5. Griffiths et al. (1990) [Phase 1]	*N*=7 investigator-subjects with histories of regular caffeine consumption; within-subjects design; subjects given capsules containing 100 mg caffeine/day for 9–14 days, then placebo capsules for 12 days, and then capsules containing 100 mg caffeine/day for 7–12 days; abstinence was biologically verified	Compared with caffeine maintenance, placebo substitution resulted in increased headache, cerebral fullness, irritable/cross/grumpy, depression, muscle pain/stiffness, lethargy/fatigue/tired/sluggish, craving, and flu-like feelings, and decreased alert/attentive/observant, well-being, social disposition, motivation for work, concentration, energy/active, urge to do tasks/work, content/satisfied, and self-confidence; these withdrawal symptoms peaked on days 1 or 2 and progressively decreased toward pre-withdrawal levels over about a week
6. Griffiths et al. (1990) [Phase 2]	*N*=7 investigator-subjects with histories of regular caffeine consumption; within-subjects design; subjects given capsules containing 100 mg caffeine/day for 6 weeks; on five occasions placebo capsules were substituted for caffeine for 1 day (separated by an average of 9 days); abstinence was biologically verified	Compared with caffeine days, intermittent placebo resulted in increased fatigue (POMS)[d], confusion–bewilderment (POMS), and total mood disturbance (POMS), and decreased vigor (POMS) and friendliness (POMS); in addition, compared with caffeine days, intermittent placebo resulted in all of the withdrawal symptoms observed in phase 1 (see above) as well as increased muzzy, drowsy/sleepy, yawning, blurred vision, lightheaded/dizzy, impaired work/thought related activities and impaired verbal ability; all of these withdrawal symptoms plus decreased anxious/nervous were also significant when intermittent placebo was compared with a chronic placebo period (days 8–12 of placebo from phase 1) [exceptions: lightheaded/dizzy, impaired verbal ability, urge to do tasks/work and motivation for work were not significant]; within-subjects analysis of both intermittent placebo versus caffeine and of intermittent placebo versus chronic placebo demonstrated that more than 57% of subjects showed increased headache, muzzy, drowsy/sleepy, impaired work/thought related activities, and decreased social disposition, concentration, and self-confidence.
7. van Dusseldorp and Katan (1990)	*N*=45 daily coffee drinkers (4–6 cups/day); within-subjects design; subjects received 5-cups/day caffeinated coffee (435 mg caffeine/day) or decaffeinated coffee, each for 6 weeks; abstinence not biologically verified	Headache was significantly more likely to occur during the first week of the decaffeinated coffee period; 42% of subjects reported headache; headaches started on the 1st or 2nd day of abstinence and lasted 1–6 days (mean 2.3 days)
8. Bruce et al. (1991)	*N*=21 habitual caffeine users (mean 389 mg/day); within subjects and across group design; subjects in one group abstained from caffeine for 24-h prior to three sessions conducted at weekly intervals; subjects in another group abstained from caffeine for 7 days before as well as between three sessions conducted at 48-h intervals; subjects in both groups received capsules containing placebo, 250-mg or 500-mg caffeine in random order; abstinence was biologically verified	After placebo, subjects in the 24-h abstinence group reported increased headache and tiredness and showed more psychomotor performance tiring than the 7-day abstinence group; in the 24-h abstinence group, compared with either dose of caffeine, placebo increased headache and tiredness on unipolar scales, and increased lethargy and drowsiness on bipolar scales (lethargic–energetic; drowsy–alert)
9. Silverman et al. (1992)	*N*=62 daily caffeine consumers (mean 235 mg/day); within-subjects design; subjects were assessed while consuming their normal caffeine intake (baseline) and after two 2-day periods during which they consumed caffeine-free diets and were administered capsules containing caffeine (matched to their usual intake) or placebo; abstinence was biologically verified	Compared with both baseline and caffeine, placebo increased irritable/cross/grumpy, blurred vision, drowsy/sleepy, yawning, lethargy/fatigued/tired/sluggish, muzzy/foggy/not clearheaded, headache, flu-like feelings, heavy feeling in arms and legs, hot and cold spells, Beck Depression Inventory scores, somatization (SCL-90-R), state and trait scales of State-Trait Anxiety Inventory, fatigue (POMS), confusion–bewilderment (POMS), total mood disturbance (POMS), and decreased well-being, desire to socialize, talkativeness, urge to do tasks/work-related activities, energy/active, content/satisfied, self-confidence, vigor (POMS), friendliness (POMS), psychomotor performance (tapping speed); compared with baseline and caffeine, during the placebo period more subjects reported moderate or severe headache (52%), used analgesics despite discouragement (13%), and showed abnormal scores on trait-anxiety (8%), vigor (11%), and fatigue (8%), and the Beck Depression Inventory (11%)
10. Evans and Griffiths (1992)	*N*=32 daily caffeine consumers (mean 343 mg/day); within subjects and across group design; subjects received capsules throughout the study; subjects in the chronic placebo condition (*N*=16) received placebo for 18 days, followed by a 3-day caffeine versus placebo choice phase, followed by another 7 days of placebo; subjects in the chronic caffeine condition (*N*=16) received caffeine for 18 days (the dose progressed from 100-mg t.i.d. to 300-mg t.i.d.); followed by a 3-day caffeine versus placebo choice phase; followed by 2 days of progressively lower doses of caffeine (approximately 183-mg t.i.d. on the 2nd day), followed by 5 days of placebo; abstinence was biologically verified	Compared with subjects in the chronic placebo condition, subjects in the chronic caffeine condition reported higher ratings of headache and lower ratings of talkativeness in the final withdrawal period; within the caffeine group, no effects occurred between the placebo and caffeine challenge days which was interpreted as indicating that 24 h of abstinence was insufficient to produce withdrawal symptoms upon termination of very high caffeine doses (i.e., 900 mg/day)

Table 1 (continued)

Reference	Design	Withdrawal signs and symptoms[b,c]
11. Hughes et al. (1993) [summarizes results from Hughes et al. (1991, 1992); Oliveto et al. (1992a,b)]	*N*=37 daily coffee drinkers (mean 552 mg/day) who reported using coffee for caffeine effects or showed withdrawal or preference for caffeine in a screening test; within-subjects design; six trials at weekly intervals; on one day subjects consumed decaffeinated coffee and on another day consumed caffeinated coffee (100 mg/serving); assessment occurred after about 24-h abstinence; abstinence not biologically verified in all subjects	Within-subjects statistical analyses showed that 30%, 24%, 24%, and 49% of subjects, respectively, reported significant increases in headache, drowsiness, fatigue, or one or more of these symptoms on decaffeinated days compared with caffeinated days
12. Strain et al. (1994)	*N*=11 daily caffeine users (median 357 mg/day) who met DSM-IV diagnostic criteria for substance dependence on caffeine; within-subjects design; subjects were assessed after two 2-day periods during which they consumed caffeine-free diets and were administered capsules containing caffeine (matched to their usual intake) or placebo; abstinence was biologically verified	Overall, 82% showed evidence of caffeine withdrawal during placebo; 64% reported maximal ratings of headache; compared with standardized norms, 27% showed extreme increases in fatigue (POMS), 45% showed extreme decreases in vigor (POMS), and 36% showed elevations in depression (Beck Depression Inventory); compared with caffeine, after placebo 55% of subjects showed significant decreases in psychomotor performance (tapping speed); 45% reported analgesic use despite discouragement; 73% reported functional impairment in normal daily activities
13. Brauer et al. (1994)[e]	*N*=11 daily coffee consumers (mean 480 mg/day); within-subjects design; over a 33-h period subjects consumed a caffeine-free diet and were administered either capsules containing placebo or 300-mg caffeine; abstinence was biologically verified	Compared with caffeine maintenance, 33-h abstinence increased headache
14. Hale et al. (1995)	*N*=18 adolescents (ages 11–15), daily cola drinkers (mean 2.3, 12-oz caffeinated colas/day); within-subjects design; six trials at weekly intervals; on one day subjects consumed caffeine-free colas ad libitum and on another day consumed caffeinated colas ad libitum (33 mg/8 oz); assessment occurred after about 24-h abstinence; abstinence not biologically verified	Compared with the caffeine, placebo increased depressed, drowsy–sleepy, and fatigue–tired, and decreased irregular heartbeat and more talkative; within-subjects analyses revealed that 33% of subjects showed significant effects on one or more symptom ratings
15. Hughes et al. (1995)	*N*=11 daily coffee drinkers (mean 5.6 cups/day) selected for showing caffeine abstinence symptoms or caffeine preference in a screening test; within-subjects design; six trials at weekly intervals; on one day subjects consumed decaffeinated coffee ad libitum and on another day consumed caffeinated coffee ad libitum (either 25 mg or 50 mg/serving); assessment occurred after about 24-h abstinence; abstinence not biologically verified[f]	Compared with the caffeine, placebo increased drowsy–sleepy–tired, headaches, fatigue–tired, lazy–sluggish, and depressed and decreased stimulated–active–energetic–excited, alert–attentive–able to concentrate, and vigor; within-subjects analyses revealed that 73% of subjects showed significant effects on one or more symptom ratings, with 45% reporting increases in drowsy–sleepy–tired; 27% reporting decreases in stimulated–active–energetic–excited, alert–attentive–able to concentrate, and vigor; 18% reporting increased fatigued–tired, depressed, and decreased content–relaxed–satisfied, and 9% reporting increased headache, irritable–frustrated–angry–cross, lazy–sluggish, and decreased talkative
16. Mitchell et al. (1995)	*N*=9 daily coffee consumers (mean 686 mg/day); within-subjects design; subjects consumed a caffeine-free diet and were administered capsules containing placebo or caffeine (50% or 100% of their usual amounts) on the day before and the day of assessment; abstinence was biologically verified	Compared with the 50% and 100% caffeine conditions, placebo (33.5-h abstinence) increased headachy, sluggish, and tired–sleepy; abstinence did not affect amount of responding on an operant task reinforced by coffee delivery
17. Richardson et al. (1995)	*N*=49 regular caffeine consumers (mean 252 mg/day) and *N*=18 non-consumers; four groups: non-consumers and three consumer groups who abstained from caffeine for either 90 min, overnight, or 7 days; subjects in each group received capsules containing placebo, 70 mg or 250 mg in counterbalanced order; abstinence not biologically verified[f]	Overnight abstinence (13–15 h) compared with 90-min abstinence produced increased ratings of angry, tired, drowsy, dejected and decreased ratings of clearheaded, friendly, and cheerful; overnight abstinence compared with 7 days of abstinence produced increased ratings of angry, tired, drowsy and dejected; overnight abstinence compared with non-consumers produced increased headache, angry, tired, drowsy, dejected and decreased clearheaded
18. Rogers et al. (1995)	*N*=24 low caffeine users (mean 47 mg/day) and *N*=25 moderate caffeine users (mean 205 mg/day); ten experimental sessions; after overnight abstinence half the subjects consumed a drink containing 70-mg caffeine and half consumed a non-caffeinated drink; assessment occurred 1 h later; abstinence not biologically verified	In moderate caffeine users, compared with subjects receiving caffeine, subjects receiving placebo reported increases in tired and decreases in cheerful, clearheaded, energetic, and lively; in contrast, no significant differences were found between caffeine and placebo in low caffeine users
19. Streufert et al. (1995)	*N*=25 caffeine users who held managerial positions (mean 565 mg/day); within-subjects design; subjects were instructed to abstain from caffeine for 36-h prior to each of 2 assessment days; the day prior to the assessment day and morning of the assessment day subjects were given either capsules containing caffeine (matched to their usual intake) or placebo; abstinence was biologically verified	Compared with caffeine, placebo was associated with increased drowsy/sleepy, yawning, lethargy/fatigue/tired/sluggish, irritable/cross/grumpy and decreased alert/attentive/observant, well-being, ability to concentrate, energy/active, need to pass water frequently[g]; compared with caffeine placebo decreased systolic blood pressure and decreased performance on complex simulated tasks (i.e., number of decisions, speed of response to information, diversity of action, number of backward integrations, and applied initiative)
20. Lader et al. (1996)[h]	*N*=40 habitual caffeine consumers (mean 360 mg/day); within and across groups staggered cohort design; after baseline assessment during usual caffeine consumption, subjects received capsules containing either placebo or caffeine (matched to their usual intake); subjects received placebo capsules for 2 consecutive days followed by caffeine capsules for 2 days or 3 days; abstinence was biologically verified	Compared with baseline, placebo increased tiredness, lethargy, sedation, and muzziness, and decreased alertness and concentration; these effects were reversed upon caffeine re-administration; compared with baseline, placebo increased EEG alpha peak magnitude and ratings of sleep quality, and decreased skin conductance, systolic blood pressure, and ratings of onset to sleep; 68% of subjects reported increased tired and lethargy; 45% reported diffuse throbbing headache, with 28% of these also reporting nausea and sickness
21. Comer et al. (1997)	*N*=12 daily caffeine users; within-subjects design; 17-day inpatient study; subjects given capsules containing 300-mg caffeine daily except for two 2-day placebo substitutions on days 5–6 and 12–13; abstinence not biologically verified but study was conducted in a residential laboratory	On placebo days subjects reported increased ratings of headache, miserable, sedated, sleepy, tired, unmotivated, and yawning, and decreased ratings of alert, anxious, energetic, and self-confident
22. Liguori et al. (1997b) [Exp 1]	*N*=8 daily caffeinated cola consumers (mean 157 mg/day); within-subjects design; six trials at weekly intervals; on one day subjects consumed caffeine-free colas ad libitum and on another day consumed caffeinated colas ad libitum (either 33 mg or 17 mg/8 oz); assessment occurred after about 24-h abstinence; abstinence not biologically verified[f]	Compared with the 33-mg condition, placebo decreased active/energy/excited, more talkative, motivated to work, and well-being; compared with the 17-mg condition, placebo increased anxious/tense/nervous, anxiety (POMS), confusion (POMS), irritable/frustrated/angry/cross, and stomachache/upset stomach, and decreased well-being, friendliness (POMS), and vigor (POMS); within-subject analysis revealed that 50% of the subjects in the 33-mg condition and 25% of the subjects in the 17-mg condition showed headache, drowsiness, or fatigue (63% showed drowsiness and/or fatigue in one or both of the conditions)

Table 1 (continued)

Reference	Design	Withdrawal signs and symptoms[b,c]
23. Liguori et al. (1997b) [Exp 2]	*N*=16 daily coffee and cola consumers (mean 579 mg/day); within-subjects design; six trials at weekly intervals; on one day subjects consumed caffeine-free colas ad libitum and another day consumed caffeinated colas ad libitum (33 mg/8 oz); assessment occurred after about 24-h abstinence; abstinence not biologically verified[f]	Compared with the caffeine, placebo increased drowsy/sleepy, fatigue/tired, headache, lazy/sluggish/slow-moving, and stomachache/upset stomach, and decreased active/energetic/excited, confident, motivated to work, well-being, and performance on a psychomotor/cognitive task; drowsiness and headache or drowsiness and fatigue reliably occurred in 2 of 16 participants
24. Liguori and Hughes (1997)	*N*=11 daily coffee and cola consumers (mean 632 mg/day); within-subjects design; subjects were tested in four caffeine versus no caffeine conditions using procedures similar to Liguori et al. (1997b); the four caffeine conditions were cola 33 mg/serving, coffee 33 mg/serving, cola 100 mg/serving, coffee 100 mg/serving; assessment occurred after about 24-h abstinence; abstinence was biologically verified	Compared with the caffeine, placebo increased drowsy/sleepy, fatigue/tired, lazy/sluggish/slow-moving, and nausea/vomiting, and decreased active/energetic/excited, alert/attentive/able to concentrate, confident, frequent urination[g], impatience, motivated to work, stronger/more vigorous/more energy, well-being, and performance on a psychomotor/cognitive task
25. Schuh and Griffiths (1997)	*N*=20 regular caffeine consumers (mean 379 mg/day); within-subjects design; subjects were assessed after two 19-h periods during which they consumed caffeine-free diets and were administered capsules containing caffeine (matched to their usual intake) or placebo; abstinence was biologically verified	Compared with caffeine, placebo increased headache, worn-out, and flu-like feelings, and decreased alert, well-being, helpful, and upset stomach; on a drug versus money choice procedure, subjects chose to forfeit money to avoid receiving placebo—this was significantly different from the caffeine condition
26. Garrett and Griffiths (1998)	*N*=28 adults; within-subjects design; each subject was exposed to four conditions each of which involved a 9–12 day exposure (capsules containing 300 mg/70 kg caffeine or placebo) followed by a 2-day challenge (caffeine or placebo): (1) acute abstinence (caffeine followed by placebo), (2) chronic abstinence (placebo followed by placebo), (3) acute caffeine (placebo followed by caffeine), (4) chronic caffeine (caffeine followed by caffeine); abstinence was biologically verified	Placebo challenge after caffeine (acute abstinence) resulted in increased confusion–bewilderment (POMS), fatigue (POMS), total mood disturbance (POMS) and decreased vigor (POMS) compared with each of the other three conditions; acute abstinence resulted in decreased alert/attentive/observant, well-being, ability to concentrate, and energy/active compared with the caffeine challenge after chronic abstinence and chronic caffeine, and increased irritable/cross/grumpy, depressed, and drowsy/sleepy relative to placebo challenge after chronic abstinence; subjects were willing to forfeit more money to avoid receiving placebo when maintained on caffeine (acute abstinence) compared with chronic caffeine and chronic placebo
27. James (1998)	*N*=36 habitual caffeine consumers (about 370 mg/day); within-subjects design; subjects received capsules throughout the study; four conditions: 6 days of caffeine followed by 1 day of placebo (acute abstinence), 6 days of caffeine followed by 1 day of caffeine (habitual use), 6 days of placebo followed by 1 day of caffeine, 6 days of placebo followed by 1 day of placebo (chronic abstinence); abstinence was biologically verified	Subjects in the acute abstinence condition reported more frequent headaches (47%) than subjects in the habitual use condition (14%) and in the chronic abstinence condition (31%); subjects in acute abstinence condition also experienced more severe and longer headaches, less alertness, better sleep quality and duration, and worsened performance on a character recognition task than the average of the three other conditions
28. Phillips-Bute and Lane (1998)	*N*=31 daily coffee consumers (mean 603 mg/day); within-subjects design; subjects abstained from caffeine overnight and then consumed either capsules containing 250-mg caffeine or placebo 4-h prior to assessment; thus 4-h abstinence was compared with an estimated 12–28 h abstinence; abstinence not biologically verified	Compared with 4-h abstinence, overnight abstinence increased fatigue (POMS), sleepy, and yawning, and decreased vigor (POMS) and systolic and diastolic blood pressure
29. Robelin and Rogers (1998)	*N*=64 daily caffeine consumers (mean 453 mg/day); between groups design; after overnight abstinence, four groups of subjects consumed three fruit-flavored drinks spaced at 75–90 min intervals; conditions were three placebo drinks or 1, 2, or 3 drinks containing caffeine (1.2-mg/kg or about 86-mg caffeine); final assessment occurred after ≥17 h of abstinence; abstinence not biologically verified[f]	Compared with subjects who received 1, 2, or 3 drinks of caffeine, subjects who received placebo showed decreased energetic mood and slower reaction time performance
30. Van Soeren and Graham (1998)	*N*=6 male athletes who were daily caffeine consumers (mean 761 mg/day); within-subjects design; subjects were tested after receiving capsules containing caffeine or placebo after 0, 2, or 4 days of abstinence from dietary caffeine; six trials were separated by ≥10 days; abstinence was biologically verified	Although not statistically analyzed, the authors reported that all subjects reported withdrawal symptoms lasting from 2 days to 4 days including severe headaches, fatigue, lethargy, and flu-like symptoms; time to exhaustion on a cycling task was not affected by the duration of dietary caffeine abstinence in either the placebo or caffeine conditions
31. Yeomans et al. (1998)[e]	*N*=36 caffeine consumers (mean 329 mg/day); within subject and across group design; on 4 days subjects abstained from caffeine overnight and were given beverages (herbal tea and fruit-flavored drinks, respectively) containing either caffeine (100 mg) or placebo at breakfast and midmorning (2 h later); there were four experimental groups: (1) breakfast caffeine/midmorning caffeine, (2) breakfast caffeine/midmorning placebo, (3) breakfast placebo/midmorning caffeine, (4) breakfast placebo/midmorning placebo; abstinence not biologically verified[f]	Mood data were collapsed across the 4 days; compared with subjects who received caffeine, subjects who received placebo with breakfast had lower ratings of lively and energetic 2 h later; compared with subjects who received placebo at breakfast and caffeine midmorning, subjects who received placebo at both breakfast and midmorning had lower ratings of energy 30 min after the midmorning beverage; the authors interpreted the differences between caffeine and placebo as reflecting caffeine-withdrawal reversal effects
32. Dews et al. (1999)	*N*=57 daily coffee drinkers (mean 200–300 mg/day caffeine immediately before abstinence); three groups of subjects given instant coffee for 14 days; the chronic caffeine group received instant caffeinated coffee throughout the study, the abrupt abstinence group received instant decaffeinated coffee for 7 consecutive days, the gradual abstinence group received gradual reductions in caffeine over 5 days; abstinence was biologically verified	No statistical analyses were reported; the authors concluded that 39% of subjects showed withdrawal in the first 2 days of abstinence in the abrupt abstinence group based on a composite withdrawal measure derived from a mood and attitude questionnaire and spontaneously reported withdrawal symptoms (e.g., headache and tiredness); 22% showed substantial decreases (≥1.5 points on a 4 point scale) in their ratings of daily functioning; on the first 2 days of abstinence 28% of the abrupt abstinence group reported headache, while 17% of the chronic caffeine group reported headache
33. Evans and Griffiths (1999) [Exp 1]	*N*=15 daily caffeine consumers (mean 241 mg/day) within-subjects design; subjects were maintained on capsules containing 300 mg caffeine/day; 2-day placebo period was repeated six times with 5–9 days of caffeine between periods; abstinence was biologically verified	Compared with caffeine days, on placebo days subjects reported increased headache, headache/poor mood, tiredness, flu-like symptoms, fatigue (POMS), and decreased vigor (POMS), friendliness (POMS), and activity/alertness
34. Evans and Griffiths (1999) [Exp 2]	*N*=17 daily caffeine consumers (mean 277 mg/day); within-subjects design; 2-day placebo period after subjects were maintained on capsules containing 100, 300, or 600 mg of caffeine/day; each subject was exposed to two 2-day placebo periods at each caffeine dose; abstinence was biologically verified	Compared with caffeine days, on placebo days after each maintenance dose subjects reported increased headache, fatigue (POMS), confusion–bewilderment (POMS), and tiredness; the range and magnitude of withdrawal symptoms increased with maintenance dose, with subjects reporting the following additional symptoms after the highest dose: increased headache/poor mood, total mood disturbance (POMS), and flu-like symptoms, and decreased friendliness (POMS), vigor (POMS), and activity–alertness; specificity of withdrawal effects can be concluded because higher doses of caffeine produced greater response to placebo with no change in baseline response to caffeine

Table 1 (continued)

Reference	Design	Withdrawal signs and symptoms[b,c]
35. Evans and Griffiths (1999) [Exp 3]	*N*=19 daily caffeine consumers (mean 294 mg/day); within-subjects design; subjects were maintained on capsules containing 300 mg caffeine/day; approximately every 7 days a lower dose of caffeine (200, 100, 50, 25 mg) or placebo was substituted for 2 days; abstinence was biologically verified	Compared with the caffeine maintenance dose of 300 mg, placebo substitution produced increased headache, headache/poor mood, tiredness, fatigue (POMS), and total mood disturbance (POMS) and decreased vigor (POMS) and activity/alertness; the range and magnitude of withdrawal symptoms increased as a function of decreasing doses of caffeine, with no withdrawal reported at 200 mg and fatigue (POMS) and tiredness reported at 100 mg
36. Evans and Griffiths (1999) [Exp 4]	*N*=25 daily caffeine consumers (263 mg/day); within-subjects design; subjects maintained on capsules containing 300 mg/day for either 1, 3, 7, or 14 consecutive days; each duration of caffeine exposure was followed by 7 days of placebo; abstinence was biologically verified	No withdrawal symptoms were shown in response to placebo after 1 day of caffeine; placebo after 3 days of caffeine resulted in increase headache/poor mood, fatigue (POMS), tiredness, flu-like symptoms, and total mood disturbance (POMS) and decrease activity/alertness; placebo after 7 days or 14 days of caffeine produced headache in addition to most of the symptoms that occurred in the 3-day condition; specificity of withdrawal effects can be concluded because longer durations of caffeine exposure produced greater response to placebo
37. Jones et al. (2000)	*N*=10 daily caffeine consumers (mean 333 mg/day); within-subjects design; before two sessions subjects abstained from caffeine for 21 h and then received capsules containing caffeine (matched to their usual intake) or placebo; subjects were also evaluated while consuming their normal caffeine intake (baseline); abstinence was biologically verified	Compared with caffeine, placebo decreased alert/attentive/observant, ability to concentrate, energy/active, vigor (POMS), and friendliness (POMS) and increased heavy feelings in arms and legs; placebo also increased velocities in middle and anterior cerebral arteries and increased EEG theta power; caffeine and baseline conditions were not significantly different on any measure
38. Swerdlow et al. (2000)	*N*=12 males (mean 173 mg/day) in the caffeine abstinence study and 18 males (mean 147 mg/day caffeine) in the non-abstinence study; in the abstinence study subjects abstained for >14 h prior to testing; in both studies subjects received either a pill containing 200 mg caffeine or placebo; abstinence not biologically verified	Compared with caffeine administration, placebo administration to high caffeine consumers (as determined by median split) produced significant elevations in a composite somatic symptom scale (feel sick, queasy, dizzy, and perspiring). Similar effects were shown for the individual symptoms
39. Yeomans et al. (2002b)	*N*=30 caffeine consumers (mean 330 mg/day); within subjects and across group design; after overnight abstinence three groups of subjects received placebo, 1-mg/kg, or 2-mg/kg caffeine in a flavored drink at breakfast on 2 test days; 60 min after the first dose subjects received a drink containing either placebo or 1-mg/kg caffeine in counterbalanced order across the 2 test days; abstinence not biologically verified	Compared with subjects given caffeine, subjects given placebo at breakfast had slower reaction times and lower alertness 45 min later; relative to placebo, caffeine given 60 min after breakfast decreased reaction time and increased alertness in subjects who received placebo at breakfast, but not in subjects who received caffeine at breakfast; the authors interpreted these results as suggesting that reversal of caffeine withdrawal is a major component of the effects of caffeine on mood and performance
40. Rogers et al. (2003)[e] [Exp 1]	*N*=10 caffeine consumers (mean 355 mg/day) and 10 non-consumers; between groups design; before four sessions subjects abstained from caffeine for approximately 15 h; abstinence not biologically verified[f]	After abstinence, caffeine consumers were less alert and more tense than non-consumers
41. Rogers et al. (2003)[e] [Exp 2]	*N*=22 caffeine consumers (mean 372 mg/day) and 20 non-consumers; between groups design; after overnight abstinence subjects received either 100 mg caffeine or placebo in a flavored drink; abstinence not biologically verified[f]	After abstinence, caffeine consumers were less alert than non-consumers
42. Tinley et al. (2003)[e]	*N*=45 caffeine consumers (mean 324 mg/day); within subjects and across groups design; for 2-weeks subjects abstained from their normal sources of caffeine and consumed tea and coffee provided by the experimenters; in one group the tea and coffee were caffeinated and in the other group they were caffeine free; subjects abstained from tea and coffee overnight before each of four test sessions conducted over the 2-week period; subjects reported mood before and after receiving a single serving of either a caffeine beverage (caffeine maintained group) or caffeine-free beverage (caffeine-free group); abstinence was biologically verified	Compared with the group that was chronically maintained on caffeine-free beverages, the group that was maintained on caffeine reported higher levels of headache after overnight abstinence; headache was alleviated after caffeine administration

[a]All studies had a caffeine-abstinence period of 12 h or greater
[b]All effects are statistically significant at $P \leq 0.05$ unless otherwise noted
[c]For consistency, when placebo and caffeine conditions are compared, the effects are described as the effects of placebo relative to caffeine
[d]POMS indicates Profile of mood states questionnaire
[e]Only those design elements that are relevant to the analysis of caffeine abstinence effects are described
[f]Although abstinence was not biologically verified, saliva samples were taken and subjects were led to believe that samples would be analyzed for compliance
[g]Likely a direct effect of caffeine rather than an effect of caffeine withdrawal
[h]Some of the results are based on authors' conclusions because not all significant comparisons were presented (Lader, personal communication, August 2002)

Table 2 Summary of single-blind and non-blind experimental studies of caffeine withdrawal[a]

Reference	Design	Withdrawal signs and symptoms[b,c]
Single-blind		
43. Driesbach and Pfeiffer (1943)	*N*=22 adults; within-subjects design; caffeine administered in capsules in increasing doses over 6–7 days to 650–780 mg/day; on the 7th or 8th day placebo was substituted for caffeine capsules; abstinence not biologically verified	Placebo substitution after caffeine resulted in lethargy in morning, cerebral fullness at noon, and headache in early afternoon, reaching peak intensity 3–6 h later; 82% of subjects reported definite to severe headache; in 33% of these subjects headache was accompanied by nausea and sometimes vomiting and serious rhinorrhea; in 55% of trials headache was reported to be as severe as the subject had ever experienced; headache was alleviated by re-administration of caffeine; other withdrawal symptoms were noted but not statistically analyzed (i.e., mental depression, drowsiness, yawning, and disinclination to work); serum protein, serum calcium, and hematocrit were significantly lower during headache and serum inorganic phosphorus was slightly higher
44. Höfer and Bättig (1994a)	*N*=120 habitual coffee users (mean 5.7 cups/day); between groups design; after a 3-day baseline period, subjects received either 9 days of caffeinated instant coffee, 9 days of decaffeinated instant coffee or 9 days of intermittent caffeinated and decaffeinated instant coffee; abstinence was biologically verified	In the intermittent group, compared with caffeine days, decaffeinated days produced increased nausea and indisposition; in the decaffeinated group, decaffeinated days compared with baseline produced increased headache, use of analgesics, indisposition, heart rate, and decreased wakefulness, well-being, day positive, motor activity, and problems falling asleep; in the decaffeinated group these effects (except for heart rate) peaked on days 1 or 2 and progressively decreased toward pre-withdrawal levels; subjects in the intermittent group showed most of these effects; 40–50% of subjects reported moderate headache in decaffeinated group and 20–30% reported more severe headache
45. Höfer and Bättig (1994b)	*N*=42 female habitual coffee drinkers (mean 6 cups/day); between groups design; after a 3-day phase of usual coffee consumption (baseline), subjects entered a second phase consisting of either 3 days of decaffeinated instant coffee or 3 days of caffeine tablets; abstinence was biologically verified	Caffeine withdrawal was defined as a statistical interaction between group and phase, with the decaffeinated coffee group showing increased headache, muscle/joint ache, sleep duration and decreased well-being, ratings of day positive, wakefulness, and motor activity; stomach/belly ache was increased in the caffeine tablet group and decreased in the decaffeinated coffee group[d]; desire for coffee was increased in the caffeine tablet group but not changed in the decaffeinated coffee group
46. Lane (1994)	*N*=14 habitual coffee drinkers (3.4 cups/day); within-subjects design; after overnight abstinence subjects were given water containing 300 mg caffeine or placebo; abstinence not biologically verified	Compared with caffeine, placebo produced increased drowsy/sleepy, lethargy/fatigue/tired/sleepy, headache, self-confidence, and heavy feelings in arms and legs, and decreased desire to socialize/talkativeness; 9 of 14 subjects reported more headache after placebo and no subjects reported more headache after caffeine; placebo was associated with decreased levels of urinary epinephrine which were interpreted by the author as an effect of caffeine rather than of caffeine withdrawal
47. Rubin and Smith (1999)	*N*=43 regular coffee or tea consumers (mean 175 mg/day); within-subjects design; after a 2-day baseline period of normal caffeine consumption, subjects consumed caffeinated coffee (or tea) for 2 days and decaffeinated coffee (or tea) for 2 days in counterbalanced order; abstinence not biologically verified	A significantly greater number of subjects reported headache during the decaffeinated period (40%) than during the baseline (14%) and caffeinated period (19%); these differences were greater in individuals who correctly identified the presence or absence of caffeine (49% in decaffeinated period, 7% in baseline, 9% in caffeinated condition)
48. Field et al. (2003)	*N*=10 low caffeine consumers (mean 41 mg/day) and 10 high caffeine consumers (mean 648 mg/day); within subjects and across groups design; before two sessions, subjects abstained from caffeine for 30 h; cerebral blood flow was assessed with perfusion magnetic resonance imaging 60–90 min after receiving capsules containing caffeine (250 mg) or placebo; abstinence not biologically verified	Compared with caffeine, placebo produced greater cerebral blood flow velocities in white matter, anterior gray matter, and posterior gray matter regions; high caffeine users showed a greater caffeine–placebo difference in the anterior gray matter than low users; across all subjects, cerebral blood flow in the placebo condition increased linearly with daily caffeine intake
Non-blind		
49. Naismith et al. (1970)	*N*=20 caffeine consumers (560 mg/day); within-subjects design; after a 10-day baseline period, subjects switched to decaffeinated coffee and abstained from all other sources of caffeine for 14 days; abstinence not biologically verified	No statistical analyses were reported; all subjects reported lassitude and severe headache which resolved by 48 h
50. Roller (1981)	*N*=1 male habitual coffee user (900–1,100 mg/day); within-subjects design; abstained from caffeine for 72-h period; 24 h into this 72-h period theophylline was administered; at the end of 72 h either caffeinated coffee (approx. 150 mg caffeine) or decaffeinated coffee was ingested in a blinded fashion	No statistical analyses were reported; headache started after about 6 h; shortly thereafter the subject reported tiredness or lassitude, then rhinorrhea and leg muscle pains, followed by diaphoresis; after 16 h the subject reported general muscle pains; these symptoms gradually increased to a maximum intensity at a later time and were suppressed by caffeinated coffee consumption but not placebo
51. Edelstein et al. (1983)	*N*=18 psychiatric patients who consumed three or more caffeinated beverages per day; within-subjects design; decaffeinated beverages were substituted for caffeinated beverages; abstinence not biologically verified	No statistical analyses were reported; headache increased during the first 1–2 weeks after decaffeinated beverages were substituted for caffeinated beverages
52. Mathew and Wilson (1985)	*N*=8 heavy (mean 986 mg/day) and 8 light (mean 126 mg/day) caffeine users; within-subjects design; after baseline assessment subjects abstained from caffeine for 24 h; abstinence not biologically verified	Compared with cerebral blood flow measurements assessed after 2-h abstinence, 24-h abstinence produced increased cerebral blood flow in several frontal regions bilaterally in heavy users but not light users
53. Rizzo et al. (1988)	*N*=20 daily caffeine users (mean 606 mg/day) and *N*=20 caffeine non-users; within-subjects design; two experimental sessions separated by 7 days; users abstained from caffeine for 2 days prior to the second session; abstinence not biologically verified	Caffeine users had slower reaction times and smaller heart rate decelerations than non-users during caffeine abstinence (session 2) but not at baseline (session 1)
54. Couturier et al. (1997)	*N*=20 adults presumed to be daily caffeine users; within-subjects design; subjects were assessed at baseline, 24 h later after complete caffeine abstinence, and 30 min and 120 min after receiving capsules containing 150 mg caffeine; abstinence was biologically verified	Subjects reported headache after abstinence with complete recovery after caffeine administration; compared with baseline cerebral blood flow velocities (left middle cerebral, basilar, and both posterior cerebral arteries) increased after abstinence; compared with abstinence cerebral blood flow velocities decreased after caffeine administration; 50% of subjects reported moderate to severe headache; 10% reported nausea and vomiting
55. Lane (1997)	*N*=16 daily caffeine consumers (mean 612 mg/day); within-subjects design; subjects were assessed on two occasions: after usual caffeine consumption and after overnight abstinence (estimated 12–28 h abstinence); abstinence not biologically verified	Compared with ad libitum caffeine consumption, caffeine abstinence increased headache, drowsy/sleepy, fatigue (POMS)[e], lethargy/fatigue/tired/sluggish, muzzy/foggy/not clearheaded, yawning, flu-like feelings, lightheaded/dizzy, heavy feeling in arms and legs, and decreased vigor (POMS), well-being, desire to socialize/talkativeness, ability to concentrate, energy/active, content/satisfied, mean arterial blood pressure; after abstinence 63% of subjects reported headache, 25% reported maximum ratings of headache, and 31% reported flu-like symptoms

Table 2 (continued)

Reference	Design	Withdrawal signs and symptoms[b,c]
56. Lane and Phillips-Bute (1998)	*N*=30 daily coffee consumers (mean 569 mg/day caffeine); within-subjects design; subjects were assessed on two occasions: after usual caffeine consumption and after overnight abstinence (estimated 12–28 h abstinence); abstinence not biologically verified	Compared with ad libitum caffeine consumption, caffeine abstinence increased headache, drowsy/sleepy, irritable/cross/grumpy; fatigue (POMS), lethargy/fatigue/tired/sluggish, muzzy/foggy/not clearheaded, yawning, anger–hostility (POMS), confusion–bewilderment (POMS), depression-dejection (POMS), and decreased vigor (POMS), well-being, desire to socialize/talkativeness, ability to concentrate, energy/active, alert/attentive/observant; urge to do task/work-related activities; hot or cold spells, need to pass water[d]; on a visual vigilance task abstinence decreased hit-rate and increased response time, and abstinence increased subjects ratings of perceived difficulty and decreased perceived importance of doing well and perceived success; after abstinence 47% reported any headache and 27% reported moderate or severe headache
57. Reeves et al. (1995, 1997, 2002); Patrick et al. (1996)	*N*=13 or 14 daily caffeine users (>300 mg/day); within-subjects design; subjects evaluated while consuming their normal caffeine diet (baseline) and again after 1, 2, and 4 days of abstinence; evaluations included topographic quantitative EEG, physician ratings of caffeine withdrawal severity as assessed during a structured interview, and a musculoskeletal examination of the spine; abstinence was biologically verified	Compared with baseline, significant quantitative EEG changes were: increase in theta absolute power, increase in delta absolute power over the frontal cortical areas, decrease in the mean frequency of both alpha and beta rhythm, increase in theta relative power, decrease in beta relative power, and change in interhemispheric coherence; resumption of caffeine following abstinence returned altered EEG values to baseline levels; all subjects reported caffeine-withdrawal symptoms and 77% had moderate or severe withdrawal severity as rated by a physician; compared with baseline, the number of somatic dysfunctions from the musculoskeletal examination was significantly greater on days 1, 2, and 4 of caffeine abstinence; the greatest number of somatic dysfunctions was reported on day 2; six subjects who had baseline EEGs containing diffuse paroxysmal slowing (DPS, a minor EEG dysrhythmia) showed significant increases in DPS firing during withdrawal and a return to baseline firing levels following caffeine resumption

[a]All studies had a caffeine abstinence period of 12 h or greater
[b]All effects are statistically significant at $P \leq 0.05$ unless otherwise noted
[c]For consistency, when placebo and caffeine conditions are compared, the effects are described as the effects of placebo relative to caffeine
[d]Likely a direct effect of caffeine rather than an effect of caffeine withdrawal
[e]POMS indicates Profile of mood states questionnaire

Table 3 Summary of survey studies of caffeine withdrawal

Reference	Design	Withdrawal signs and symptoms
58. Goldstein and Kaizer (1969)	*N*=183 female coffee consumers surveyed about the effects they would experience if morning coffee was omitted	Endorsement of symptoms increased as the number of cups of coffee consumed increased; among heavy coffee users (5–10 cups/day) the percentages reporting specific symptoms were 58% feel half awake, 24% lethargic, 21% irritable, 18% sleepy, 16% unable to work effectively, 15% restless, 8% headache
59. Winstead (1976)	*N*=135 mostly adult inpatients on psychiatric ward; survey of occurrence of caffeine-withdrawal symptoms	26% of heavy caffeine users (>500 mg/day) reported experiencing "anxiety withdrawal symptoms"
60. Greden et al. (1978)	*N*=83 psychiatric inpatients; surveyed about the occurrence of headache on omission of morning coffee	11% endorsed experiencing headache
61. Greden et al. (1980)	*N*=205 medical inpatients; questioned about the occurrence of headache upon stopping caffeine	20% of total sample (or 28% of the sample of 152 after those who answered "don't know" were excluded) reported caffeine-withdrawal headache; those reporting headache had higher mean caffeine intake (616 mg/day) than those not reporting headache (395 mg/day)
62. Victor et al. (1981)	*N*=124 general medical inpatients; survey of the occurrence of caffeine-withdrawal headache	24% of subjects endorsed having experienced caffeine-withdrawal headache
63. Hughes et al. (1998)	*N*=162 caffeine consumers; surveyed via telephone about caffeine abstinence and withdrawal symptoms	44% of caffeine consumers reported having abstained from caffeine for ≥24 h in the past year; of those, 24% reported headache, 27% drowsiness, 21% fatigue, 10% anxiety, 4% depression, 3% nausea or vomiting, 28% strong desire to use, 20% irritability, 21% yawning, 11% difficulty concentrating, 18% less motivated to work
64. Dews et al. (1999)	*N*=6,815 adults who reported daily caffeine use were asked if they had "problems or symptoms on stopping caffeine in the past"	11% reported withdrawal symptoms upon stopping caffeine; of those, 25% reported symptoms severe enough to interfere with normal daily activities (e.g., lost time from work); headache was the most common symptom reported; it is unknown what percentage of daily users had actually abstained from caffeine
65. Kendler and Prescott (1999)	*N*=1,642 women in a population-based twin registry interviewed about their caffeine use; individuals who reported stopping or cutting down their caffeine consumption were asked about caffeine-withdrawal symptoms	24% of subjects who reported stopping or cutting down their caffeine consumption reported having experienced headache plus one or more of the following: marked fatigue or drowsiness, marked anxiety or depression, and nausea or vomiting
66. Bernstein et al. (2002); Oberstar et al. (2002)	*N*=36 adolescent daily caffeine consumers (mean 244 mg/day) who endorsed two or more DSM-IV caffeine dependence criteria during telephone prescreening; interviewed and assessed for caffeine dependence based on DSM-IV substance dependence criteria; 21 of these subjects were reassessed 1 year later	Based on both interviews, 81% met the withdrawal criterion; 100% of subjects who met criteria for DSM-IV caffeine dependence reported withdrawal symptoms; the percentage of subjects reporting specific symptoms were 59% drowsy/tired, 56% fatigued, 56% sluggish/slowed down, 56% headache, 32% restless/cannot sit still, 29% nervous/anxious, 21% sick/nauseated/vomiting, 21% drink caffeine so you do not feel bad, and 9% sad/depressed

Table 4 Summary of withdrawal symptoms reported in experimental and survey studies described in Tables 1, 2, 3[a]

Symptom	Acute abstinence versus baseline[b]	Acute abstinence versus caffeine[b]	Acute abstinence in caffeine consumers versus non-consumers[b]	Acute abstinence versus chronic abstinence[b]	Time-limited abstinence effects[b]	Percentage of subjects showing effect in experimental studies[c]	Percentage of subjects reporting symptom in survey studies[d]
Headache	4, 9, 20, 44, 45, 47, 49, 50, 51, 54	1, 2, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 21, 23, 25, 27, 30, 33, 34, 35, 36, 43, 46, 47, 55, 56	17	6, 8, 27, 42	4, 5, 7, 44, 49, 51	1: 25% of trials (heavy users) [control 3%] 4: 100% headache (control 14%) 6: 79% headache[e]* 7: 42% headache (control 10%) 9: 52% moderate or severe headache (control 2%) 11: 30% headache* 12: 64% maximum headache (control 0%) 15: 9% headache* 20: 45% diffuse throbbing headache 27: 47% headache (control 14%) 32: 28% headache (control 17%) 43: 82% definite to severe headache, 55% of trials severe as ever experienced 44: 40–50% moderate headache, 20–30% more severe headache 46: 64% headache (control 0%) 47: 40% headache (control 14%) 49: 100% headache 54: 50% moderate or severe headache 55: 63% headache (control 6%), 25% maximum headache (control 0%) 56: 47% headache, 27% moderate or severe headache	58: 8% headache 60: 11% headache 61: 20% headache 62: 24% headache 63: 24% headache 65: 24% headache plus additional symptom 66: 56% headache
Tiredness/fatigue	4, 9, 20, 49, 50	2, 5, 6, 8, 9, 11, 12, 14, 15, 16, 17, 18, 19, 21, 23, 24, 25, 26, 28, 30, 33, 34, 35, 36, 43, 46, 55, 56	17	6, 8, 17, 26	4, 5, 17, 20, 49	6: 57% lethargy/fatigue[e]* 9: 8% abnormal high fatigue (control 0%) 11: 24% fatigue* 12: 27% extreme fatigue (control 9%) 15: 18% fatigued/tired* 20: 68% tired and lethargy 49: 100% lassitude	58: 24% lethargic 63: 21% fatigue 66: 56% fatigued
Decreased energy/activeness	4, 9	2, 5, 6, 8, 9, 12, 15, 18, 19, 21, 22, 23, 24, 26, 28, 29, 31, 33, 34, 35, 37, 55, 56	2	6, 26	4, 5	6: 64% ↓ energy/active[e]* 9: 11% abnormal scores (control 0%) 12: 45% extreme ↓ in vigor (control 0%) 15: 27% ↓ stimulated/active/energy/excited*	
Decreased alertness/attentiveness	4, 20	2, 5, 6, 8, 15, 19, 21, 24, 25, 26, 27, 33, 34, 35, 36, 37, 39, 56	2, 40, 41	6, 26	4, 5	6: 50% ↓ alert/attentive[e]* 15: 27% ↓ alert/attentive/able to concentrate*	
Drowsiness/sleepiness	4, 9, 20, 44, 45	2, 6, 8, 9, 11, 14, 15, 17, 19, 21, 23, 24, 28, 46, 55, 56	2, 17	6, 17, 26	4, 44	6: 64% drowsy–sleepy[e]* 11: 24% drowsiness* 15: 45% drowsy/sleepy/tired* 22: 63% drowsiness/fatigue* 23: 13% drowsiness*	58: 18% sleepy, 58% feel-half awake 63: 27% drowsiness 66: 59% drowsy/tired
Decreased contentedness/well-being	9, 44, 45	2, 5, 6, 9, 17, 18, 19, 21, 22, 23, 24, 25, 26, 55, 56	2	6, 26	5, 44	6: 64% ↓ well-being[e]*, 50% ↓ content/satisfied[e]* 15: 18% ↓ content/relaxed/satisfied*	
Decreased desire to socialize	4, 9	2, 5, 6, 9, 10, 14, 17, 22, 33, 34, 37, 46, 55, 56		6	5	6: 79% ↓ social disposition[e]* 15: 9% ↓ talkative*	
"Flu-like" symptoms	9	5, 6, 9, 25, 30, 33, 34, 36, 55		6	5	55: 31% flu-like symptoms (control 0%)	
Depressed mood	9	5, 6, 9, 12, 14, 15, 17, 56	17	6, 17, 26	5	6: 14% depressed[e] 9: 11% abnormal scores BDI (control 2%) 12: 36% elevations on BDI (control 0%) 15: 18% depressed*	63: 4% depression 66: 9% sad/depressed

Table 4 (continued)

Symptom	Acute abstinence versus baseline[b]	Acute abstinence versus caffeine[b]	Acute abstinence in caffeine consumers versus non-consumers[b]	Acute abstinence versus chronic abstinence[b]	Time-limited abstinence effects[b]	Percentage of subjects showing effect in experimental studies[c]	Percentage of subjects reporting symptom in survey studies[d]
Difficulty concentrating	20	5, 6, 19, 26, 37, 55, 56		6, 26	5	6: 79% ↓ able to concentrate[e]*	63: 11% difficulty concentrating
Irritability	9	2, 5, 6, 9, 19, 22, 56	2	6, 26	5	6: 29% irritable/cross/grumpy[e]* 15: 9% irritable/frustrated/angry/cross*	58: 21% irritable 63: 20% irritability
Unmotivated for work	9	5, 6, 9, 21, 22, 23, 24, 56			5	6: 57% ↓ motivation for work[e]* 6: 64% ↓ urge to do work[e]*	58: 16% unable to work effectively 63: 18% ↓ motivated to work
Muzzy/foggy/not clearheaded	9, 20	6, 9, 17, 18, 55, 56	17	6		6: 71% muzzy[e]*	
Yawning	9	6, 9, 19, 21, 28, 55, 56		6		6: 43% yawning[e]*	63: 21% yawning
Decreased self-confidence	9	5, 6, 9, 21, 23, 24, 46		6	5	6: 64% ↓ self-confidence[e]*	
Confusion–bewilderment	9	6, 9, 22, 26, 34, 56		26			
Total mood disturbance	9	6, 9, 26, 34, 35, 36		26			
Nausea/vomiting/upset stomach		22, 23, 24, 38, 43, 44				6: 29% upset stomach[e]* 20: 13% nausea and sickness with headache 43: 33% nausea (sometimes vomiting) along with headache 54: 10% nausea and vomiting	63: 3% nausea or vomiting 66: 21% sick/nauseated/vomiting
Muscle pain/stiffness	45, 50	5, 6		6	5	6: 43% muscle pain[e]*	
Anxiety/nervousness	9	9, 22	2, 40			9: 8% abnormal scores anxiety (control 0%)	59: 26% anxiety withdrawal symptoms 63: 10% anxiety 66: 29% nervous/anxious
Heavy feelings in arms and legs	9	9, 37, 46, 55					
Increased sleep duration/quality	20, 44, 45	27					
Analgesics use	44	9, 12			44	9: 13% analgesics use (control 2%) 12: 45% analgesics use	
Craving		5, 6		6	5	6: 43% craving for caffeine*	63: 28% strong desire to use
Lightheaded/dizzy		6, 38, 55					
Blurred vision	9	6, 9		6		6: 14% blurred vision[e]*	
Anger/hostility		17, 56	17	17			
Hot and cold spells	9	9, 56					

[a]Numbers in table refer to the entry number in Tables 1, 2, 3
[b]The strengths and weaknesses of each of the types of comparisons presented in columns 2–6 are described in the text. Studies in columns 4–6 are more rigorous because the effects are not confounded by the direct effects of caffeine
[c]This column (column 7) shows the percentage of subjects reporting the symptom in experimental studies (as summarized in columns 2–6). For comparison, when available, the percentage of subjects reporting the symptom in the control condition (i.e., baseline or caffeine condition) is shown in brackets. For studies that conducted within-subject analyses of differences between the abstinence and control conditions, an asterisk (*) indicates the percentage of subjects who showed a statistically significant difference at $P<0.05$
[d]Percentage of subjects reporting symptom in survey studies: this column shows the percentage of individuals reporting the occurrence of a symptom presumably based on their previous experience in the natural environment
[e]Incidence data for this study were collapsed across two conditions: acute abstinence versus caffeine and acute abstinence versus chronic abstinence

data on the independence of specific caffeine-withdrawal symptoms (e.g., factor analysis), the listing provides a useful framework for characterizing the results of caffeine-withdrawal studies. In Table 4, symptoms are sequenced from those documented (i.e., shown in columns 2–6) in the greatest number of experimental studies to those documented in the fewest. Table 4 also differentiates experiments according to five of the most frequently used experimental methodologies that have been used to draw inferences about caffeine-withdrawal symptoms and signs. Finally, Table 4 shows the percentages of individuals reporting withdrawal symptoms in both experimental and survey studies.

Experimental methodologies

Several different experimental methodologies have been used to draw inferences about the occurrence of caffeine withdrawal. As understanding the strengths and weaknesses of each of these methodologies is critical to drawing meaningful conclusions about the validity of the findings, this section will briefly list and critique the most commonly used experimental methodologies. The first five experimental methodologies (corresponding to columns 2–6 in Table 4) involve different comparisons with acute caffeine abstinence.

Acute abstinence versus preceding caffeine baseline (not counterbalanced)

In this within-subjects comparison, symptoms or signs during acute caffeine abstinence are compared with those during a preceding baseline of ad libitum caffeine consumption. This comparison may have good ecological validity because it can involve a naturally occurring pattern of caffeine consumption followed by abrupt abstinence. A limitation of this comparison is that baseline versus abstinence differences may be due to the simple absence of the direct effects of caffeine during abstinence (i.e., a caffeine offset effect rather than a time-limited withdrawal effect). Another limitation is that observed differences could be confounded by order effects (i.e., conditions are not counterbalanced).

Acute abstinence versus caffeine

In this comparison, which could involve within subjects or across groups designs, symptoms or signs during acute abstinence are compared with those during caffeine consumption, with conditions counterbalanced or randomized across subjects. As with the comparison with a preceding baseline caffeine condition, this comparison may have good ecological validity in modeling naturally occurring effects of caffeine abstinence. Although not confounded by order effects, this comparison has the limitation that caffeine versus abstinence differences may be due to the simple absence of the direct effects of caffeine during abstinence.

Acute abstinence in caffeine consumers versus non-consumers

In this between-groups comparison, symptoms or signs during acute abstinence in caffeine consumers are compared with those in non-consumers. As both groups are caffeine abstinent, it can be concluded that any difference observed is not confounded by the direct effects of caffeine. However, the possible confounding effects of population differences between caffeine consumers and non-consumers cannot be ruled out because of the self-selected nature of these groups.

Acute abstinence versus chronic abstinence

In this comparison, which could be within subjects or across groups, symptoms or signs during acute abstinence are compared with those during chronic abstinence (e.g., 1 week or more of caffeine abstinence). As both conditions involve caffeine abstinence, it can be concluded that any difference observed is not confounded by the direct effects of caffeine. Although this comparison provides more conclusive evidence of withdrawal effects than the preceding comparisons, the approach is conservative because it may underestimate the incidence or magnitude of withdrawal effects if symptoms or signs persist in the chronic abstinence condition.

Time-limited abstinence effects

By definition, a drug withdrawal symptom or sign should increase upon acute abstinence and then decrease over time with continued drug abstinence. A demonstration of such time-limited effects is not confounded by the direct effects of caffeine and is important for confirming that the effects observed are withdrawal related rather than reflecting caffeine offset effects (i.e., a return to the normal drug-free state).

Other methodologies

In addition to the five approaches described above, several other types of experimental methodologies can help to inform the interpretation of caffeine-withdrawal effects. Although not included in Table 4, studies using these other methodologies are discussed in the following section on symptoms and signs of caffeine withdrawal.

Variation in caffeine maintenance dose Demonstration that the severity or incidence of a symptom or sign increases with increases in the daily caffeine maintenance dose before abstinence helps to confirm that the withdrawal effect reflects a pharmacological process.

Acute decreases in caffeine maintenance dose When lower caffeine doses are substituted for the usual caffeine maintenance dose, the demonstration that the severity or incidence of a symptom or sign increases as the substituted dose decreases helps to confirm that the withdrawal effect reflects a pharmacological process.

Manipulation of duration of caffeine maintenance Demonstration that the severity or incidence of a symptom or sign increases with increases in the duration of daily caffeine maintenance dose before abstinence helps to confirm that the withdrawal effect reflects a pharmacolo-

gical process.

Re-administration of caffeine reverses abstinence effects After a period of abstinence during which the severity or incidence of a symptom or sign develops, the demonstration that re-administration of caffeine rapidly and dose dependently reverses the abstinence effects helps to confirm that the withdrawal effect reflects a pharmacological process.

Symptoms and signs of caffeine withdrawal

Symptoms of caffeine withdrawal

In this section, the withdrawal symptoms (i.e., categories of self-reported changes in mood or behavior) that were assessed in the studies listed in Tables 1, 2, and 3, and summarized in Table 4, are individually discussed and evaluated. For some symptoms, relevant case reports are also discussed if they contribute to the evaluation. As in Table 4, the symptoms are sequenced from those that were documented in the greatest number of studies to those that were documented in the fewest number.

Of relevance to the assessment of each symptom is information about the "hit-rate" (i.e., the ratio of the number of times a symptom was found to be significant relative to the number of times it was assessed). For this analysis, the number of studies in which each symptom was documented was taken from the 57 experimental studies described in Tables 1 and 2 (and summarized in columns 2–6 of Table 4). The number of studies in which each symptom was assessed was obtained from an evaluation of the same 57 experimental studies. In several studies (Comer et al. 1997; Schuh and Griffiths 1997; Garrett and Griffiths 1998; Jones et al. 2000) all of the symptoms assessed could not be determined from the published article, and this information was obtained from the authors. [Methodological note: in the rare instance in which a study used a compound symptom descriptor (e.g., alert/attentive/observant/able to concentrate) that could potentially apply to two symptom categories (e.g., alert/attentiveness and difficulty concentrating), the data were counted in the single category that it best represented (e.g., alert/attentiveness was counted as assessed and difficulty concentrating was coded as not assessed).]

In interpreting the hit-rate, it should be noted that most of the statistically significant effects reported are based on group mean data. Thus, a high hit-rate indicates that the abstinence condition is readily differentiated from the comparison condition and usually reflects an intermediate to high incidence of the symptom. A low hit-rate indicates that the abstinence condition is not readily differentiated from the comparison condition. However, it is important to recognize that a low hit-rate does not mean that a symptom is not valid because such a symptom may have a low incidence and thus be undetected in a group statistical analysis. Furthermore, a symptom with a low hit-rate may also be clinically important to the extent that it may have profound effects in a small percentage of the population (e.g., psychotic symptoms in the general population). Finally, a failure to detect a particular effect may reflect methodological shortcomings of a study (e.g., insufficient period of abstinence, small sample size, insensitive measures).

Validity criteria For purposes of this review, the criteria for concluding that a symptom is valid was the statistical demonstration of the symptom in six or more studies that include two or more double-blind studies that used methodologies in which the conclusion of caffeine-withdrawal effects was not confounded by the direct effects of caffeine (i.e., Table 4, columns 4–6). As a conservative approach, two studies that used the same group of subjects (i.e., studies 5 and 6 in Table 4) were considered to be a single study for purposes of judging validity.

Headache (descriptors: headache and headachy) Headache has been the most frequently assessed symptom (48 experimental studies and 6 survey studies). Headache was found in 37 of 48 (77%) of the experimental studies in which it was assessed. The median percentage of individuals reporting headache in 19 experimental studies was 47%, ranging from 9% to 100% across studies (Table 4). Of the 7 experimental studies that assessed headache severity, the median percentage of subjects reporting moderate to severe or maximum headache was 50%. In 7 survey studies, the median percentage of caffeine users reporting caffeine-withdrawal headache was 24%, ranging from 8% to 56%.

Headache as a caffeine-withdrawal symptom has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4) and by comparing acute caffeine abstinence in caffeine consumers with non-consumers (Table 4). Studies have also shown that abstinence-induced headache is time-limited (Table 4) and is rapidly (usually within 30–60 min) and often completely reversed after re-administration of caffeine (Driesbach and Pfeiffer 1943; Goldstein et al. 1969; Roller 1981; Couturier et al. 1997; Tinley et al. 2003), with the magnitude of reversal being an increasing function of the re-administered caffeine dose (Goldstein et al. 1969). Studies have also shown that the severity and incidence of headache after abstinence were increasing functions of caffeine maintenance dose (Goldstein 1964; Silverman et al. 1992; Evans and Griffiths 1999) and duration of caffeine dosing (Evans and Griffiths 1999) before abstinence. Finally, when different caffeine doses were substituted for the usual maintenance dose, the severity and incidence of headache increased as the substituted dose decreased (Evans and Griffiths 1999). Caffeine-withdrawal headache has been characterized in these experimental studies as well as in case reports as being gradual in development (Driesbach and Pfeiffer 1943; Greden et al. 1980; Roller 1981; Griffiths et al. 1990), diffuse (Driesbach and Pfeiffer 1943; Greden 1974; Greden et al. 1980; Lader et al. 1996),

throbbing (Driesbach and Pfeiffer 1943; Greden 1974; Greden et al. 1980; Lader et al. 1996), severe (Griffiths and Woodson 1988; cf. Table 4), intensified with exercise and Valsalva maneuver (Driesbach and Pfeiffer 1943), and phenomenologically distinct from migraine headache (Driesbach and Pfeiffer 1943).

Clinical reports, correlational analysis, and cluster analysis of withdrawal symptoms have indicated that non-headache symptoms and signs of caffeine withdrawal do not always co-vary with the presence of headache and can occur in the absence of headache (Griffiths and Woodson 1988; Griffiths et al. 1990; Lader et al. 1996; Garrett and Griffiths 1998; Evans and Griffiths 1999). This indicates that non-headache symptoms represent distinct features of the caffeine-withdrawal syndrome that can occur independently of headache.

In summary, headache has been very frequently studied, has an intermediate incidence, and has been demonstrated under a wide range of different methodological conditions. It is concluded that headache is a valid withdrawal symptom.

Tiredness/fatigue (descriptors: tiredness, tired, fatigue, lazy, sluggish, lazy/sluggish/slow-moving, lethargic, lethargy/fatigue/tired/sleepy, sluggish/slowed down, worn-out, and lassitude) Tiredness/fatigue was demonstrated in 32 of 38 studies (84%). In 7 experimental studies providing incidence data (Table 4), the median percentage of individuals showing tiredness/fatigue was 27%. In 3 survey studies, the percentage of subjects reporting tiredness/fatigue ranged between 21% and 56%. Tiredness/fatigue has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4), and by comparing acute caffeine abstinence in caffeine consumers with that in non-consumers (Table 4). Studies have also shown that abstinence-induced tiredness/fatigue is time limited (Table 4), completely reversed after re-administration of caffeine (Roller 1981), and an increasing function of the duration of caffeine maintenance before abstinence (Evans and Griffiths 1999). Furthermore, when different caffeine doses are substituted for the usual maintenance dose, the magnitude of tiredness/fatigue increases as the substituted dose decreases (Evans and Griffiths 1999). Severity of tiredness/fatigue also appears to increase at higher daily caffeine maintenance doses (Rogers et al. 1995).

In summary, tiredness/fatigue has been very frequently studied, has a low to moderate incidence, and has been demonstrated under a wide range of methodological conditions. It is concluded that tiredness/fatigue is a valid withdrawal symptom.

Decreased energy/activeness (descriptors: decreased energy, energetic, active, stimulated/active/energetic/excited, vigor, lively, stronger/more vigorous/more energy) Decreased energy/activeness was demonstrated in 24 of 32 experimental studies (75%). In 4 experimental studies providing incidence data (Table 4), the median percentage of individuals showing decreased energy/activeness was 36%. Decreased energy/activeness has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4), and by comparing acute caffeine abstinence in caffeine consumers with that in non-consumers (Table 4). Studies have have also shown that abstinence-induced decreased energy/activeness is time limited (Table 4) and is rapidly (i.e., within 30–60 min) and completely reversed after re-administration of caffeine (Goldstein et al. 1969). Studies have also shown that the severity of decreased energy/activeness is an increasing function of the caffeine maintenance dose before abstinence (Rogers et al. 1995; Evans and Griffiths 1999).

In summary, decreased energy/activeness has been very frequently studied, has an intermediate incidence, and has been demonstrated under a wide range of methodological conditions. It is concluded that decreased energy/activeness is a valid withdrawal symptom.

Decreased alertness/attentiveness (descriptors: decreased alertness, alert/attentive/observant, alert/attentive/able to concentrate, and activity/alertness) Decreased alertness/attentiveness was demonstrated in 22 of 31 experimental studies (71%). Two experimental studies reported incidence data of 27% and 50% (Table 4). Decreased alertness/attentiveness has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4), and by comparing acute caffeine abstinence in caffeine consumers with that in non-consumers (Table 4). Studies have also shown that abstinence-induced decreased alertness/attentiveness is time limited (Table 4) and is rapidly (i.e., within 30–60 min) and completely reversed after re-administration of caffeine (Goldstein et al. 1969), with the magnitude of reversal being an increasing function of the re-administered caffeine dose (Goldstein et al. 1969). In addition, deficits in alertness/attentiveness are an increasing function of caffeine maintenance dose before abstinence (Rogers et al. 1995; Evans and Griffiths 1999). Finally, when different caffeine doses are substituted for the usual maintenance dose, the magnitude of alertness/attentiveness decreases as the substituted dose decreases (Evans and Griffiths 1999).

In summary, decreased alertness/attentiveness has been very frequently studied, may have an intermediate incidence, and has been demonstrated under a wide range of methodological conditions. It is concluded that decreased alertness/attentiveness is a valid withdrawal symptom.

Drowsiness/sleepiness (descriptors: drowsiness, sleepy, drowsy/sleepy/tired, sedated, feel half awake, and decreased wakefulness) Drowsiness/sleepiness was demonstrated in 21 of 27 experimental studies (78%). Across 5 experimental studies providing incidence data (Table 4),

the median percentage of individuals showing drowsiness/sleepiness was 45%. In 3 survey studies, the percentage of subjects reporting tiredness/fatigue ranged between 18% and 59%. Drowsiness/sleepiness has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4), and by comparing acute caffeine abstinence in caffeine consumers with that in non-consumers (Table 4). Studies have also shown that abstinence-induced drowsiness/sleepiness is time limited (Table 4) and is rapidly (i.e., within 30–60 min) and completely reversed after re-administration of caffeine (Goldstein et al. 1969), with the magnitude of reversal being an increasing function of the re-administered caffeine dose (Goldstein et al. 1969). Severity is positively correlated with daily caffeine dose before abstinence (Silverman et al. 1992).

In summary, drowsiness/sleepiness has been very frequently studied, has an intermediate incidence, and has been demonstrated under a wide range of methodological conditions. It is concluded that drowsiness/sleepiness is a valid withdrawal symptom.

Decreased contentedness/well-being (descriptors: decreased contentedness, content/satisfied, well-being, day positive, cheerful, happy, and increased miserable) Decreased contentedness/well-being was demonstrated in 17 of 28 experimental studies (61%). In 2 experimental studies, 18% and 64% of participants showed decreases in measures of contentedness/well-being (Table 4). Decreased contentedness/well-being has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4), and by comparing acute caffeine abstinence in caffeine consumers with that in non-consumers (Table 4). Studies have also shown that abstinence-induced decreased contentedness/well-being is time limited (Table 4) and is rapidly (i.e., within 30–60 min) and completely reversed after re-administration of caffeine (Goldstein et al. 1969), with the magnitude of reversal being an increasing function of the re-administered caffeine dose (Goldstein et al. 1969). Severity also appears to increase with higher daily maintenance caffeine doses before abstinence (Rogers et al. 1995).

In summary, decreased contentedness/well-being has been very frequently studied, may have an intermediate incidence, and has been demonstrated under a wide range of methodological conditions. It is concluded that decreased contentedness/well-being is a valid withdrawal symptom.

Decreased desire to socialize (descriptors: decreased desire to socialize, talkativeness, social disposition, and friendliness) Decreased desire to socialize was demonstrated in 15 of 28 experimental studies (54%). One experimental study reported incidence data of 79% for decreased social disposition and a second study reported 9% for decreased talkativeness (Table 4). Decreased desire to socialize has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4). Studies have also shown that abstinence-induced decreased desire to socialize is time limited (Table 4) and that the magnitude is an increasing function of caffeine maintenance dose before abstinence (Evans and Griffiths 1999).

In summary, decreased desire to socialize has been very frequently studied with varied incidence. Although it has been demonstrated under several different methodological conditions, it does not presently fulfill the criteria for validity.

Flu-like symptoms (descriptors: "flu-like symptoms" and "flu-like feelings") An increase in this category was demonstrated in 9 of 17 (53%) experimental studies. One experimental study reported incidence data of 31% for flu-like symptoms (Table 4). Flu-like symptoms as a symptom category have been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4). Studies have also shown that abstinence-induced flu-like symptoms are time-limited (Table 4) and that the severity of flu-like symptoms is an increasing function of caffeine maintenance dose before abstinence (Lane and Phillips-Bute 1998; Evans and Griffiths 1999).

In summary, the flu-like symptoms category has been frequently studied, appears to have an intermediate incidence, and has been demonstrated under several methodological conditions. In addition to the foregoing studies, one study (Swerdlow et al. 2000) showed caffeine-abstinence-induced increases in a composite scale that included flu-like symptoms (i.e., feel sick, queasy, dizzy, and perspiring). It seems plausible that endorsement of flu-like symptoms is related to a constellation of somatic symptoms that include nausea/vomiting, muscle pain/stiffness, and heavy feelings in arms and legs (these individual symptoms are discussed below). Although most of the experimental studies demonstrating statistical increases in flu-like symptoms have involved comparisons of caffeine abstinence to a caffeine administration condition, the category appears to reflect a genuine withdrawal effect because endorsement of flu-like symptoms is time limited (Griffiths et al. 1990) and it is implausible that such placebo versus caffeine differences represent a direct effect of caffeine in suppressing naturally occurring flu-like symptoms. Thus, even though the flu-like symptoms category fails to meet our a priori criteria for validity, the category appears to be a valid caffeine-withdrawal effect. Furthermore, the flu-like symptoms category may be clinically important because it may reflect significant distress.

Depressed mood (descriptors: depression, dejection, sad/depressed, and elevated scores on the Beck Depression Inventory) Symptoms of depressed mood were demonstrated in 9 of 29 experimental studies (31%). In 4

experimental studies providing incidence data, the median percentage of individuals reporting depressed mood was 16% (range 11–36%; Table 4). In 2 survey studies, the percentage of subjects reporting depression was 4% and 9%. Depressed mood has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4), and by comparing acute caffeine abstinence in caffeine consumers with that in non-consumers (Table 4). Studies also showed that abstinence-induced depressed mood is time limited (Table 4).

In summary, depressed mood has been very frequently studied, has a low to moderate incidence, and has been demonstrated under a wide range of methodological conditions. It is concluded that depressed mood is a valid withdrawal symptom.

Difficulty concentrating (descriptors: difficulty concentrating, decreased concentration, and decreased ability to concentrate) Difficulty concentrating was demonstrated in 8 of 12 experimental studies (67%). One experimental study reported incidence data of 79% and one survey study found that 11% of respondents reported difficulty concentrating (Table 4). Difficulty concentrating has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4). Studies have also shown that abstinence-induced difficulty concentrating is time limited (Table 4), and the severity is positively correlated with daily caffeine dose before abstinence (Lane 1997).

In summary, difficulty concentrating has been moderately frequently studied, may have a high incidence, and has been demonstrated under a wide range of methodological conditions. It is concluded that difficulty concentrating is a valid withdrawal symptom.

Irritability (descriptors: irritability, irritable/cross/grumpy, and irritable/frustrated/angry/cross) Irritability was demonstrated in 8 of 23 experimental studies (35%). Two experimental studies reported incidence data of 29% and 9% (Table 4). In 2 survey studies, the percentage of subjects reporting irritability during caffeine abstinence was 21% and 20%. Irritability has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4), and by comparing acute caffeine abstinence in caffeine consumers with that in non-consumers (Table 4). Studies have also shown that abstinence-induced irritability is time limited (Table 4) and is rapidly (i.e., within 60 min) and completely reversed after re-administration of caffeine (Goldstein et al. 1969), with the magnitude of reversal being an increasing function of the re-administered caffeine dose (Goldstein et al. 1969).

In summary, irritability has been very frequently studied, has a low to moderate incidence, and has been demonstrated under a wide range of methodological conditions. It is concluded that irritability is a valid withdrawal symptom.

Unmotivated for work (descriptors: decreased motivation for work, urge to do tasks/work-related activities, and increased unmotivated) Being unmotivated for work was demonstrated in 8 of 16 experimental studies (50%). One experimental study reported incidence data of 57% for decreased motivation for work and 64% for decreased urge to do work (Table 4). In 2 survey studies, the percentage of subjects reporting being unmotivated for work was 16% and 18%. Unmotivated for work has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition and with a caffeine administration condition (Table 4). Studies have also shown that abstinence-induced "unmotivated for work" is time limited (Table 4), and the severity is positively correlated with daily caffeine dose before abstinence (Lane 1997).

In summary, unmotivated for work has been frequently studied, has an intermediate incidence, and has been demonstrated under several methodological conditions. It has also been described anecdotally (Driesbach and Pfeiffer 1943). Although the data are suggestive, further research is needed to determine the validity of being unmotivated for work as a withdrawal symptom.

Muzzy/foggy/not clearheaded (descriptors: muzzy/foggy/not clearheaded, muzziness, muddled, and decreased clearheaded) Muzzy/foggy/not clearheaded was demonstrated in 7 of 18 experimental studies (39%). One experimental study reported incidence data of 71% (Table 4). Muzzy/foggy/not clearheaded has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4), and by comparing acute caffeine abstinence in caffeine consumers with that in non-consumers (Table 4). Studies have also shown that abstinence-induced muzzy/foggy/not clearheaded is time limited (Table 4), and the severity is positively correlated with daily caffeine dose before abstinence (Lane 1997).

In summary, muzzy/foggy/not clearheaded has been frequently studied, may have a high incidence, and has been demonstrated under a wide range of methodological conditions. It is concluded that muzzy/foggy/not clearheaded is a valid withdrawal symptom.

Yawning (no other descriptors) Self-reported yawning was demonstrated in 7 of 12 experimental studies (58%). One experimental study reported incidence data of 43% and one survey study found that 21% of respondents reported yawning (Table 4). Yawning has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4). Studies have also shown that abstinence-induced yawning is time limited (Table 4), and the severity is positively correlated with daily caffeine dose before abstinence (Silverman et al. 1992).

In summary, yawning has been moderately frequently studied, may have an intermediate incidence, and has been demonstrated under several methodological conditions. Although the data are suggestive, further research is needed to determine the validity of yawning as a withdrawal symptom.

Decreased self-confidence (descriptors: decreased self-confidence and confident) Decreased self-confidence was found in 7 of 17 experimental studies (41%). One experimental study reported incidence data of 64% (Table 4). Decreased self-confidence has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4). Studies have also shown that abstinence-induced decreased self-confidence is time limited (Table 4).

In summary, decreased self-confidence has been frequently studied and may have an intermediate incidence. Although it has been demonstrated under a several different methodological conditions, it does not presently fulfill criteria for validity.

Confusion–bewilderment [POMS] (no other descriptors) Confusion/bewilderment was found in 6 of 21 experimental studies (29%). Confusion–bewilderment has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4). Studies have also shown that abstinence-induced confusion–bewilderment is time limited (Table 4).

In summary, confusion–bewilderment has been very frequently studied and has been demonstrated under several methodological conditions. Although the data are suggestive, it does not presently fulfill criteria for validity.

Total mood disturbance [POMS] (no other descriptors) Total mood disturbance has been shown in 6 of 12 experimental studies (50%). Total mood disturbance has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4). Studies have also shown that the severity of total mood disturbance is an increasing function of caffeine maintenance dose before abstinence (Evans and Griffiths 1999).

In summary, total mood disturbance has been moderately frequently studied and has been demonstrated under several methodological conditions. Although the data are suggestive, further research is needed to determine validity.

Nausea/vomiting (descriptors: nausea/vomiting, nausea and sickness, sick/nauseated/vomiting, vomiting, queasy, and upset stomach) Nausea/vomiting has been demonstrated in 6 of 24 experimental studies (25%). In 4 experimental studies providing incidence data (Table 4), the median percentage of individuals reporting nausea/vomiting was 21% (range 10–33%). In 2 survey studies, the percentage of subjects reporting nausea/vomiting during caffeine abstinence was 3% and 21%. Nausea/vomiting has been demonstrated in studies comparing acute caffeine abstinence with a caffeine administration condition (Table 4).

In summary, nausea/vomiting has been very frequently studied and has a low to moderate incidence. Although in experimental studies nausea/vomiting has only been demonstrated statistically by comparing caffeine abstinence with a caffeine administration condition, it appears to be a genuine withdrawal symptom because it is implausible that such placebo versus caffeine differences represent a direct effect of caffeine in suppressing naturally occurring nausea/vomiting. Instances of withdrawal-induced nausea/vomiting have been reported in case reports (Rainey 1985; Cacciatore et al. 1996), experimental studies (Griffiths et al. 1990; Silverman et al. 1992; Strain et al. 1994), and survey studies (Hughes et al. 1998; Oberstar et al. 2002). Thus, even though nausea/vomiting fails to meet our a priori criterion for validity based on experimental studies alone, nausea/vomiting appears to be a valid caffeine-withdrawal symptom. Furthermore, it may be a clinically important symptom because it is likely to reflect significant distress. It seems plausible that this symptom is related to a constellation of symptoms that include other somatic complaints and endorsement of flu-like symptoms.

Muscle pain/stiffness (descriptors: muscle pain/stiffness, muscle joint ache, general muscle pains, and leg muscle pains) Muscle pain/stiffness has been demonstrated in 4 of 15 experimental studies (27%). The incidence of muscle pain/stiffness was 43% in one study (Table 4). Muscle pain/stiffness has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4). One study also showed that abstinence-induced muscle pain/stiffness is time limited (Table 4).

In summary, muscle pain/stiffness has been studied frequently, may have an intermediate incidence, and has been demonstrated under a range of methodological conditions. The symptom of muscle pain/stiffness has been described in case reports (Cobbs 1982; Stringer and Watson 1987) and is consistent with one report, which involved a musculoskeletal examination during caffeine abstinence (Reeves et al. 1997). Although additional studies are needed to fulfill our a priori validity criteria, the conclusion that muscle pain/stiffness represents a true withdrawal symptom unconfounded by the direct effects of caffeine seems reasonable because it is improbable that caffeine suppresses naturally occurring muscle pain/stiffness.

Anxiety/nervousness (descriptors: anxiety, anxious, nervous, tense, and elevated scores on the State-Trait Anxiety Inventory) Increased anxiety/nervousness has been demonstrated in 4 of 34 experimental studies (12%; Table 4)]. However, decreased anxiety/nervousness has been demonstrated in 2 of the 36 studies (Griffiths et al. 1990; Comer et al. 1997). One experimental study reported incidence data of 8% for increased anxiety (Table 4). In 3 survey studies, the percentage of subjects reporting increased anxiety during abstinence ranged between 10% and 29%. Anxiety/nervousness has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition and a caffeine administration condition (Table 4), and by comparing acute caffeine abstinence in caffeine consumers with that in non-consumers (Table 4).

Despite the fact that marked anxiety is proposed as a caffeine-withdrawal symptom in DSM-IV-TR (American Psychiatric Association 2000), anxiety/nervousness does not fulfill the validity criteria. It is of note that 32 experimental studies using a variety of methodologies failed to show increased anxiety/nervousness, none of the positive studies used the most rigorous experimental design involving a chronic abstinence condition, and 2 experimental studies demonstrated significant decreases (Griffiths et al. 1990; Comer et al. 1997). However, it is also noteworthy that anxiety/nervousness has been described as a withdrawal symptom in case reports (Gibson 1981; Cobbs 1982; Rainey 1985; Adams et al. 1993) and that anxiety/nervousness is also endorsed as a withdrawal symptom at low to moderate rates in three survey studies (Table 4). Although further research is needed, it may be that the increased anxiety/nervousness associated with caffeine withdrawal in non-blind case reports and survey studies reflects increased anxiety in anticipation of experiencing unpleasant effects of caffeine abstinence.

Heavy feelings in arms and legs (no other descriptors) Heavy feelings in arms and legs were demonstrated in 4 of 9 experimental studies (44%). Heavy feelings in arms and legs have been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4). Although the data are suggestive, further research is needed to determine the validity of heavy feelings in arms and legs as a withdrawal symptom.

Increased nighttime sleep duration/quality (descriptors: self-report ratings of sleep quality, duration, and onset to sleep) Self-reported increased nighttime sleep duration/quality was demonstrated in 4 of 4 experimental studies. In the two studies that assessed sleep duration, the increase was about 30 min (Höfer and Bättig 1994b; James 1998). Increased nighttime sleep duration/quality has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition and a caffeine administration condition (Table 4).

Although increased nighttime sleep has been rarely studied during caffeine abstinence, the magnitude of increased sleep duration is notable. The limited methodologies in which it has been assessed do not permit differentiation between an effect of caffeine in decreasing sleep and a time limited caffeine-withdrawal effect. Further research is needed to determine whether this is a valid withdrawal symptom.

Analgesic use (no other descriptors) Self-reported analgesic use was demonstrated in 3 of 3 experimental studies. Two of these studies explicitly discouraged analgesic use (Silverman et al. 1992; Strain et al. 1994). Two experimental studies reported incidence data of 13% and 45% (Table 4). Analgesic use has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition and a caffeine administration condition (Table 4). Studies also showed that abstinence-induced analgesic use was time limited (Table 4).

Although analgesic use during caffeine abstinence has been rarely assessed, it is a potential indicator of the clinical significance of caffeine-withdrawal distress and is worthy of future study. Whether avoidance of caffeine withdrawal contributes to chronic use of caffeine-containing analgesics as suggested by some reports (Strain and Griffiths 1998; Bigal et al. 2002; but cf. Feinstein et al. 2000) also merits further study.

Craving/strong desire to use (no other descriptors) Craving/strong desire to use was demonstrated in 2 of 2 experimental studies. One experimental study reported incidence data of 43% and one survey study reported that 28% of respondents reported a strong desire to use (Table 4). Craving/strong desire to use has been demonstrated in studies comparing acute caffeine abstinence with a caffeine administration condition and has been shown to be time limited (Table 4).

Although craving is often reported anecdotally during caffeine abstinence in the natural environment (Rippere 1984; Gilbert 1986), it has been rarely assessed as a caffeine-withdrawal symptom. Further research is needed to determine its validity. Given its potential importance for understanding habitual caffeine consumption, a priority should be given to including measures of craving in future caffeine-withdrawal research.

Blurred vision (no other descriptors) Blurred vision was demonstrated in 2 of 11 experimental studies (18%). The incidence of blurred vision was 14% in one experimental study (Table 4). It has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition, a caffeine administration condition, and a chronic caffeine abstinence condition (Table 4). One study also showed that abstinence-induced blurred vision was time limited (Table 4).

In summary, blurred vision has been studied moderately frequently, may have a low incidence, and has been demonstrated under several methodological conditions. The symptom of blurred vision is also consistent with a

case report (Cobbs 1982). Further research is needed to determine its validity.

Lightheaded/dizzy (no other descriptors) Lightheaded/dizzy was demonstrated in 3 of 18 experimental studies (17%). Lightheaded/dizzy has been demonstrated only in studies comparing acute caffeine abstinence with a caffeine administration condition.

Although lightheaded/dizzy has been frequently studied, it has only been demonstrated in three studies, one of which was not blind. It is concluded that there is little evidence supporting lightheaded/dizzy as a caffeine-withdrawal symptom.

Anger/hostility (descriptors: anger–hostility and angry) Anger/hostility was demonstrated in 2 of 20 experimental studies (10%). It has been demonstrated in studies comparing acute caffeine abstinence with a caffeine administration condition and a chronic caffeine abstinence condition (Table 4), and by comparing acute caffeine abstinence in caffeine consumers with that in non-consumers (Table 4). Studies have also shown that abstinence-induced anger/hostility is time limited (Table 4).

Although anger/hostility has been very frequently studied using various methodologies, it has only been demonstrated in two studies, one of which was not blind. It is concluded that there is little evidence to suggest that anger/hostility is a caffeine-withdrawal symptom.

Hot and cold spells (no other descriptors) This symptom was demonstrated in 2 of 8 experimental studies (25%). Hot and cold spells have been demonstrated only in studies comparing acute caffeine abstinence with a baseline or a caffeine administration condition. Further research is needed to determine the validity.

Rhinorrhea (runny nose) [(descriptors: rhinorrhea and runny nose)] Not shown in Table 4, rhinorrhea was demonstrated in one non-blind study (Roller 1981) of 12 experimental studies that used a variety of methodologies. Caffeine-withdrawal-induced rhinorrhea was also described anecdotally in two reports (Driesbach and Pfeiffer 1943; Greden et al. 1980). It is concluded that there is little evidence to suggest that rhinorrhea is a caffeine-withdrawal symptom.

Diaphoresis (perspiration) [(descriptors: diaphoresis, perspiring, and sweating)] Not shown in Table 4, this symptom was demonstrated in 2 of 19 experimental studies (11%). It is concluded that there is little evidence to suggest that diaphoresis is a caffeine-withdrawal symptom.

Limb tremor (no other descriptors) Not shown in Table 4, this symptom was demonstrated in none of 10 experimental studies using a variety of methodologies. These observations are consistent with seven studies that failed to document objective measures of hand tremor during caffeine abstinence (discussed below). It is concluded that there is little evidence to suggest that self-reported limb tremor is a caffeine-withdrawal symptom.

Miscellaneous symptom categories for which there is no empirical support Several additional symptoms of potential interest were evaluated in the studies described in Tables 1 and 2 and were not significantly affected by caffeine abstinence in any study. The symptoms, with the number of studies in which they were evaluated indicated in parentheses, are heart pounding/palpitations (15), frequent urination (13), jittery/shaky (11), difficulty sleeping (10), increased hunger/appetite (10), muscle cramps (8), loss of sex drive (8), diarrhea (7), calm/relaxed (7), muscle twitches (5), irregular heartbeat (5), ringing in ears (5), thirsty (5), restless (4), shaky/weakness (3), constipation (2), chills (1), and numbing or tingling of extremities (1).

Signs of caffeine withdrawal

In this section, withdrawal signs (i.e., objectively measured behavioral or physiological effects) that were assessed in the studies listed in Tables 1 and 2 are individually discussed and evaluated.

Impaired behavioral and cognitive performance This category is comprised of tasks designed to assess various aspects of performance impairment. Of 23 experimental studies that assessed performance during caffeine abstinence, 11 (48%) reported significant impairment on one or more measures. More specifically, impairment of tapping speed occurred in 3 of 8 studies (Bruce et al. 1991; Silverman et al. 1992; Strain et al. 1994), impairment of visual vigilance occurred in 2 of 4 studies (Lane and Phillips-Bute 1998; Yeomans et al. 2002b), decreased reaction time occurred in 2 of 7 studies (Rizzo et al. 1988; Robelin and Rogers 1998), impaired performance on a digit symbol substitution task occurred in 2 of 11 studies (Liguori and Hughes 1997; Liguori et al. 1997b), impaired performance on a character recognition task occurred in 1 study (James 1998), and impairment in 5 of 7 measures in a complex cognitive problem-solving task occurred in 1 study (Streufert et al. 1995). Four studies assessing memory found no evidence for impairment during caffeine abstinence. With regard to incidence, one experimental study reported incidence data of 55% for decreased tapping speed (Strain et al. 1994). Methodologically, impaired performance has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition (Silverman et al. 1992), a caffeine administration condition (Silverman et al. 1992; Strain et al. 1994; Streufert et al. 1995; Liguori and Hughes 1997; Liguori et al. 1997b; James 1998; Lane and Phillips-Bute 1998; Robelin and Rogers 1998; Yeomans et al. 2002b), and a chronic caffeine abstinence condition (Bruce et al. 1991), and by comparing acute caffeine abstinence in caffeine consumers with that in non-consumers (Rizzo et

al. 1988). Studies have also shown that abstinence-induced impaired behavioral performance is time limited (Bruce et al. 1991).

In summary, impaired behavioral or cognitive performance has been very frequently studied, may have an intermediate incidence, and has been demonstrated under a range of methodological conditions. Furthermore, the types of impairments observed (i.e., psychomotor speed, vigilance, and cognitive performance) appear consistent with the profile of validated withdrawal symptoms such as tiredness/fatigue, decreased alertness, and difficulty concentrating. It should be noted, however, that this category is comprised of heterogeneous measures of performance impairment and, at present, there is not enough information to reach a conclusion about the validity of any specific performance measure. Future research should focus on measures that appear to be most sensitive to caffeine abstinence, including tapping, vigilance, reaction time, and complex cognitive problem solving.

Increased cerebral blood flow Increased cerebral blood flow velocity has been demonstrated in 4 of 4 experimental studies (Mathew and Wilson 1985; Couturier et al. 1997; Jones et al. 2000; Field et al. 2003; cf. Tables 1, 2). Increased cerebral blood flow has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition (Mathew and Wilson 1985; Couturier et al. 1997) and a caffeine administration condition (Jones et al. 2000; Field et al. 2003). The magnitude of this effect is positively correlated with daily caffeine dose before abstinence (Mathew and Wilson 1985; Field et al. 2003).

The several studies indicating that caffeine abstinence is associated with increases in cerebral blood flow are of particular interest because the effect may be related to a vascular mechanism underlying the common withdrawal symptom of headache (cf. Jones et al. 2000). However, the methodologies of the studies conducted to date do not permit differentiation of the effects of caffeine per se on cerebral blood flow from the effects of caffeine withdrawal. Further research is needed to determine the validity of increased cerebral blood flow as a withdrawal sign.

Changes in EEG Changes in quantitative electroencephalography (EEG) during caffeine abstinence was demonstrated in 3 of 3 experimental studies (Lader et al. 1996; Jones et al. 2000; Reeves et al. 2002; cf. Tables 1, 2). Effects included increases in EEG theta power (Jones et al. 2000; Reeves et al. 2002), which have been associated with drowsiness. However, across studies, findings have been inconsistent across different EEG measures. Changes in EEG have been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition (Lader et al. 1996; Reeves et al. 2002) and a caffeine administration condition (Jones et al. 2000).

Although a few studies suggest that quantitative EEG measures might provide a physiological measure or correlate of caffeine withdrawal, the methodologies do not permit differentiation of the effects of caffeine per se on EEG from the effects of caffeine withdrawal. Further research is needed to validate changes in EEG as a withdrawal sign.

Decreased blood pressure Of 11 experimental studies that assessed blood pressure, three demonstrated decreases in systolic blood pressure (Streufert et al. 1995; Lader et al. 1996; Phillips-Bute and Lane 1998) and one each showed decreases in diastolic (Phillips-Bute and Lane 1998) and arterial (Lane 1997) blood pressure. The small magnitude of this effect (about 6 mmHg for systolic blood pressure) suggests that, if this effect is time limited, it is not clinically important. Decreased blood pressure has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition (Lader et al. 1996) and a caffeine administration condition (Streufert et al. 1995; Lane 1997; Phillips-Bute and Lane 1998). One study showed the effect to be time limited (Lader et al. 1996).

The studies cited above, as well as several studies that explicitly focused on cardiovascular outcome measures (Robertson et al. 1981; Ammon et al. 1983), do not provide convincing evidence that caffeine abstinence acutely decreases blood pressure.

Decreased motor activity Decreased motor activity assessed using electronic activity monitors was demonstrated in 2 of 2 experimental studies (Höfer and Bättig 1994a,b; cf. Table 2). Decreased motor activity has been demonstrated in studies comparing acute caffeine abstinence with a preceding baseline condition (Höfer and Bättig 1994a,b), and the effect was time limited (Höfer and Bättig 1994a).

Although decreased motor activity has been only rarely studied, it has face validity as a caffeine-withdrawal sign because it plausibly could co-vary with the well-validated symptoms of increased tiredness/fatigue and decreased energy/activeness. Further research is needed to establish the validity.

Skin conductance One experimental study assessed and found a significant effect (decrease) in skin conductance during caffeine abstinence relative to a preceding baseline condition (Lader et al. 1996; cf. Table 1). Further research is needed to establish its validity.

Urinary epinephrine and norepinephrine Of two studies that assessed urinary epinephrine and norepinephrine (Robertson et al. 1981; Lane 1994; cf. Tables 1, 2), one showed decreased levels of epinephrine during caffeine abstinence relative to a caffeine condition (Lane 1994). The author interpreted this as an effect of caffeine rather than caffeine withdrawal. Further research is needed.

Heart rate Of 9 experimental studies that assessed heart rate, only one reported a significant effect (increase) during caffeine abstinence (Höfer and Bättig 1994a). The effect was neither time limited nor reversed by re-administration of caffeine (Höfer and Bättig 1994a). It is

concluded that there is no meaningful evidence that caffeine abstinence affects heart rate.

Hand tremor Of 7 experimental studies that assessed objective measures of hand tremor, none showed a significant effect of caffeine abstinence. These observations are consistent with 10 studies that showed that caffeine abstinence did not affect subjective measures of limb tremor (reviewed in Tables 1, 2, and discussed above). It is concluded that there is little to suggest that caffeine abstinence affects hand tremor.

Incidence of clinically significant distress or impairment in daily functioning

In individuals reporting caffeine-withdrawal symptoms, the severity can vary from mild to extreme. Clinically significant distress and/or impairment of normal daily activities (e.g., work absence or going to bed because of symptoms) upon caffeine abstinence have been reported in clinical evaluations and experimental studies dating back over 170 years (Kingdon 1883; Bridge 1893; Driesbach and Pfeiffer 1943; Goldstein and Kaizer 1969; Greden et al. 1980; Rainey 1985; Smith 1987; Griffiths et al. 1990; Silverman et al. 1992; Adams et al. 1993; Weil and Rosen 1993, p 187; Hampl et al. 1994; Strain et al. 1994; Cacciatore et al. 1996; Lader et al. 1996). Information about the proportion of regular caffeine consumers who are at risk for experiencing clinically significant distress and/or functional impairment during abrupt caffeine abstinence is available from both prospective experimental studies and retrospective survey studies.

Prospective experimental studies showing clinically significant distress or impairment

Six prospective experimental studies provide information on the incidence of clinically significant distress or functional impairment during caffeine abstinence. With regard to the experimental studies, in one double-blind study of 11 people who fulfilled criteria for DSM-IV substance dependence applied to caffeine use (median intake 357 mg/day), 73% experienced significant disruptions in normal daily activities during a period of experimentally induced caffeine abstinence, including leaving or missing work, making errors or costly mistakes at work, inability to care for children, and inability to complete school work (Strain et al. 1994). Five experimental studies have been conducted in normal subject populations. One study, conducted in 22 medical and graduate students who consumed 650–780 mg/day experimentally administered caffeine before abstinence, reported that headache "as extreme in severity as the subjects had ever experienced" occurred in 55% of 38 trials (Driesbach and Pfeiffer 1943). A double-blind study of 62 caffeine consumers (mean intake 235 mg/day), who had no knowledge that the study was about caffeine, found that during caffeine abstinence 52% of subjects reported moderate to severe headache, and 8–11% showed abnormally high scores on standardized depression and fatigue scales (Silverman et al. 1992). In an open-ended interview, several of these subjects also reported severe functional impairment. In another double-blind study, 45% of 40 caffeine consumers (mean intake 360 mg/day) reported a "diffuse, throbbing headache," with 28% of those also reporting "nausea and sickness" (Lader et al. 1996). A third double-blind study evaluated the incidence of functional impairment during abrupt caffeine abstinence in a group of 18 subjects (mean intake 231 mg/day) who reported having had problems or symptoms when previously stopping caffeine (Dews et al. 1999). The study found that 39% of subjects spontaneously reported caffeine-withdrawal symptoms and 22% showed substantial decreases (≥1.5 points on a 4 point scale) in their ratings of daily functioning (e.g., at work and leisure activities), although none of the subjects reported symptoms judged to be "incapacitating" by the authors. Limitations of this study, which have been discussed elsewhere (Griffiths et al. 2003), include the relatively unstructured and unmonitored conditions under which data were obtained and the relatively low caffeine maintenance dose. Finally, one non-blind trial of caffeine abstinence reported 10% of 20 caffeine consumers reported nausea and vomiting (Couturier et al. 1997).

Overall, the incidence of clinically significant distress or functional impairment in prospective experimental studies with normal subjects has varied from about 10% to as high as 55% (median 13%). The estimate of 13% is lower than the 73% rate of functional impairment shown in subjects who met DSM-IV criteria for substance dependence applied to caffeine (Strain et al. 1994). The difference is not due to differences in caffeine intake (the usual maintenance dose in the dependent subjects was in the range of that of the studies in the normal subjects), suggesting that the caffeine-dependent subjects may represent a subpopulation vulnerable to severe withdrawal effects. It should be recognized that the 13% incidence rate for normal subjects could underestimate the rate of occurrence in the general population. Although unstudied, it seems reasonable to suppose that there may be a substantial subject selection bias in caffeine research in the general population, with individuals who experience clinically significant withdrawal being less likely to volunteer for a study in which caffeine abstinence might be a possibility.

Retrospective survey studies showing clinically significant distress or impairment

Four retrospective survey studies provide information on the percentage of respondents reporting clinically significant distress or functional impairment during caffeine abstinence. A survey study of 183 women showed that the percentage endorsing that they would experience classic caffeine-withdrawal symptoms (headache, lethargy, and

sleepiness) without their morning coffee increased as a function of the number of cups of coffee consumed (Goldstein and Kaizer 1969). Consistent with functional impairment, endorsement of being "unable to work effectively" also increased with cups consumed, with the effect reported by 9% of all coffee consumers and 16% of heavy consumers (>5 cups/day). In a population-based random digit dial telephone survey study, caffeine consumers were questioned about their experience with caffeine withdrawal (Hughes et al. 1998). Of 71 who reported having stopped or reduced caffeine for at least 24 h during the past year, 11% reported experiencing headache and other withdrawal symptoms that interfered with their performance. This figure was 24% among the subgroup who reported stopping caffeine in an attempt at permanent abstinence. A third study asked a wide variety of questions of people who telephoned to volunteer for a paid clinical research trial (Dews et al. 1999). Of 6,815 daily caffeine consumers, 2.6% reported that problems or symptoms during caffeine abstinence were severe enough to interfere with normal activity (e.g., inability to concentrate at work; lost time at work). The low rate of endorsement of functional impairment in this study may have been due to a failure to exclude individuals who had not actually abstained from caffeine, as well as possible under reporting of symptoms because of a desire to participate in a paid research trial. A final retrospective survey was conducted in 36 adolescent caffeine consumers who endorsed two or more DSM-IV substance dependence criteria applied to caffeine use (Oberstar et al. 2002). Twenty-one percent reported the caffeine-withdrawal symptom of "sick/nauseated/vomiting."

Overall, the percentage of respondents reporting clinically significant distress or functional impairment in retrospective survey studies varied between 2.6% and 11% (median 9%) in general survey studies, and was 21% in caffeine-dependent adolescent subjects. The median estimate from the general survey studies is quite similar to the estimate from prospective experimental studies (9% and 13%, respectively). As with the experimental studies, there are several limitations inherent to survey studies that may result in underestimates. First, a portion of habitual caffeine consumers may be unaware of caffeine-withdrawal symptoms because they never have had a period of sustained abstinence. Furthermore, it has been demonstrated that as little as 25 mg/day of caffeine can prevent some withdrawal symptoms (Evans and Griffiths 1999). Thus, small amounts of caffeine that are unknowingly consumed on days believed to be "caffeine-free" days may lead to an underestimation of the incidence of clinically significant distress during complete abstinence. Finally, it is possible that caffeine-withdrawal symptoms such as headache, fatigue, nausea, and muscle aches could be misattributed to other causes or ailments (e.g., common cold).

Expectancies and caffeine withdrawal

It has been speculated that knowledge and expectation are the prime determinants of caffeine-withdrawal symptoms (Rubin and Smith 1999; Dews et al. 2002), leading to the conclusion that caffeine withdrawal is "controversial" (Dews et al. 1999; Rubin and Smith 1999). In drug research, the importance of expectancies has long been acknowledged (Marlatt and Rohsenow 1980; Fillmore 1994), and double-blind experimental methodologies were explicitly developed to help control for expectancy effects. However, what is known about withdrawal symptoms from abused drugs, including alcohol, opioids, sedatives, and cocaine, has been inferred from clinical observations rather than documented in experimental studies in which placebo was substituted for active drug under blind conditions (Martin 1977; Weddington et al. 1990). In contrast, the great majority (74%) of the 57 experimental studies of caffeine withdrawal outlined in Tables 1 and 2 were conducted under double-blind conditions, with an additional 11% conducted under single-blind conditions. Thus, caffeine-withdrawal research, in particular, seems to distinguish itself as having controlled for expectancy effects better than most other research on drug withdrawal.

One approach to assessing the impact of expectancies on caffeine withdrawal is to compare the incidence of caffeine-withdrawal headache that has been reported in double-blind and single-blind studies (studies 1–48 in Tables 1 and 2) to that reported in non-blind studies (studies 49–55 in Table 2). The median incidence of headache (derived from column 7 of Table 4) for the blind and non-blind studies that reported such data is 45% and 57%, respectively, suggesting a modest effect of expectancy.

However, it is important to recognize that the impact of expectancies is not entirely eliminated using double-blind methods. Even in double-blind studies, expectancies can play a role if subjects have knowledge of the purpose and conditions of the study. For instance, in extreme cases, subjects could be told that the purpose of a study is to investigate caffeine withdrawal and that they will be receiving either caffeine or placebo. This information could functionally unblind subjects if they could discriminate between conditions based on immediate pharmacological effects or on early symptoms of withdrawal (Dews et al. 1999; Rubin and Smith 1999).

To address this issue, the blind studies in Tables 1 and 2 were re-reviewed for information relevant to possible expectancy effects. This analysis revealed that many of the blind studies provided or probably provided sufficient information such that subjects could have been aware that the study involved caffeine or caffeine withdrawal. However, a substantial number of blind studies went to some lengths to keep subjects uninformed about purpose or experimental conditions. For example, several studies conducted at Johns Hopkins (Silverman et al. 1992; Schuh and Griffiths 1997; Garrett and Griffiths 1998; Jones et al. 2000) instructed subjects that they could receive a variety of compounds found in foods and beverages (e.g.,

chlorogenic acids, determines, caffeine, tannin, sugar, theophylline, or inactive placebo). To further divert attention away from caffeine, the dietary restrictions were written without reference to caffeine and included various foods and substances that do not contain caffeine (i.e., saccharin, aspartame [Nutrasweet], oysters, mussels, almonds, coconuts, poppy seeds, and all beverages except milk, fruit juice, and water). Furthermore, as the research unit at Johns Hopkins conducts a large number of studies with a wide range of drugs other than caffeine, it is unlikely that conduct of these studies at that site would have created subject expectations that the study involved caffeine. Two studies from other laboratories also used instructions and methods that reduced the likelihood of expectancy effects (Comer et al. 1997; Dews et al. 1999). Finally, several studies ruled out expectancy effects by using debriefing procedures to explicitly determine what subjects understood or inferred about the experimental conditions (van Dusseldorp and Katan 1990; Rogers et al. 1995; James 1998; Robelin and Rogers 1998; Yeomans et al. 1998, 2002b; Tinley et al. 2003). From these studies in which expectancy effects are judged to be unlikely, the median incidence of headache (derived from column 7 of Table 4) for the studies that reported such data is 42%, which is similar to the incidence of headache for all blind studies (45%). Furthermore, the profile of other symptoms demonstrated in these studies in which expectancy effects were unlikely is similar to those demonstrated in the larger set of studies.

In conclusion, while it is undoubtedly true that, as with the assessment of other clinical phenomena, expectancies could play some role in caffeine withdrawal, the evidence that caffeine withdrawal is pharmacologically based is overwhelming, and analysis of the published data does not support the hypothesis that expectancies are a primary determinant of caffeine-withdrawal symptoms. It should also be recognized that, to the extent that expectancies may modestly enhance caffeine-withdrawal symptoms (as suggested from the comparison of blind and non-blind studies described above), blind research studies may actually underestimate the incidence and severity of withdrawal that occurs under more naturalistic clinically relevant conditions. Future research should evaluate this possibility using a methodology such as the balanced placebo design, which experimentally manipulates both caffeine abstinence and expectancy of abstinence (Marlatt and Rohsenow 1980; Juliano and Brandon 2002).

Time course of caffeine withdrawal

Numerous studies have shown that caffeine-withdrawal symptoms typically emerge 12–24 h after abrupt caffeine abstinence (Driesbach and Pfeiffer 1943; Goldstein 1964; Goldstein et al. 1969; Griffiths et al. 1986, 1990; Richardson et al. 1995; Schuh and Griffiths 1997; Swerdlow et al. 2000; Tinley et al. 2003), which is consistent with the short half-life of caffeine (4–6 h). Some evidence suggests that symptoms may emerge later (>24 h) after abstinence from higher doses (e.g., 900 mg/day) of caffeine (Bruce et al. 1991; Evans and Griffiths 1992). In the few studies that provided detailed time-course information for individual subjects, onset of withdrawal symptoms have been reported as early as 6 h (Roller 1981) and as late as 43 h (Griffiths et al. 1990) after abstinence. Caffeine-withdrawal symptoms have been shown to reach peak intensity between 20 h and 51 h after abstinence (Griffiths et al. 1986, 1990; Evans and Griffiths 1992; Brauer et al. 1994; Höfer and Bättig 1994a,b; Lader et al. 1996). The duration of caffeine withdrawal has been shown to be 2–9 days (Griffiths et al. 1986, 1990; van Dusseldorp and Katan 1990; Höfer and Bättig 1994a), and the possibility of withdrawal headaches occurring up to 21 days has been suggested (Richardson et al. 1995).

Parametric determinants of caffeine withdrawal

Chronic caffeine maintenance dose

There is good evidence that the incidence or severity of caffeine withdrawal increases with increases in the chronic daily caffeine maintenance dose. The best evidence for this relationship comes from a prospective study that experimentally manipulated caffeine maintenance dose (100, 300, and 600 mg/day) and showed monotonic increases in several withdrawal measures, with significantly greater headache and headache/poor mood demonstrated after abstinence from 600 mg than 100 mg/day (Evans and Griffiths 1999). This study and a previous study (Griffiths et al. 1990) also demonstrated that significant caffeine withdrawal occurred after abstinence from a dose as low as 100 mg/day.

The relationship between withdrawal incidence or severity and usual caffeine dose has also been demonstrated in studies of self-reported caffeine maintenance dose, including retrospective survey studies (Goldstein and Kaizer 1969), experimental studies (Goldstein 1964; Silverman et al. 1992; Rogers et al. 1995; Lader et al. 1996; Lane 1997; Lane and Phillips-Bute 1998), and studies of post-operative headache (Galletly et al. 1989; Fennelly et al. 1991). It should be noted, however, that the relationship between withdrawal and self-reported caffeine intake appears relatively weak because it has not been demonstrated in some studies (Verhoeff and Millar 1990; Hughes et al. 1993; Höfer and Bättig 1994a), and significant correlations between withdrawal measures and caffeine intake are low and inconsistent across different withdrawal measures (Silverman et al. 1992; Lane 1997; Lane and Phillips-Bute 1998).

Acute decreases in caffeine maintenance dose

When lower caffeine doses are substituted for the usual maintenance dose, withdrawal severity increases as the substituted dose decreases. One study maintained indivi-

duals on 300 mg caffeine/day and then substituted a range of lower doses (Evans and Griffiths 1999). The study showed that a substantial reduction in caffeine dose (to ≤100 mg/day) was necessary to produce caffeine withdrawal and that even a dose of 25 mg/day was sufficient to avoid significant caffeine-withdrawal headache. This result suggests that a substantial percentage reduction in caffeine consumption is necessary to manifest the full caffeine-withdrawal syndrome.

Duration of caffeine maintenance

Three studies demonstrated that caffeine withdrawal can occur after a relatively short duration of caffeine maintenance (Driesbach and Pfeiffer 1943; Griffiths et al. 1986; Evans and Griffiths 1999). One of these studies (Evans and Griffiths 1999), which was conducted in caffeine consumers who were caffeine abstinent for 7 days before the period of caffeine maintenance, showed no withdrawal effects after a single day of exposure to caffeine (300 mg/day). However, significant withdrawal symptoms occurred after 3 consecutive days of caffeine, with somewhat greater severity demonstrated after 7 and 14 consecutive days of exposure. Another study (Driesbach and Pfeiffer 1943) showed that caffeine-withdrawal headache occurred in three individuals who normally totally abstained from caffeinated beverages, but who were given increasing doses of caffeine over 6 days or 7 days up to 650–780 mg/day.

Within-day frequency of dosing during caffeine maintenance

Most studies of caffeine withdrawal have involved caffeine abstinence after a maintenance period that involved multiple caffeine doses each day. The only study to vary the within-day frequency of caffeine dosing showed that the range and severity of caffeine-withdrawal symptoms was similar when caffeine maintenance involved 300 mg taken as single dose in the morning compared with 100 mg taken at three time points across the day (Evans and Griffiths 1999). This indicates that once-a-day dosing with caffeine is sufficient for producing withdrawal symptoms.

Re-administration of caffeine reverses abstinence effects

After a period of abstinence during which the severity or incidence of a symptom or sign develops, re-administration of caffeine rapidly (usually within 30–60 min) and often completely reverses withdrawal (Driesbach and Pfeiffer 1943; Goldstein et al. 1969; Roller 1981; Couturier et al. 1997; Tinley et al. 2003), with the magnitude of reversal being an increasing function of the re-administered caffeine dose (Goldstein et al. 1969).

Individual differences in caffeine withdrawal

There are differences within and across individuals with respect to the incidence of caffeine withdrawal. As discussed above and shown in Table 4, only about 50% of subjects in experimental studies report headache after any single occasion of caffeine abstinence, and the severity of headache can vary from mild to extreme. One study that examined six repeated blind abstinence trials in seven subjects maintained on 100 mg/day of caffeine documented differences within and across subjects: one subject never showed substantial headache, some subjects showed consistent headaches, while others reported headaches on some trials but not others (Griffiths et al. 1990). A second study that analyzed the effects of six repeated abstinence trials showed that at least 36% of subjects, who showed statistically significant elevations in headache, failed to report this effect consistently across repeated trials (Hughes et al. 1993). There is evidence that genetic factors may play a role in some differences among individuals. One study of 1,934 female twins found that there was significantly greater concordance of DSM-IV-defined caffeine withdrawal among monozygotic twins (41%) than dizygotic twins (18%), yielding an estimated broad heritability of 35% (Kendler and Prescott 1999).

Other than the role of chronic maintenance dose (discussed previously), very little is known about the determinants of individual differences in caffeine withdrawal. The results of one study suggested that individuals who eliminated caffeine slowly were less likely to experience sedation during withdrawal (Lader et al. 1996). Whether females, individuals with histories of previous drug dependence including cigarette smoking, or individuals with polymorphisms in the A_1 and A_{2A} adenosine receptor genes are at greater risk of caffeine withdrawal is worthy of future research (Strain et al. 1994; Dews et al. 1999; Alsene et al. 2003).

The role of caffeine withdrawal in the habitual consumption of caffeine

Research indicates that avoidance of abstinence-associated withdrawal symptoms plays a central role in the habitual consumption of caffeine. This relationship has been shown in retrospective questionnaire studies (Goldstein and Kaizer 1969) and in double-blind experimental studies that assessed direct behavioral measures of caffeine reinforcement or preference (Griffiths et al. 1986; Hughes et al. 1993; Liguori and Hughes 1997; Schuh and Griffiths 1997; Garrett and Griffiths 1998) and beverage flavor preferences (Rogers et al. 1995; Yeomans et al. 1998, 2000a, 2001, 2002a; Tinley et al. 2003).

One study of caffeine reinforcement, for example, showed that moderate caffeine consumers who reported caffeine-withdrawal symptoms (i.e., headache, drowsiness) after drinking decaffeinated coffee were more than twice as likely to choose caffeinated over decaffeinated

coffee in choice tests (Hughes et al. 1993). 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 et al. 1986; Garrett and Griffiths 1998).

Withdrawal also plays an important role in the development of preferences for flavors paired with caffeine. In these studies, caffeine consumers who abstained from caffeine overnight and were repeatedly exposed to a novel flavored drink paired with caffeine showed increased ratings of drink pleasantness or preference compared with caffeine consumers who received placebo-paired drinks (Rogers et al. 1995; Yeomans et al. 1998). It has been demonstrated that the development of such flavor preference requires that subjects be caffeine deprived at training and testing (Yeomans et al. 1998, 2000b, 2001, 2002a). Furthermore, the effects are not observed in caffeine non-consumers or in long-term abstinent consumers (Rogers et al. 1995; Tinley et al. 2003). It seems likely that, in the natural environment, withdrawal-dependent conditioned flavor preferences play an important role in development of strong consumer preferences for specific kinds of caffeine-containing beverages.

DSM-IV-TR and ICD-10 diagnostic criteria for caffeine withdrawal

The potential for caffeine withdrawal to cause clinically significant distress or impairment in functioning is reflected by the inclusion of caffeine withdrawal as an official diagnosis in ICD-10 (World Health Organization 1992a,b) and as a proposed research diagnosis in DSM-IV-TR (American Psychiatric Association 2000). Caffeine withdrawal was included in DSM-IV as a proposed diagnosis rather than an official diagnosis to encourage further research on the range and specificity of caffeine-withdrawal symptoms (Hughes 1994). The DSM-IV-TR proposed research criteria for withdrawal are: (A) prolonged daily use of caffeine; (B) abrupt cessation of caffeine use or reduction in the amount of caffeine used, closely followed by 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 mental disorder.

The official ICD-10 diagnosis for withdrawal from caffeine does not specify specific symptoms for making the diagnosis (World Health Organization 1992a,b). The ICD-10 diagnostic criteria for research includes the diagnosis of a "withdrawal state from other stimulants, including caffeine" (World Health Organization 1993). The criteria involve: (A) cessation or reduction of caffeine use after prolonged use; (B) dysphoric mood (for instance, sadness or anhedonia); and (C) two or more of the following: (1) lethargy and fatigue, (2) psychomotor retardation or agitation, (3) craving for stimulant drugs, (4) increased appetite, (5) insomnia or hypersomnia, (6) bizarre or unpleasant dreams.

Proposed revision of DSM-IV-TR and ICD-10 diagnostic criteria for caffeine withdrawal

The great majority of the research literature on caffeine withdrawal has been published since the DSM-IV Work Group (in 1994) and the World Health Organization (in 1993) formulated their respective criteria for proposed research diagnoses (cf. Tables 1, 2, 3). This section focuses on a proposed revision of the DSM, although many of the considerations would be applicable to a revision of ICD-10. The research summarized in this review further documents that caffeine withdrawal may be severe enough to warrant clinical attention, which was questioned in DSM-III-R (American Psychiatric Association 1987). Moreover, the research literature now provides a sound empirical basis for updating the criteria for caffeine withdrawal. Problems with the DSM-IV-TR criteria are that they (1) do not reflect the apparent independence of headache and non-headache withdrawal symptoms (cf. section on headache); (2) do not include symptoms that have now been well-validated; and (3) include a symptom (i.e., anxiety) for which there is little empirical support.

Based on the current evaluation of the research literature, we now propose that part B of the DSM research criteria be changed to indicate that a caffeine-withdrawal diagnosis requires: abrupt cessation of caffeine use or reduction in the amount of caffeine used, closely followed by three or more of the following: (1) headache, (2) fatigue or drowsiness, (3) dysphoric mood, depressed mood, or irritability, (4) difficulty concentrating, and (5) flu-like somatic symptoms, nausea, vomiting, or muscle pain/stiffness.

The proposed five clusters of symptoms are based on the 13 symptoms from this review that are the best candidates for describing the caffeine-withdrawal syndrome. The new criteria address the 1994 DSM-IV Work Group concerns that there were too few validated symptoms and there may be overlap between fatigue and drowsiness (Hughes 1994). The decision to propose the diagnosis based on three of the five clusters is a conservative strategy to prevent over-diagnosis of the disorder, which was also a concern of the DSM-IV Work Group (Hughes 1994). Although some of the proposed symptoms have high prevalence and other etiologies, this is also true of other withdrawal diagnoses recognized by DSM (e.g., cocaine withdrawal, nicotine withdrawal, opioid withdrawal).

It should be recognized that although the individual symptoms have been empirically validated, the symptom clusters are conceptually rather than empirically derived. It would be informative if future research with a suitably

large group of individuals assessed all of the symptoms validated in this review and used statistical procedures to empirically differentiate among clusters of symptoms (e.g., cluster analysis or multiple regression), as well as determine their ability to predict clinically significant distress.

Summary/conclusions

The present paper represents the most comprehensive review and analysis of the effects of caffeine abstinence in humans published to date. The purpose of this analysis was to empirically validate specific symptoms and signs, and to appraise important features of the caffeine-withdrawal syndrome.

Of 49 symptom categories and 9 sign categories identified from 57 experimental and 9 retrospective survey studies, the following 10 symptom categories fulfilled methodologically rigorous validity criteria: headache, tiredness/fatigue, decreased energy/activeness, decreased alertness/attentiveness, drowsiness/sleepiness, decreased contentedness/well-being, depressed mood, difficulty concentrating, irritability, and muzzy/foggy/not clearheaded. In addition, flu-like symptoms, nausea/vomiting, and muscle pain/stiffness were judged likely to represent valid symptom categories. The percentage of subjects reporting headache was 50% in experimental studies and 24% in retrospective survey studies. The percentage of subjects reporting clinically significant distress or functional impairment was 13% in prospective experimental studies and 9% in retrospective survey studies.

Data supporting the following 13 symptom and sign categories were judged as suggestive and in need of further research: decreased desire to socialize, unmotivated for work, decreased self-confidence, total mood disturbance (POMS), yawning, heavy feelings in arms and legs, increased nighttime sleep quality/duration, analgesic use, craving/strong desire to use, impaired behavioral and cognitive performance (objectively measured), decreased motor activity (objectively measured), increased cerebral blood flow, and EEG changes.

Onset of withdrawal symptoms typically occurs 12–24 h after abstinence, with peak intensity occurring at 20–51 h, and duration of withdrawal ranging between 2 days and 9 days. Re-administration of caffeine rapidly and often completely reverses withdrawal. The incidence or severity of symptoms increases with increases in the chronic daily maintenance dose. Symptoms may occur upon abstinence from chronic caffeine exposure at doses as low as 100 mg/day, and upon abstinence following only 3–7 days of caffeine exposure at higher doses. There is good evidence that avoidance of withdrawal symptoms plays a central role in the habitual consumption of caffeine by increasing the reinforcing effects of caffeine and preference for tastes paired with caffeine. Overall, the evidence that caffeine withdrawal is pharmacologically based is overwhelming, and analysis of the published data does not support the hypothesis that expectancies are a primary determinant of caffeine-withdrawal symptoms.

In addition to the previously discussed research priorities concerning the DSM-IV diagnosis of caffeine withdrawal, future studies should determine the validity of the symptom and sign categories identified above as in need of further research, and investigate how vulnerability to caffeine withdrawal is affected by gender, drug abuse histories, caffeine metabolism, genetics, behavioral conditioning, personality, and other factors. It would be valuable if future reports of research on caffeine withdrawal provided individual subject data in addition to the usual group data to provide further information about individual differences in severity of the withdrawal syndrome. Future research should provide more detailed information about the time course (i.e., onset, duration, and offset) of individual withdrawal symptoms. Furthermore, the impact of gradual reduction of caffeine on withdrawal symptoms should be characterized. Although tolerance and withdrawal are thought to be functionally related phenomena, no research has investigated the relationship between the extent of caffeine tolerance and magnitude of withdrawal. Finally given the high rate of caffeine use in children, caffeine withdrawal in children deserves much more systematic study (Goldstein and Wallace 1997; Bernstein et al. 1998).

In conclusion, although descriptions in the medical literature of the caffeine-withdrawal syndrome date back more than 170 years, a solid empirical parametric analysis of the phenomenon has only begun to emerge in recent years. Arguably, the caffeine-withdrawal syndrome has been more rigorously and completely characterized than withdrawal from any other drug and can now serve as a model system for evaluating drug withdrawal phenomena. Despite this progress, we can anticipate that future research with caffeine will provide further valuable insights into the world's most widely consumed mood-altering drug, as well as insights into drug withdrawal effects more generally.

Acknowledgements Preparation of this manuscript was supported, in part, by National Institute on Drug Abuse grant R01 DA03890. Roland Griffiths has been a consultant to pharmaceutical companies, International Food Information Counsel, International Life Sciences Institute, and the legal profession on issues related to caffeine effects, withdrawal, and dependence. The authors thank Kristen McCausland and Kimberly Mudd for their assistance with data management.

Appendix A—Studies that did not statistically document symptom or sign

Symptom or sign	Studies[a]
Alertness/attentiveness	10, 14, 16, 22, 23, 28, 38, 46, 55
Anger/hostility	4, 6, 9, 10, 15, 18, 22, 25, 26, 27, 28, 33, 34, 35, 36, 37, 46, 55
Anxiety/nervousness	4, 5, 6, 10, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29, 33, 34, 35, 36, 37, 41, 44, 45, 46, 55, 56
Blood pressure	3, 13, 38, 43, 44, 45, 54
Blurred vision	5, 19, 21, 25, 26, 37, 46, 55, 56
Calm/relaxed[b]	16, 17, 18, 21, 27, 31, 39
Chills	21
Circular lights task[b]	4
Confusion–bewilderment	4, 5, 10, 15, 17, 18, 21, 25, 28, 33, 35, 36, 37, 46, 55
Constipation[b]	5, 6
Contentedness/well-being	4, 10, 14, 15, 20, 27, 28, 29, 37, 39, 46
Depression	2, 4, 10, 18, 19, 20, 21, 22, 23, 24, 25, 28, 29, 33, 34, 35, 36, 37, 46, 55
Desire to socialize	15, 18, 19, 21, 23, 24, 25, 26, 27, 28, 29, 35, 36
Diaphoresis	5, 6, 9, 14, 15, 19, 20, 21, 22, 23, 24, 25, 26, 37, 46, 55, 56
Diarrhea[b]	5, 6, 14, 15, 22, 23, 24
Difficulty sleeping/insomnia[b]	9, 14, 15, 19, 21, 22, 23, 24, 46, 55
Difficulty concentrating	21, 25, 28, 46
Digit symbol substitution task	9, 14, 15, 20, 21, 22, 28, 37, 55
Divided attention[b]	21
Drowsiness/sleepiness	5, 10, 18, 22, 25, 37
Energy/activeness	10, 14, 16, 17, 25, 36, 42, 46
Flu-like symptoms	19, 21, 26, 28, 35, 37, 46, 56
Frequent urination[b]	9, 14, 15, 19, 22, 23, 24, 25, 26, 37, 46, 55, 56
Grammatical/logical reasoning[b]	28, 55
Hand tremor (objectively measured)[b]	14, 15, 17, 20, 22, 23, 24
Headache	14, 19, 22, 24, 26, 28, 29, 31, 37, 40, 41
Heart pounding/palpitations	9, 14, 15, 19, 20, 21, 22, 23, 24, 25, 26, 37, 46, 55, 56
Heart rate	3, 13, 19, 38, 43, 45, 54, 55
Heavy feelings in arms and legs	19, 21, 25, 26, 56
Hot and cold spells	19, 25, 26, 37, 46, 55
Hunger/appetite[b]	17, 18, 20, 21, 22, 23, 24, 29, 31, 42
Irregular heartbeat	14, 15, 22, 23, 24
Irritability	4, 10, 14, 15, 16, 20, 21, 23, 24, 25, 28, 29, 37, 46, 55
Jittery/shaky[b]	5, 6, 9, 28, 31, 37, 40, 41, 42, 46, 55
Lightheaded/dizzy	5, 9, 14, 15, 19, 20, 21, 22, 23, 24, 25, 26, 37, 46, 56
Limb tremor[b]	5, 6, 9, 19, 25, 26, 37, 46, 55, 56
Loss of sex drive[b]	9, 19, 25, 26, 37, 46, 55, 56
Memory/recall[b]	9, 21, 28, 37
Muscle cramps[b]	9, 19, 25, 26, 37, 46, 55, 56
Muscle pain/stiffness	9, 19, 20, 21, 25, 26, 37, 44, 46, 55, 56
Muscle twitches[b]	14, 15, 22, 23, 24
Muzzy/foggy/not clear-headed	5, 8, 19, 25, 26, 28, 29, 31, 37, 42, 46
Nausea/vomiting/upset stomach	2, 4, 5, 6, 9, 10, 14, 15, 19, 20, 21, 25, 26, 37, 45, 46, 55, 56
Numbing or tingling in extremities	21
Numerical Stroop task[b]	9
Problem solving tasks	19
Reaction time	9, 17, 28, 41, 55
Restless[b]	21, 22, 23, 24
Rhinorrhea	5, 6, 9, 19, 21, 25, 26, 37, 46, 55, 56
Ringing in ears[b]	14, 15, 22, 23, 24
Self-confidence	17, 18, 19, 22, 25, 26, 29, 37, 55, 56
Shaky/weakness[b]	22, 23, 24
Symbol copy test[b]	20
Tapping speed	17, 20, 28, 29, 55
Thirst/thirsty[b]	17, 18, 29, 31, 42
Tiredness/fatigue	10, 22, 27, 31, 37, 42
Total mood disturbance	10, 25, 33, 37, 41, 46
Unmotivated for work	14, 19, 25, 26, 28, 37, 46, 55
Urinary epinephrine or norepinephrine	3
Yawning	5, 25, 26, 37, 46
Visual vigilance	20, 21

[a]Numbers in table refer to the entry number in Tables 1 and 2[b]Symptom or sign was not documented in any study

References

Adams D, Ditzler T, Haning WF (1993) Primary caffeine dependence: a case report. Hawaii Med J 52:190–191 (see also page 194)

Alsene K, Deckert J, Sand P, de Wit H (2003) Association between A2a receptor gene polymorphisms and caffeine-induced anxiety. Neuropsychopharmacology 28:1694–1702

American Psychiatric Association (1987) Diagnostic and statistical manual of mental disorders, 3rd edn. American Psychiatric Association, Washington (revised)

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Washington

American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Washington (text revision)

Ammon HP, Bieck PR, Mandalaz D, Verspohl EJ (1983) Adaptation of blood pressure to continuous heavy coffee drinking in young volunteers: a double-blind crossover study. Br J Clin Pharmacol 15:701–706

Barone JJ, Roberts HR (1996) Caffeine consumption. Food Chem Toxicol 34:119–129

Bernstein GA, Carroll ME, Dean NW, Crosby RD, Perwien AR, Benowitz NL (1998) Caffeine withdrawal in normal school-age children. J Am Acad Child Adolesc Psychiatry 37:858–865

Bernstein GA, Carroll ME, Thuras PD, Cosgrove KP, Roth ME (2002) Caffeine dependence in teenagers. Drug Alcohol Depend 66:1–6

Bigal ME, Sheftell FD, Rapoport AM, Tepper SJ, Lipton RB (2002) Chronic daily headache: identification of factors associated with induction and transformation. Headache 42:575–581

Brauer LH, Buican B, de Wit H (1994) Effects of caffeine deprivation on taste and mood. Behav Pharmacol 5:111–118

Brice CF, Smith AP (2002) Effects of caffeine on mood and performance: a study of realistic consumption. Psychopharmacology (Berl) 164:188–192

Bridge N (1893) Coffee-drinking as a frequent cause of disease. Trans Assoc Am Physicians 8:281–288

Bruce M, Scott N, Lader M, Marks V (1986) The psychopharmacological and electrophysiological effects of single doses of caffeine in healthy human subjects. Br J Clin Pharmacol 22:81–87

Bruce M, Scott N, Shine P, Lader M (1991) Caffeine withdrawal: a contrast of withdrawal symptoms in normal subjects who have abstained from caffeine for 24 hours and for 7 days. J Psychopharmacol 5:129–134

Cacciatore R, Helbling A, Jost C, Hess B (1996) Episodic headache, diminished performance and depressive mood. Schweiz Rundsch Med Prax 85:727–729

Cobbs LW (1982) Lethargy, anxiety, and impotence in a diabetic. Hosp Pract (Off Ed) 17:67 (see also pages 70 and 73)

Comer SD, Haney M, Foltin RW, Fischman MW (1997) Effects of caffeine withdrawal on humans living in a residential laboratory. Exp Clin Psychopharmacol 5:399–403

Couturier EG, Laman DM, van Duijn MA, van Duijn H (1997) Influence of caffeine and caffeine withdrawal on headache and cerebral blood flow velocities. Cephalalgia 17:188–190

Denaro CP, Benowitz NL (1991) Caffeine metabolism: disposition in liver disease and hepatic-function testing. In: Watson RR (ed) Drug and alcohol abuse reviews. Liver pathology and alcohol, vol 2. The Human, Totowa, pp 513–539

Dews PB, Curtis GL, Hanford KJ, O'Brien CP (1999) The frequency of caffeine withdrawal in a population-based survey and in a controlled, blinded pilot experiment. J Clin Pharmacol 39:1221–1232

Dews PB, O'Brien CP, Bergman J (2002) Caffeine: behavioral effects of withdrawal and related issues. Food Chem Toxicol 40:1257–1261

Driesbach RH, Pfeiffer C (1943) Caffeine-withdrawal headache. J Lab Clin Med 28:1212–1219

Dusseldorp M van, Katan MB (1990) Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial. BMJ 300:1558–1559

Edelstein BA, Keaton-Brasted C, Burg MM (1983) The effects of caffeine withdrawal on cardiovascular and gastrointestinal responses. Health Psychol 2:343–352

Evans SM, Griffiths RR (1992) Caffeine tolerance and choice in humans. Psychopharmacology (Berl) 108:51–59

Evans SM, Griffiths RR (1999) Caffeine withdrawal: a parametric analysis of caffeine dosing conditions. J Pharmacol Exp Ther 289:285–294

Evans SM, Critchfield TS, Griffiths RR (1994) Caffeine reinforcement demonstrated in a majority of moderate caffeine users. Behav Pharmacol 5:231–238

Feinstein AR, Heinemann LA, Dalessio D, Fox JM, Goldstein J, Haag G, Ladewig D, O'Brien CP (2000) Do caffeine-containing analgesics promote dependence? a review and evaluation. Clin Pharmacol Ther 68:457–467

Fennelly M, Galletly DC, Purdie GI (1991) Is caffeine withdrawal the mechanism of postoperative headache? Anesth Analg 72:449–453

Field AS, Laurienti PJ, Yen YF, Burdette JH, Moody DM (2003) Dietary caffeine consumption and withdrawal: confounding variables in quantitative cerebral perfusion studies? Radiology 227:129–135

Fillmore MT (1994) Investigating the behavioral effects of caffeine: the contribution of drug-related expectancies. Pharmacopsychoecologia 7:63–73

Fredholm BB, Bättig K, Holmen J, Nehlig A, Zvartau EE (1999) Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol Rev 51:83–133

Galletly DC, Fennelly M, Whitwam JG (1989) Does caffeine withdrawal contribute to postanaesthetic morbidity? Lancet 1:1335

Garrett BE, Griffiths RR (1998) Physical dependence increases the relative reinforcing effects of caffeine versus placebo. Psychopharmacology (Berl) 139:195–202

Gibson CJ (1981) Caffeine withdrawal elevates urinary MHPG excretion. N Engl J Med 304:363

Gilbert RJ (1986) Caffeine, the most popular stimulant. Chelsea House, New York

Gilbert RM (1984) Caffeine consumption. In: Spiller GA (ed) The methylxanthine beverages and foods: chemistry, consumption, and health effects. Alan R. Liss, New York, pp 185–213

Goldstein A (1964) Wakefulness caused by caffeine. Arch Exp Pathol Pharmakol 248:269–278

Goldstein A, Kaizer S (1969) Psychotropic effects of caffeine in man. III. A questionnaire survey of coffee drinking and its effects in a group of housewives. Clin Pharmacol Ther 10:477–488

Goldstein A, Wallace ME (1997) Caffeine dependence in schoolchildren? Exp Clin Psychopharmacol 5:388–392

Goldstein A, Kaizer S, Whitby O (1969) Psychotropic effects of caffeine in man. IV. Quantitative and qualitative differences associated with habituation to coffee. Clin Pharmacol Ther 10:489–497

Greden JF (1974) Anxiety or caffeinism: a diagnostic dilemma. Am J Psychiatry 131:1089–1092

Greden JF, Fontaine P, Lubetsky M, Chamberlin K (1978) Anxiety and depression associated with caffeinism among psychiatric inpatients. Am J Psychiatry 135:963–966

Greden JF, Victor BS, Fontaine P, Lubetsky M (1980) Caffeine-withdrawal headache: a clinical profile. Psychosomatics 21:411–413 (see also pages 417 and 418)

Griffiths RR, Mumford GK (1996) Caffeine reinforcement, discrimination, tolerance, and physical dependence in laboratory animals and humans. In: Schuster CR, Kuhar MJ (eds) Pharmacological aspects of drug dependence: toward an integrated neurobehavioral approach (Handbook of Experimental Pharmacology). Springer, Berlin Heidelberg New York, pp 315–341

Griffiths RR, Woodson PP (1988) Caffeine physical dependence: a review of human and laboratory animal studies. Psychopharmacology (Berl) 94:437–451

Griffiths RR, Bigelow GE, Liebson IA (1986) Human coffee drinking: reinforcing and physical dependence producing effects of caffeine. J Pharmacol Exp Ther 239:416–425

Griffiths RR, Evans SM, Heishman SJ, Preston KL, Sannerud CA, Wolf B, Woodson PP (1990) Low-dose caffeine physical dependence in humans. J Pharmacol Exp Ther 255:1123–1132

Griffiths RR, Juliano LM, Chausmer AL (2003) Caffeine pharmacology and clinical effects. In: Graham AW, Schultz TK, Mayo-Smith M, Ries RK, Wilford BB (eds) Principles of addiction medicine, 3rd edn. American Society of Addiction Medicine, Chevy Chase, pp 193–224

Hale KL, Hughes JR, Oliveto AH, Higgins ST (1995) Caffeine self-administration and subjective effects in adolescents. Exp Clin Psychopharmacol 3:364–370

Hampl KF, Stotz G, Schneider MC (1994) Postoperative transient hemihypaesthesia and severe headache associated with caffeine withdrawal. Anaesthesia 49:266–267

Hampl KF, Schneider MC, Ruttimann U, Ummenhofer W, Drewe J (1995) Perioperative administration of caffeine tablets for prevention of postoperative headaches. Can J Anaesth 42:789–792

Hindmarch I, Quinlan PT, Moore KL, Parkin C (1998) The effects of black tea and other beverages on aspects of cognition and psychomotor performance. Psychopharmacology (Berl) 139:230–238

Höfer I, Bättig K (1994a) Cardiovascular, behavioral, and subjective effects of caffeine under field conditions. Pharmacol Biochem Behav 48:899–908

Höfer I, Bättig K (1994b) Psychophysiological effects of switching to caffeine tablets or decaffeinated coffee under field conditions. Pharmacopsychoecologia 7:169–177

Horst K, Buxton RE, Robinson WD (1934) The effect of the habitual use of coffee or decaffeinated coffee upon blood pressure and certain motor reactions of normal young men. J Pharmacol Exp Ther 52:322–337

Hughes JR (1994) Caffeine withdrawal, dependence, and abuse. In: American psychiatric association: diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Washington, pp 129–134

Hughes JR, Oliveto AH (1997) A systematic survey of caffeine intake in Vermont. Exp Clin Psychopharmacol 5:393–398
Hughes JR, Higgins ST, Bickel WK, Hunt WK, Fenwick JW, Gulliver SB, Mireault GC (1991) Caffeine self-administration, withdrawal, and adverse effects among coffee drinkers. Arch Gen Psychiatry 48:611–617
Hughes JR, Hunt WK, Higgins ST, Bickel WK, Fenwick JW, Pepper SL (1992) Effect of dose on the ability of caffeine to serve as a reinforcer in humans. Behav Pharmacol 3:211–218
Hughes JR, Oliveto AH, Bickel WK, Higgins ST, Badger GJ (1993) Caffeine self-administration and withdrawal: incidence, individual differences and interrelationships. Drug Alcohol Depend 32:239–246
Hughes JR, Oliveto AH, Bickel WK, Higgins ST, Badger GJ (1995) The ability of low doses of caffeine to serve as reinforcers in humans: A replication. Exp Clin Psychopharmacol 3:358–363
Hughes JR, Oliveto AH, Liguori A, Carpenter J, Howard T (1998) Endorsement of DSM-IV dependence criteria among caffeine users. Drug Alcohol Depend 52:99–107
James JE (1997) Understanding caffeine. Sage, Thousand Oaks
James JE (1998) Acute and chronic effects of caffeine on performance, mood, headache, and sleep. Neuropsychobiology 38:32–41
Jones HE, Herning RI, Cadet JL, Griffiths RR (2000) Caffeine withdrawal increases cerebral blood flow velocity and alters quantitative electroencephalography (EEG) activity. Psychopharmacology (Berl) 147:371–377
Juliano LM, Brandon TH (2002) Effects of nicotine dose, instructional set, and outcome expectancies on the subjective effects of smoking in the presence of a stressor. J Abnorm Psychol 111:88–97
Kendler KS, Prescott CA (1999) Caffeine intake, tolerance, and withdrawal in women: a population-based twin study. Am J Psychiatry 156:223–228
Kenemans JL, Wieleman JS, Zeegers M, Verbaten MN (1999) Caffeine and stroop interference. Pharmacol Biochem Behav 63:589–598
Kingdon (1883) Effects of tea and coffee drinking. Lancet II:47–48
Lader M, Cardwell C, Shine P, Scott N (1996) Caffeine withdrawal symptoms and rate of metabolism. J Psychopharmacol 10:110–118
Lane JD (1994) Neuroendocrine responses to caffeine in the work environment. Psychosom Med 56:267–270
Lane JD (1997) Effects of brief caffeinated-beverage deprivation on mood, symptoms, and psychomotor performance. Pharmacol Biochem Behav 58:203–208
Lane JD, Phillips-Bute BG (1998) Caffeine deprivation affects vigilance performance and mood. Physiol Behav 65:171–175
Lieberman HR, Wurtman RJ, Emde GG, Coviella IL (1987) The effects of caffeine and aspirin on mood and performance. J Clin Psychopharmacol 7:315–320
Liguori A, Hughes JR (1997) Caffeine self-administration in humans: 2. A within-subjects comparison of coffee and cola vehicles. Exp Clin Psychopharmacol 5:295–303
Liguori A, Hughes JR, Grass JA (1997a) Absorption and subjective effects of caffeine from coffee, cola and capsules. Pharmacol Biochem Behav 58:721–726
Liguori A, Hughes JR, Oliveto AH (1997b) Caffeine self-administration in humans: 1. Efficacy of cola vehicle. Exp Clin Psychopharmacol 5:286–294
Mackenzie TB, Popkin MK, Dziubinski J, Sheppard JR (1981) Effects of caffeine withdrawal on isoproterenol-stimulated cyclic adenosine monophosphate. Clin Pharmacol Ther 30:436–438
Marlatt GA, Rohsenow DJ (1980) Cognitive processes in alcohol use: expectancy and the balanced placebo design. In: Mello NK (ed) Advances in substance abuse: behavioral and biological research. JAI, Greenwich, pp 159–199
Martin WR (1977) Drug addiction I: morphine, sedative/hypnotic and alcohol dependence. Springer, New York Berlin Heidelberg
Mathew RJ, Wilson WH (1985) Caffeine consumption, withdrawal and cerebral blood flow. Headache 25:305–309
McGowan JD, Altman RE, Kanto WP (1988) Neonatal withdrawal symptoms after chronic maternal ingestion of caffeine. South Med J 81:1092–1094
Mitchell SH, de Wit H, Zacny JP (1995) Caffeine withdrawal symptoms and self-administration following caffeine deprivation. Pharmacol Biochem Behav 51:941–945
Mumford GK, Benowitz NL, Evans SM, Kaminski BJ, Preston KL, Sannerud CA, Silverman K, Griffiths RR (1996) Absorption rate of methylxanthines following capsules, cola and chocolate. Eur J Clin Pharmacol 51:319–325
Naismith DJ, Akinyanju PA, Szanto S, Yudkin J (1970) The effect, in volunteers, of coffee and decaffeinated coffee on blood glucose, insulin, plasma lipids and some factors involved in blood clotting. Nutr Metab 12:144–151
Nehlig A (1999) Are we dependent upon coffee and caffeine? A review on human and animal data. Neurosci Biobehav Rev 23:563–576
Nikolajsen L, Larsen KM, Kierkegaard O (1994) Effect of previous frequency of headache, duration of fasting and caffeine abstinence on perioperative headache. Br J Anaesth 72:295–297
Oberstar JV, Bernstein GA, Thuras PD (2002) Caffeine use and dependence in adolescents: one-year follow-up. J Child Adolesc Psychopharmacol 12:127–135
Oliveto AH, Hughes JR, Higgins ST, Bickel WK, Pepper SL, Shea PJ, Fenwick JW (1992a) Forced-choice versus free-choice procedures: caffeine self-administration in humans. Psychopharmacology (Berl) 109:85–91
Oliveto AH, Hughes JR, Pepper SL, Bickel WK, Higgins ST (1992b) Low doses of caffeine can serve as reinforcers in humans. In: Problems of drug dependence, 1990 NIDA research monograph no. 178. U.S. Government Printing Office, Washington, p 442
Patrick G, Reeves RR, Struve FA (1996) Does caffeine cessation increase firing rates of diffuse paroxysmal slowing dysrhythmia? A serendipitous observation. Clin Electroencephalogr 27:78–83
Phillips-Bute BG, Lane JD (1998) Caffeine withdrawal symptoms following brief caffeine deprivation. Physiol Behav 63:35–39
Rainey JT (1985) Headache related to chronic caffeine addiction. Tex Dent J 102:29–30
Reeves RR, Struve FA, Patrick G, Bullen JA (1995) Topographic quantitative EEG measures of alpha and theta power changes during caffeine withdrawal: preliminary findings from normal subjects. Clin Electroencephalogr 26:154–162
Reeves RR, Struve FA, Patrick G (1997) Somatic dysfunction increase during caffeine withdrawal. J Am Osteopath Assoc 97:454–456
Reeves RR, Struve FA, Patrick G (1999) The effects of caffeine withdrawal on cognitive P300 auditory and visual evoked potentials. Clin Electroencephalogr 30:24–27
Reeves RR, Struve FA, Patrick G (2002) Topographic quantitative EEG response to acute caffeine withdrawal: a comprehensive analysis of multiple quantitative variables. Clin Electroencephalogr 33:178–188
Richardson NJ, Rogers PJ, Elliman NA, O'Dell RJ (1995) Mood and performance effects of caffeine in relation to acute and chronic caffeine deprivation. Pharmacol Biochem Behav 52:313–320
Rippere V (1984) Some varieties of food intolerance in psychiatric patients: an overview. Nutr Health 3:125–136
Rizzo AA, Stamps LE, Fehr LA (1988) Effects of caffeine withdrawal on motor performance and heart rate changes. Int J Psychophysiol 6:9–14
Robelin M, Rogers PJ (1998) Mood and psychomotor performance effects of the first, but not of subsequent, cup-of-coffee equivalent doses of caffeine consumed after overnight caffeine abstinence. Behav Pharmacol 9:611–618
Robertson D, Wade D, Workman R, Woosley RL, Oates JA (1981) Tolerance to the humoral and hemodynamic effects of caffeine in man. J Clin Invest 67:1111–1117

Rogers PJ, Richardson NJ, Elliman NA (1995) Overnight caffeine abstinence and negative reinforcement of preference for caffeine-containing drinks. Psychopharmacology (Berl) 120:457–462
Rogers PJ, Martin J, Smith C, Heatherley SV, Smit HJ (2003) Absence of reinforcing, mood and psychomotor performance effects of caffeine in habitual non-consumers of caffeine. Psychopharmacology (Berl) 167:54–62
Roller L (1981) Caffeinism: subjective quantitative aspect of withdrawal syndrome. Med J Aust 1:146
Rubin GJ, Smith AP (1999) Caffeine withdrawal and headaches. Nutr Neurosci 2:123–126
Schuh KJ, Griffiths RR (1997) Caffeine reinforcement: the role of withdrawal. Psychopharmacology (Berl) 130:320–326
Silverman K, Evans SM, Strain EC, Griffiths RR (1992) Withdrawal syndrome after the double-blind cessation of caffeine consumption. N Engl J Med 327:1109–1114
Sjaastad O, Bakketeig LS (2004) Caffeine-withdrawal headache: the Vaga study of headache epidemiology. Cephalalgia 24:241–249
Smit HJ, Rogers PJ (2000) Effects of low doses of caffeine on cognitive performance, mood and thirst in low and higher caffeine consumers. Psychopharmacology (Berl) 152:167–173
Smith AP (1996) Caffeine dependence: an alternative view. Nat Med 2:494
Smith R (1987) Caffeine withdrawal headache. J Clin Pharm Ther 12:53–57
Strain EC, Griffiths RR (1998) Characteristics of patients with chronic use of OTC analgesics containing caffeine. In: Problems of drug dependence, 1997 NIDA research monograph no. 178. U.S. Government Printing Office, Washington, p 286
Strain EC, Mumford GK, Silverman K, Griffiths RR (1994) Caffeine dependence syndrome. Evidence from case histories and experimental evaluations. J Am Med Assoc 272:1043–1048
Streufert S, Pogash R, Miller J, Gingrich D, Landis R, Lonardi L, Severs W, Roache JD (1995) Effects of caffeine deprivation on complex human functioning. Psychopharmacology (Berl) 118:377–384
Stringer KA, Watson WA (1987) Caffeine withdrawal symptoms. Am J Emerg Med 5:469
Swerdlow NR, Eastvold A, Gerbranda T, Uyan KM, Hartman P, Doan Q, Auerbach P (2000) Effects of caffeine on sensorimotor gating of the startle reflex in normal control subjects: impact of caffeine intake and withdrawal. Psychopharmacology (Berl) 151:368–378
Thomas DB (1988) Neonatal abstinence syndrome. Med J Aust 148:598
Tinley EM, Yeomans MR, Durlach PJ (2003) Caffeine reinforces flavour preference in caffeine-dependent, but not long-term withdrawn, caffeine consumers. Psychopharmacology (Berl) 166:416–423
Van Soeren MH, Graham TE (1998) Effect of caffeine on metabolism, exercise endurance, and catecholamine responses after withdrawal. J Appl Physiol 85:1493–1501
Verhoeff FH, Millar JM (1990) Does caffeine contribute to postoperative morbidity? Lancet 336:632
Victor BS, Lubetsky M, Greden JF (1981) Somatic manifestations of caffeinism. J Clin Psychiatry 42:185–188
Watson JM, Lunt MJ, Morris S, Weiss MJ, Hussey D, Kerr D (2000) Reversal of caffeine withdrawal by ingestion of a soft beverage. Pharmacol Biochem Behav 66:15–18
Weber JG, Ereth MH, Danielson DR (1993) Perioperative ingestion of caffeine and postoperative headache. Mayo Clin Proc 68:842–845
Weddington WW, Brown BS, Haertzen CA, Cone EJ, Dax EM, Herning RI, Michaelson BS (1990) Changes in mood, craving, and sleep during short-term abstinence reported by male cocaine addicts. A controlled, residential study. Arch Gen Psychiatry 47:861–868
Weil A, Rosen W (1993) From chocolate to morphine: everything you need to know about mind-altering drugs. Houghton Mifflin, Boston
Winstead DK (1976) Coffee consumption among psychiatric inpatients. Am J Psychiatry 113:1447–1450
World Health Organization (1992a) The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. World Health Organization, Geneva
World Health Organization (1992b) International statistical classification of diseases and related health problems, 10th revision. World Health Organization, Geneva
World Health Organization (1993) The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research. World Health Organization, Geneva
Yeomans MR, Spetch H, Rogers PJ (1998) Conditioned flavour preference negatively reinforced by caffeine in human volunteers. Psychopharmacology (Berl) 137:401–409
Yeomans MR, Jackson A, Lee MD, Nesic J, Durlach PJ (2000a) Expression of flavour preferences conditioned by caffeine is dependent on caffeine deprivation state. Psychopharmacology (Berl) 150:208–215
Yeomans MR, Jackson A, Lee MD, Steer B, Tinley E, Durlach P, Rogers PJ (2000b) Acquisition and extinction of flavour preferences conditioned by caffeine in humans. Appetite 35:131–141
Yeomans MR, Ripley T, Lee MD, Durlach PJ (2001) No evidence for latent learning of liking for flavours conditioned by caffeine. Psychopharmacology (Berl) 157:172–179
Yeomans MR, Pryke R, Durlach PJ (2002a) Effect of caffeine-deprivation on liking for a non-caffeinated drink. Appetite 39:35–42
Yeomans MR, Ripley T, Davies LH, Rusted JM, Rogers PJ (2002b) Effects of caffeine on performance and mood depend on the level of caffeine abstinence. Psychopharmacology (Berl) 164:241–249