Caffeine Dependence Syndrome

Evidence From Case Histories and Experimental Evaluations

Eric C. Strain, MD; Geoffrey K. Mumford, PhD; Kenneth Silverman, PhD; Roland R. Griffiths, PhD

Objective.—The extent to which daily caffeine use is associated with a substance dependence syndrome similar to that associated with other psychoactive drugs is unknown. The purpose of this study was to assess volunteers who reported problems with their use of caffeine for evidence suggesting a diagnosis of caffeine dependence based on the generic criteria for substance dependence from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*).

Design.—Case-series evaluations.

Setting.—An academic research center.

Participants.—Self-identified adults who believed they were psychologically or physically dependent on caffeine.

Main Outcome Measure.—Diagnoses made by a psychiatrist using a structured clinical interview that included a section on caffeine dependence based on generic criteria for *DSM-IV* substance dependence.

Secondary Outcome Measure.—Double-blind caffeine-withdrawal evaluation.

Results.—Ninety-nine subjects were screened for the study, and 16 were identified as having a diagnosis of caffeine dependence. Median daily caffeine intake was 357 mg, and 19% of subjects consumed less than the national (US) daily average of caffeine. Criteria used for making diagnoses (and rates of their prevalence) were as follows: withdrawal (94%), use continued despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by caffeine use (94%), persistent desire or unsuccessful efforts to cut down or control use (81%), and tolerance (75%). Eleven subjects underwent the double-blind caffeine-withdrawal evaluation portion of the study, and nine (82%) of the 11 showed objective evidence of caffeine withdrawal, including eight of 11 with functional impairment.

Conclusions.—These results, together with other experimental evidence, suggest that caffeine exhibits the features of a typical psychoactive substance of dependence. It is valuable to recognize caffeine dependence as a clinical syndrome, since some people feel compelled to continue caffeine use despite desires and recommendations to the contrary.

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From the Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, Md.

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Reprint requests to Department of Psychiatry, Behavioral Pharmacology Research Unit, The Johns Hopkins University School of Medicine, 5510 Nathan Shock Dr, Baltimore, MD 21224 (Dr Griffiths).

CAFFEINE has been consumed by humans for hundreds if not thousands of years[1] and is currently the most widely used psychoactive substance in the world.[2] Throughout the world, the preferred mode for consuming caffeine occurs in markedly different forms (eg, drinking coffee, tea, maté, soft drinks; chewing kola nuts; consuming cocoa and guarana products) and in widely different, but culturally well-integrated, social contexts (eg, the coffee break in the United States, teatime in the United Kingdom, kola nut chewing in Nigeria). The wide generality of caffeine consumption is also reflected in the high prevalence of its use in the United States, where more than 80% of adults regularly consume behaviorally active doses of caffeine[3,4] and the average daily consumption of caffeine is estimated to be 280 mg per adult consumer.[5]

For editorial comment see p 1065.

Caffeine tends to produce a pattern of subjective effects that varies as a function of dose. Although low doses, in the range of 20 to 200 mg, generally produce mild positive subjective effects (eg, increased feelings of well-being, alertness, energy),[6,7] higher doses, in the range of 200 to 800 mg, can produce negative effects (eg, nervousness, anxiety), especially in volunteers who are usually caffeine abstinent.[8-10] Consistent with the mild positive subjective effects of caffeine observed at low doses, human studies have also shown that caffeine can function as a reinforcer (ie, it maintains self-administration or is preferentially chosen over placebo), and studies in animals have also demonstrated that caffeine can function as a reinforcer under certain experimental conditions.[11] Studies examining the relationship between caffeine and various illnesses (eg, cardiovascular disease, cancer, increased cholesterol concentration, low birth

weight) generally have failed to find evidence suggesting that typical daily doses of caffeine are etiologically related to these conditions or have yielded ambiguous and contradictory results.[12] Thus, the wide use and cultural acceptance of caffeine can be understood in the context of this combination of positive subjective and reinforcing effects with relatively few adverse effects.

While caffeine is consumed by a large segment of the population, it is not known whether some consumers have a pattern of caffeine use that would qualify them for a diagnosis of abuse or dependence as defined by the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*).[13,14] These diagnoses in *DSM-IV* are based on a set of generic criteria, with substance dependence a more severe disorder than abuse. Although physical dependence, as evidenced by a withdrawal syndrome, is sometimes erroneously equated with the diagnosis of dependence, in fact, withdrawal is only one component of the *DSM-IV* diagnosis of dependence. While evidence suggests that abruptly stopping caffeine consumption sometimes produces a distinct clinical syndrome characterized by headache, lethargy, and depression,[11,15,16] the presence of a withdrawal syndrome is only one of the criteria used for a diagnosis of substance dependence, and it is neither necessary nor sufficient for making the diagnosis.

The primary purpose of the current study was to assess volunteers self-identified as being caffeine dependent—that is, reporting problems associated with their use of caffeine—for evidence suggesting a diagnosis of caffeine dependence based on the criteria from *DSM-IV* as applied by a psychiatrist employing a standardized structured interview. A secondary purpose of the study was to subsequently evaluate these volunteers for evidence of caffeine withdrawal. This withdrawal assessment provided a means for objectively testing one of the common, but not necessary, features of dependence. The identification of selected volunteers with problematic caffeine use consistent with a *DSM-IV* diagnosis of substance dependence would provide valuable clinical support for the establishment of a distinct syndrome of caffeine dependence, and would provide an opportunity to assess the clinical features of people with a substance dependence syndrome for caffeine.

METHODS

Subjects

Participants were a self-identified group of adults recruited through newspaper notices that sought study volunteers who believed they were psychologically or physically dependent on caffeine (contained in coffee, tea, soda, or tablets). Subjects were included in the study if they were 18 to 50 years old; had at least a high school diploma or equivalent; had a normal blood pressure, heart rate, and electrocardiogram (ECG); had no physical condition contraindicating the consumption of caffeine (eg, palpitations, arrhythmias); had not used illicit drugs in the past 6 months; were not pregnant; consumed caffeine on a daily basis; and reported problems associated with their caffeine use, based on screening questions derived from the *DSM-III-R* (*Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*[17]) diagnosis of psychoactive substance dependence (criteria as described in the "Diagnostic Interview" section below). The study was approved by the local institutional review board.

Study Procedures

Subjects were initially screened for suitability by telephone, using a questionnaire that reviewed their medical and psychiatric history, including use of alcohol, nicotine, and caffeine, as well as both prescription and illicit drugs. Screening questionnaires were reviewed by one of the investigators (E.C.S), and eligible participants were then requested to come to the research unit for further evaluation. A total of 99 applicants were screened by telephone. Subjects were told they were participating in a study evaluating the effects of food components on mood and behavior. There were two phases to the study, and 27 of the 99 applicants were eligible and willing to participate in the first phase, during which subjects reported to the laboratory on two or more occasions, signed consent, completed a history questionnaire, underwent a physical examination including an ECG and screening blood tests, and completed 1 week of food diaries. They also underwent a standardized psychiatric interview (described below) that included an assessment of caffeine dependence based on *DSM-IV* criteria for substance dependence. Sixteen of the 27 were diagnosed as caffeine dependent. One of these 16 was medically disqualified from further participation because of newly diagnosed hypertension. Eleven of the remaining 15 were willing to participate in the second phase of the study, a double-blind caffeine-withdrawal evaluation that is described below.

Diagnostic Interview

Subjects were interviewed utilizing the Structured Clinical Interview for *DSM-III-R* (SCID),[18] with a modified E-module (that section on psychoactive substance use disorders) that followed the format of the original SCID E-module and included questions regarding caffeine dependence. Interviews were conducted by the same psychiatrist (E.C.S.), and the *DSM-III-R* criteria were coded to allow all diagnoses to be made using *DSM-IV*. Three of seven criteria must be present for a *DSM-IV* diagnosis of substance dependence. While all diagnostic criteria in the modified E-module were probed, only four criteria were considered when making a diagnosis of dependence, and participants were required to fulfill three of these four criteria to qualify for a diagnosis of caffeine dependence. These four criteria were chosen to represent clinically meaningful aspects of pathological use of a substance that is widely available and culturally accepted. The four *DSM-IV* criteria were tolerance (criterion 1); withdrawal (criterion 2); persistent desire or unsuccessful efforts to cut down or control use (criterion 4); and use continued despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by substance use (criterion 7). The remaining three criteria were excluded because of concern that these criteria would trivialize the diagnosis or did not apply to a substance widely available and culturally accepted. The three excluded criteria were substance often taken in larger amounts or over a longer period than intended (criterion 3); a great deal of time spent in activities necessary to obtain, use, or recover from the effects of the substance (criterion 5); and important social, occupational, or recreational activities given up or reduced because of substance use (criterion 6).

Double-Blind Caffeine-Withdrawal Evaluation

In the second phase of the study, participants were required to complete a battery of assessments on three occasions, once as a set of practice tests while following their normal eating patterns, and then again at the end of each of two 2-day study periods. Subjects adhered to a caffeine-free diet during these 2-day periods, which were generally separated by 1 week and occurred on the same weekdays.

To achieve a blind caffeine-free diet, participants were instructed, both verbally and in writing, to maintain certain dietary restrictions during the 2-day study periods and were further instructed that the purpose of these restrictions was to examine the effects on mood and behavior of compounds nor-

Table 1.—Participants With Caffeine Dependence (n=16)*

Subject	Race/ Gender	Age, y	Marital Status	Currently Smoking†	Other Psychiatric Diagnoses‡		Caffeine Intake, mg/d§	Primary Vehicle§	Caffeine Dependence (*DSM-IV* Criterion Numbers)‖
					Past	Present			
502	WM	33	M	Yes	1	None	2548	Coffee	1, 2, 4, 7
506	WF	43	D	No	2, 3	3	231	Soft drink	1, 2, 4, 7
509	WF	44	S	Yes	1, 2	None	642	Coffee	1, 2, 4, 7
517	WF	48	D	Yes	1, 2, 3, 4	None	1038	Coffee	2, 4, 7
525	WF	32	S	No	1	None	1029	Coffee	1, 4, 7¶
531	WM	50	S	No	1, 2, 3	None	302	Soft drink	1, 2, 4, 7
532	WF	33	M	No	None	None	430	Soft drink	2, 4, 7
535	WF	36	M	No	None	None	342	Soft drink	1, 2, 4, 7¶
542	BF	44	S	Yes	1, 3	None	589	Coffee	1, 2, 7
543	WF	31	S	Yes	1	None	295	Coffee	1, 2, 7
544	WF	31	S	No	1, 2, 4	3	371	Soft drink	1, 2, 4
545	WF	21	M	No	None	None	320	Tea	1, 2, 7¶
548	WF	42	M	No	1, 2	None	270	Soft drink	2, 4, 7¶
549	WF	31	S	No	1, 2	None	129	Soft drink	1, 2, 4, 7¶
550	WF	41	M	No	None	None	516	Coffee	2, 4, 7¶
551	BF	42	D	No	None	None	300	Coffee	1, 2, 4, 7¶

**DSM-IV* indicates *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; D, divorced; S, single; and M, married.

†Nicotine dependence is not included in the Structured Clinical Interview for *DSM-III-R* (SCID).[18] Current smoking status was obtained during the medical history.

‡Diagnoses in remission (past) or current (present) based on the SCID interview: 1 indicates substance use disorder; 2, mood disorder; 3, anxiety disorder; and 4, eating disorder.

§Based on the 7-day food diary. The primary vehicle, which was determined from the food diaries, was defined as the substance that accounted for the majority of that subject's caffeine intake.

‖All subjects qualified for a provisional diagnosis of caffeine dependence based on assessment of four generic *DSM-IV* criteria for substance use disorder[13]: 1 indicates tolerance; 2, withdrawal; 4, persistent desire or unsuccessful efforts to cut down or control use; and 7, use continued despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by substance use.

¶Indicates subjects who were advised by their physician to reduce or eliminate caffeine consumption but who failed to do so.

mally found in the foods and beverages of their daily diet. These restrictions were given without reference to caffeine. The only beverages allowed were milk, fruit juices, and water; chocolate products were prohibited. To divert attention from caffeine, food items without caffeine were also restricted, including shellfish and all foods containing saccharin or aspartame (Nutrasweet). Finally, because subjects having withdrawal symptoms might be tempted to take analgesic drugs, subjects were told not to take any medications without first contacting one of the investigators.

During the two 2-day study periods, subjects received capsules containing, in random order, either caffeine in an amount equal to their individual average daily caffeine consumption or placebo. The average daily caffeine consumption was calculated from each subject's food diaries, using standard caffeine amounts contained in the specific food items consumed.[8] Subjects were told that their capsules would contain placebo or one of several compounds (chlorogenic acids, diterpines, caffeine, tannin, sugar, or theophylline) commonly found in foods and beverages. Assessments occurred on the second day of each of the 2-day study periods and occurred a minimum of 3 hours after the administration of the last capsule (usually between 4 PM and 6 PM on the second day).

Placebo (powdered lactose) and caffeine (anhydrous) were administered in opaque, hard, size 0 gelatin capsules under double-blind conditions. On each day of the placebo and caffeine periods, capsule administration times were spaced throughout the day to match the pattern of the individual's reported caffeine consumption. The maximum amount of caffeine in a single capsule was 200 mg, and the maximum dose of caffeine administered at one time was 400 mg (two capsules). Subjects typically ingested capsules at three administration times during the day; as many as seven administration times were used to accommodate the dosing of subjects using very high doses of caffeine. Subjects came to the laboratory for the first administration each day, which was done under observation, and then were given packets of capsules with instructions regarding the timing of subsequent administrations. In addition, participants were given emergency contact cards with investigators' telephone numbers, in case questions or problems arose during the study.

Assessments, which were administered on the second day of each 2-day study period, included the Beck Depression Inventory (BDI), a 21-item questionnaire designed to assess depressive symptoms[19,20]; the Profile of Mood States (POMS), a 65-item questionnaire designed to assess mood states[21]; and the Study Questionnaire, a 33-item checklist that assessed symptoms related to caffeine withdrawal (eg, headache, drowsy/sleepy).[15] The end of the Study Questionnaire included a question regarding the use of any medications during the time of the dietary restrictions. Participants completed the BDI, POMS, and Study Questionnaire based on how they had felt that day and during the previous day. After completing the questionnaires, the subjects completed a tapping task in which they were instructed to press a button 200 times as fast as they could. Three consecutive tapping trials, separated from one another by approximately 10 seconds, were conducted. This task has been shown to be sensitive to the effects of caffeine withdrawal.[15] Subjects were then interviewed by an investigator blind to the order of the study conditions, who reviewed the subjects' experiences during the study period, including any evidence of functional impairment.

Analysis of Salivary Caffeine

Five-milliliter samples of saliva were collected at each laboratory visit during the second phase of the study to assess compliance with the dietary restrictions. Salivary caffeine concentrations were measured as previously described.[7,22] No subjects showed evidence of violation of the dietary restrictions during the 2-day placebo dosing study period.

RESULTS

Results From the Diagnostic Interview

After telephone screening, 27 subjects participated in the first phase of the

Table 2.—Double-Blind Caffeine-Withdrawal Evaluation Results (n=11)*

Subject	Headache	Fatigue (POMS)	Vigor (POMS)	Depression (BDI)	Tapping (Mean)	Analgesic Use	Functional Impairment†
502	0/2	5/28‡	23/1‡	5/16‡	281/201‡	No	Moderate (screaming at his children)
506	1/3‡	16/20	25/12	5/23‡	284/262‡	Yes	Severe (missed work; emesis)
509	2/2	9/5	9/11	4/5	300/283‡	No	None
525	1/3‡	3/23	13/2‡	3/7	421/290‡	No	Severe (multiple costly mistakes at work; left work early; went to bed early)
531	1/3‡	0/4	17/10	8/14	240/259	Yes	Mild (unable to complete schoolwork)
532	0/3‡	1/27‡	30/2‡	5/24‡	294/291	Yes	Severe (canceled son's birthday party; called spouse home early because of inability to care for children)
535	1/3‡	5/13	15/2‡	0/6	377/354‡	Yes	Severe (could not perform work responsibilities, ie, sat in office awake with lights off and head down; went to bed 2 hours early; needed spouse to care for children)
543	0/M	3/2	19/21	0/3	345/346	No	None
544	0/3‡	0/28‡	28/5	2/15‡	303/283‡	No	Severe (data-entry errors at work; went to bed 4.5 hours early; unable to do recreational reading)
548	1/3‡	7/17	13/2‡	11/12	340/391	Yes	Severe (stopped doing errands; spent time napping; failed to do household chores, ie, making child's lunch, preparing for child's school activities; did not exercise)
550	1/0	25/7	4/21	1/0	408/411	No	None

*Withdrawal test data are presented as caffeine score/placebo score.

†*Functional impairment* was defined as a disruption of usual work or social behavior. Descriptions refer to functional impairment during the placebo study periods. One subject (506) also reported severe functional impairment during the caffeine study period (stayed home from work, broke two glasses).

‡Designates scores showing significant caffeine-withdrawal symptoms during the placebo trial: headache (rating of 3 on a scale ranging from 0 [not at all] to 3 [severe] from the Study Questionnaire[15]); fatigue and vigor (2 SD above and below, respectively, the norm for college students on the Profile of Mood States [POMS] questionnaire[21]); depression (15 or above on the Beck Depression Inventory [BDI][20]); tapping (no overlap between three caffeine trials and three placebo trials); and functional impairment (based on the subject's verbal description of changes in work and behaviors). M indicates missing data.

study, which included food diaries and a psychiatric interview. Sixteen of these participants fulfilled criteria for a current diagnosis of caffeine dependence as determined by the SCID (Table 1). The 16 subjects had a mean age of 38 years and a mean of 16 years of education; 14 (88%) were women, and 12 (75%) were employed. Their median daily consumption of caffeine was 357 mg (range, 129 to 2548 mg), and they primarily consumed either coffee or soft drinks (50% and 44% of subjects, respectively). Subjects fulfilled a mean of 3.4 of the four criteria for caffeine dependence: 12 (75%) met criterion 1 (tolerance), 15 (94%) met criterion 2 (withdrawal), 13 (81%) met criterion 4 (persistent desire or unsuccessful efforts to cut down or control use), and 15 (94%) met criterion 7 (use continued despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by substance use). Seven of the subjects fulfilling criterion 7 reported a history of physical conditions such as acne rosacea, pregnancy, palpitations, and gastrointestinal problems that had led physicians to recommend that they reduce or eliminate caffeine consumption; all seven had failed to comply with the physicians' recommendations.

Only two subjects (13%) had an additional current psychiatric diagnosis besides caffeine dependence (Table 1), and both had diagnoses of anxiety disorders. Eleven (69%) of the subjects had a psychiatric diagnosis in remission, most commonly another substance use disorder (either abuse or dependence—10 subjects [63%]), followed by mood disorders (seven subjects [44%]), anxiety disorders (four subjects [25%]), or eating disorders (three subjects [19%]). The most common class of substance use disorders in remission was alcohol; nine subjects (57%) had a diagnosis of alcohol abuse or dependence. The mean length of time in remission per alcohol diagnosis was 9.8 years, and the mean length of time in remission for all substance use disorders was 7.9 years. Besides caffeine, according to the SCID none of the subjects fulfilled diagnostic criteria for any substance use disorder in the year prior to study participation. However, subjects were not assessed for a diagnosis of nicotine dependence, since it is not included in the SCID; five subjects (502, 509, 517, 542, 543) were currently daily cigarette smokers as determined from the medical history (Table 1). These five smokers tended to have a higher mean daily caffeine consumption than the 11 subjects who did not smoke (1022 mg vs 385 mg, respectively).

Results From the Double-Blind Caffeine-Withdrawal Evaluation

Fifteen of the 16 subjects given a diagnosis of caffeine dependence were eligible to participate in the second phase of the study (the double-blind caffeine-withdrawal evaluation, which was identified to subjects as an assessment of compounds commonly found in foods and beverages). One subject was ineligible to participate because of hypertension newly diagnosed during the physical examination; four of the subjects were not willing to participate in the second phase of the study. Results for the 11 subjects who participated in this phase of the study are presented in Table 2. Nine (82%) of the subjects showed evidence of caffeine withdrawal during the placebo period. Seven (64%) of the participants reported maximal ratings of headache (from the Study Questionnaire) during the days on which they received placebo, and seven (64%) showed significant elevations in ratings of fatigue or depression, or decreases in ratings of vigor (from the BDI and POMS). Five subjects (45%) used an analgesic (eg, acetaminophen), although they had been discouraged from doing so. In the interview following the caffeine and placebo periods, eight (73%) of the subjects reported functional impairment in normal daily activities during the placebo (caffeine-withdrawal) period. In contrast, only one subject reported functional impairment during the caffeine period.

COMMENT

This study identified the characteristics of caffeine use in a population of volunteers self-identified as having problems with caffeine, using a structured interview and *DSM-IV* criteria for a diagnosis of substance dependence, and found 16 volunteers with a diagnosis of caffeine dependence. Since evidence of withdrawal is one of the criteria for a diagnosis of dependence (although it is not necessary for the diagnosis), these volunteers were then challenged with a

double-blind caffeine-withdrawal evaluation as a means for objectively testing one aspect of this diagnosis; nine (82%) of the subjects who participated in the challenge phase showed evidence of caffeine withdrawal. These results suggest that caffeine can produce a clinical dependence syndrome similar to those produced by other psychoactive substances.

Participants in this study reported a wide range in daily caffeine consumption, from 129 to 2548 mg per day. The diagnosis of caffeine dependence was not simply related to a high daily dose of caffeine; three subjects with a diagnosis of caffeine dependence had a daily consumption less than the average daily consumption of caffeine in the United States (280 mg per adult consumer[5]). However, this study did not assess caffeine blood levels, and it is known that caffeine elimination (and thus actual caffeine exposure) can vary widely among individuals and can be influenced by factors such as cigarette smoking, pregnancy, and liver disease.[23] Future studies should determine the relationship between a diagnosis of caffeine dependence and actual caffeine exposure.

Over 80% of the subjects fulfilled criteria 2 (withdrawal), 4 (persistent desire or unsuccessful efforts to cut down or control use), or 7 (use continued despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by substance use). In addition, 75% met criterion 1 (tolerance). This profile of criteria demonstrates that the diagnosis of caffeine dependence was not simply the result of participants' awareness of being physically dependent on or tolerant to caffeine (that is, endorsing criteria 1 and 2). The high prevalence of criteria 4 and 7 suggests that the use of caffeine, like use of other psychoactive substances, can be difficult to stop for some people.

Interestingly, the two subjects (543 and 550) who did not show evidence of caffeine withdrawal during the experimental withdrawal phase of the study reported a history of having symptoms of a caffeine-withdrawal syndrome during the SCID interview. Analysis of saliva samples showed both subjects were compliant with the caffeine dietary restrictions. The absence of caffeine withdrawal during the placebo period in these two subjects is consistent with results from a previous study that showed, within an individual, a single episode of experimental caffeine cessation may underestimate that subject's vulnerability to showing withdrawal, since there is considerable within-subject variability in the withdrawal effects produced across repeated episodes of caffeine cessation.[24]

The primary purpose of this study was to determine if there were caffeine consumers who fulfilled the criteria for a diagnosis of caffeine dependence as determined by a standardized psychiatric interview. The inclusion of the caffeine-withdrawal evaluation in this study was an attempt to objectively test one criterion used in the diagnosis of dependence, but evidence of caffeine withdrawal is neither necessary nor sufficient to make a diagnosis of caffeine dependence. The presence of a withdrawal syndrome suggests that a patient is physically dependent on a substance, but the presence of physical dependence (ie, a withdrawal syndrome) does not mean that the person fulfills diagnostic criteria for a dependence syndrome. For example, it is possible for a pattern of substance use to qualify for a diagnosis of substance dependence without evidence of physical dependence—ie, a withdrawal syndrome (eg, hallucinogens, short-term binge alcohol use); it is also possible for substance use to produce a withdrawal syndrome without fulfilling criteria for a diagnosis of substance dependence (eg, chronic opioid use in the treatment of pain). We have previously shown that caffeine withdrawal can occur in consumers of typical daily doses of caffeine,[15] although the relationship between caffeine withdrawal and a diagnosis of caffeine dependence was not determined in that study. The present results suggest that caffeine withdrawal is common in volunteers with a diagnosis of caffeine dependence.

While there were few concurrent psychiatric disorders in this population, there were high rates of past psychiatric disorders (Table 1). The most common psychiatric disorders in remission were other substance use disorders (10 subjects [63%], excluding nicotine dependence), with the most prevalent drug class being alcohol. Nine subjects (57%) had a past diagnosis of alcohol abuse or dependence. In addition, five subjects smoked tobacco cigarettes daily, and four of the five had a past diagnosis of alcohol abuse or dependence. (Subject 509 had a past diagnosis of stimulant dependence.) This tendency for caffeine, alcohol, and nicotine disorders to cluster has been previously reported.[25] While these five subjects from the current study are a limited sample, the finding that almost all these smokers with a diagnosis of caffeine dependence had a history of alcohol abuse or dependence is an intriguing observation that should be further characterized.

Seven subjects had a past diagnosis of a mood disorder, either bipolar disorder (one subject) or major depressive disorder (six subjects), and the mean time in remission for these mood disorders was 5.7 years. This rate of mood disorders (44%) is higher than expected for the general population, as determined by the National Comorbidity Survey.[26] The higher-than-expected rate of mood disorders found in these subjects with a diagnosis of caffeine dependence is similar to earlier findings of an association between one mood disorder (major depression) and the diagnosis of nicotine dependence.[27-29]

The wide use of caffeine, its cultural acceptance, and the absence of significant medical problems associated with its use[12] may lead to questions regarding the need for advancing a formal diagnosis of caffeine dependence analogous to those for other drugs with more clear morbidity (such as alcohol, nicotine, cocaine, and opioids). Establishing the diagnosis of caffeine dependence is not meant to detract from the general concept of substance dependence, but is meant to demonstrate the common features of substance dependence across psychoactive substance classes, and also to serve the clinically useful purpose of identifying people previously unrecognized as having problematic caffeine use. The volunteers for this study reported a variety of problems associated with their caffeine use, including arguments with family members and friends over their use, going to extremes to obtain caffeine-containing products, using them in potentially dangerous situations, and continuing to use them despite being told not to by physicians. Several subjects in the study were interested in learning about how to stop using caffeinated products, since they had been unsuccessful in doing so on their own. Thus, it is valuable to recognize caffeine dependence as a distinct clinical syndrome because there are people who feel compelled to continue to use caffeine, despite a strong desire to the contrary.

This study did not attempt to determine the prevalence of a diagnosis of caffeine dependence. In a survey that used *DSM-III-R* criteria modified to include a diagnosis of caffeine dependence, Hughes et al[4] reported that 17% of 166 respondents fulfilled criteria for moderate or severe caffeine dependence in the past year. Notably, the study by Hughes et al was a telephone survey, restricted to a relatively small epidemiologic sample in Vermont, and used all nine criteria from *DSM-III-R*. The current study was not an attempt to determine the prevalence of a diagnosis of caffeine dependence, it employed a face-to-face standardized psychiatric interview, and it used only four of the seven *DSM-IV* criteria. The more restrictive diagnostic approach used in this study, and the recruitment of partici-

pants self-identified as having problems with caffeine, may have resulted in the set of extreme cases of caffeine dependence reported herein. It would be valuable to determine the prevalence of a diagnosis of caffeine dependence in a large sample of the general population, especially with concurrent assessments for other psychiatric disorders, such as other substance dependence disorders.

CONCLUSION

This study provides clinical evidence supporting a caffeine dependence syndrome similar to substance dependence syndromes for other drugs. Previous studies have shown that subjects can be intoxicated with the excessive use of caffeine and that caffeine can produce a withdrawal syndrome when subjects stop habitual use.[30] The results of this study provide evidence that subjects also can become clinically dependent on caffeine. The recognition of syndromes of intoxication, withdrawal, and dependence suggests that caffeine is like other psychoactive drugs. The identification of a caffeine dependence syndrome suggests several areas deserving further exploration, including investigation of the prevalence of the syndrome, the occurrence of comorbid disorders, and the behavioral and physiological factors that may potentiate the development of caffeine dependence. In addition to providing valuable data about the descriptive features and clinical importance of caffeine dependence, further characterization of the dependence syndrome of the most widely used psychoactive drug in the world may also serve as a useful model for understanding the dependence syndromes of other drugs.

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