

Caffeine Use Disorder: A Comprehensive Review and Research Agenda

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Caffeine is the most commonly used drug in the world. Although consumption of low to moderate doses of caffeine is generally safe, an increasing number of clinical studies are showing that some caffeine users become dependent on the drug and are unable to reduce consumption despite knowledge of recurrent health problems associated with continued use. Thus, the World Health Organization and some health care professionals recognize caffeine dependence as a clinical disorder. In this comprehensive literature review, we summarize published research on the biological evidence for caffeine dependence; we provide a systematic review of the prevalence of caffeine dependence and rates of endorsement of clinically meaningful indicators of distress and functional impairment among habitual caffeine users; we discuss the diagnostic criteria for Caffeine Use Disorder—a condition for further study included in the *Diagnostic and Statistical Manual of Mental Disorders (5th ed.)*; and we outline a research agenda to help guide future clinical, epidemiological, and genetic investigations of caffeine dependence. Numerous controlled laboratory investigations reviewed in this article show that caffeine produces behavioral and physiological effects similar to other drugs of dependence. Moreover, several recent clinical studies indicate that caffeine dependence is a clinically meaningful disorder that affects a nontrivial proportion of caffeine users. Nevertheless, more research is needed to determine the reliability, validity, and prevalence of this clinically important health problem.

Introduction

CAFFEINE IS THE MOST widely used drug in the world.¹ In the United States, more than 90% of adults use it regularly, and, among them, average consumption is more than 200 mg of caffeine per day²—more caffeine than is contained in two 6-ounce cups of coffee or five 12-ounce cans of soft drinks.^{3,4} Although consumption of low to moderate doses of caffeine is generally safe, consumption of higher doses by vulnerable individuals can lead to increased risk for negative health consequences, including cardiovascular problems and perinatal complications.^{5,6} Moreover, a number of recent studies show that some caffeine users become addicted to or dependent on caffeine.^{7–23} Many of these individuals are unable to reduce consumption despite knowledge of recurrent health problems associated with continued caffeine use.^{17,20,21}

We begin the present review by providing a brief statement about caffeine dependence nomenclature and summarizing the published literature on the biological evidence for caffeine

dependence. We then discuss the diagnostic criteria for Caffeine Use Disorder, a condition for further study recently published in the *Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5)*.²⁴ We also provide a systematic review of the clinical evidence for Caffeine Use Disorder and rates of endorsement of the DSM-5 diagnostic criteria for this research diagnosis. Finally, because this diagnosis is intended to stimulate a further study of Caffeine Use Disorder, we conclude the article with a discussion of future research directions.

Nomenclature

For the purposes of this review, the terms used to describe an individual's inability to control caffeine use despite negative physical or psychological consequences associated with continued use (i.e., caffeine dependence, Caffeine Dependence Syndrome, Caffeine Use Disorder, and caffeine addiction) will be used interchangeably, with preference given to

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the term, “caffeine dependence,” because this term has been used most frequently in the published literature to date. Terms that refer to specific mental or behavioral diagnoses (e.g., Caffeine Dependence Syndrome, Caffeine Use Disorder, and Substance Use Disorder) as defined by health care organizations (i.e., World Health Organization and American Psychiatric Association) will be capitalized.

Overview of Biological Evidence for Caffeine Dependence

Neuropharmacology

Caffeine acts as an antagonist at adenosine receptors, thereby blocking endogenous adenosine.^{25,26} Functionally, caffeine produces a range of effects opposite those of adenosine, including the behavioral stimulant effects associated with the drug.²⁷ Importantly, caffeine has been shown to stimulate dopaminergic activity by removing the negative modulatory effects of adenosine at dopamine receptors.²⁸ Studies suggest that dopamine release in the nucleus accumbens shell may be a specific neuropharmacological mechanism underlying the addictive potential of caffeine.^{29–32} Notably, dopamine release in this brain region is also caused by other drugs of dependence, including amphetamines and cocaine.^{33,34} In addition to the direct effects of caffeine on adenosine receptors, a recent study has shown that paraxanthine, the primary metabolite of caffeine in humans, produces increased locomotor activity, as well as increases in extracellular levels of dopamine through a phosphodiesterase inhibitory mechanism.³⁵

Up-regulation of the adenosine system after chronic caffeine administration appears to be a neurochemical mechanism underlying caffeine withdrawal syndrome.³⁶ This mechanism results in increased functional sensitivity to adenosine during caffeine abstinence, and it likely plays an important role in the behavioral and physiological effects produced by caffeine withdrawal.

Behavioral pharmacology

Subjective effects. Low to moderate doses of caffeine have been shown to increase self-reported liking of the drug³⁷ as well as other positive subjective effects,^{38,39} including increased well-being, energy, alertness, and sociability—drug effects that are qualitatively similar to some of the positive subjective effects produced by other stimulants (e.g., *d*-amphetamine and cocaine). Although the positive subjective effects of caffeine occur among nonhabitual users and those on caffeine-free diets, these effects are enhanced by physical dependence, likely due to suppression of withdrawal symptoms.⁴

Reinforcement. Reinforcement is an essential behavioral mechanism that influences rates of operant behavior, including drug use. A drug is said to function as a reinforcer when drug administration increases the future likelihood of drug use (e.g., increased drug self-administration or increased choice of drug over placebo). Low to moderate doses of caffeine have been shown to function as reinforcers in both human and nonhuman animal subjects.^{36,40,41} Although there is variability across subjects, human studies show that many individuals reliably choose caffeine compared with placebo. Moreover, research has shown that caffeine is more likely to function as a reinforcer among individuals with a

history of heavy caffeine use,²⁷ and avoidance of caffeine withdrawal has been shown to play a central role in the reinforcing effects of caffeine in habitual users.^{42–47} As might be expected, caffeine reinforcement has been shown to covary with the positive subjective effects of the drug. Individuals who choose caffeine tend to report positive subjective effects after drug administration, while those who do not choose caffeine tend to report more negative subjective effects.^{38,43}

Conditioned taste preference. When a reinforcer is repeatedly paired with a neutral stimulus, this stimulus can also acquire reinforcing properties by virtue of respondent (i.e., Pavlovian) conditioning. Thus, in studies using a conditioned flavor preference paradigm, caffeine can engender a preference for a novel flavored beverage when the drug is repeatedly paired with that flavor.^{48–51} For example, ratings of how much individuals like a novel flavored beverage significantly increase when the beverage is paired with caffeine; while ratings for the beverage decrease when it is paired with a placebo.⁵² Suppression of withdrawal symptoms plays a primary role in the development of caffeine flavor preferences,^{51,53,54} and it seems likely that these conditioned taste preferences play an important role in the development of strong consumer preferences for specific types and brands of caffeinated beverages.⁴

Withdrawal. Caffeine withdrawal refers to a time-limited syndrome that develops after cessation of chronic (e.g., daily) caffeine administration. Caffeine withdrawal has been shown to occur in a range of nonhuman animal species,⁴⁰ and a clearly defined caffeine withdrawal syndrome has also been well documented in humans.^{17,55} Common symptoms include headache, fatigue, difficulty concentrating, and dysphoric mood.^{55,56} Low doses of caffeine have been shown to suppress these symptoms.⁵⁷

Tolerance. Tolerance to caffeine occurs when the physiological, behavioral, and/or subjective effects of caffeine decrease after repeated exposure to the drug, such that the same dose of caffeine no longer produces equivalent effects, or a higher dose of caffeine is needed to produce similar effects. Caffeine tolerance has been demonstrated among several nonhuman animal species (e.g., mice, rats, and monkeys), using a range of behavioral measures (e.g., locomotor activity, seizure, and drug discrimination).²⁷ Tolerance has also been reliably demonstrated in humans. For example, a number of studies have shown tolerance to the subjective effects of caffeine,³⁸ as well as to the drug’s sleep disruptive effects,⁵⁸ and several other physiological effects, including diuresis, oxygen consumption, and blood pressure.⁵⁹ Although complete tolerance does not occur at low doses, tolerance to some of the effects of caffeine can occur after chronic administration of very high doses of the drug (i.e., 750–1200 mg/day).⁴

Genetics

As with other drug dependencies, caffeine dependence appears to be influenced, in part, by genotype. Studies comparing human monozygotic and dizygotic twins have shown heritabilities of caffeine use, tolerance, and withdrawal ranging from 35% to 77%.^{60–63} The magnitude of heritability for

caffeine dependence markers is similar to those for nicotine and alcohol.^{64,65}

Genetic polymorphisms in the adenosine A2A receptor gene (*ADORA2A*) are associated with caffeine consumption⁶⁶; sensitivity to the effects of caffeine after sleep deprivation; and the effects of caffeine on anxiety,^{67–69} sleep,^{70,71} blood pressure,⁷² and psychomotor vigilance.⁷³ In addition, variability in the cytochrome P450 1A2 (*CYP1A2*) gene, which codes for the primary enzyme responsible for caffeine metabolism, is associated with variability in caffeine consumption.^{74–76} Moreover, individuals who carry the variant of the *CYP1A2* gene that slows caffeine metabolism have been shown to be at increased risk for hypertension and myocardial infarction associated with coffee use.^{66,77} Recent genome-wide meta-analyses have found associations between caffeine use and variants of the *CYP1A2* gene and aryl hydrocarbon receptor gene (*AHR*), which regulates *CYP1A2*.^{78–80}

Current Status of Caffeine Dependence Diagnosis

World Health Organization

The World Health Organization developed *The International Statistical Classification of Diseases and Related Health Problems (10th Revision; ICD-10)*, the most recent international medical diagnostic system (<http://apps.who.int/classifications/icd10/browse/2008/en#>, accessed January 2013). The *ICD-10* recognizes the diagnosis of Caffeine Dependence Syndrome.^{81,82} This disorder is defined as a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and which typically include a strong desire to take the drug, difficulties in controlling use, persisting in use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.

American Psychiatric Association

The American Psychiatric Association recently published the *DSM-5*, the latest edition of the *Diagnostic and Statistical Manual of Mental Disorders*. The nomenclature and diagnostic criteria of substance-related and addictive disorders differs between this edition of the manual and previous editions. Specifically, the disorders of Substance Abuse and Substance Dependence found in the *DSM-IV*⁸³ have been combined and are now referred to as Substance Use Disorder in the *DSM-5*. Although neither the *DSM-IV* nor the *DSM-5* officially recognizes these disorders applied to caffeine, the *DSM-5* recognizes Caffeine Use Disorder as a condition for further study. Table 1 shows the diagnostic criteria for Caffeine Use Disorder. These criteria are similar, but not identical, to those for Caffeine Dependence Syndrome in the *ICD-10*. The Caffeine Use Disorder criteria also overlap considerably with the older *DSM-IV* criteria for Substance Abuse and Substance Dependence. A footnote in Table 1 notes many of the similarities and differences between the *DSM-5* Caffeine Use Disorder diagnosis and the *DSM-IV* diagnoses for Substance Abuse and Substance Dependence.

The *DSM-5* diagnostic schema for Substance Use Disorder includes 11 criteria. Endorsement of any two of these criteria will fulfill the diagnostic requirement. However, to ensure identification of only those cases with sufficient clinical im-

portance to warrant labeling of a mental disorder, the *DSM-5* diagnostic schema for the study of Caffeine Use Disorder includes fewer diagnostic criteria (i.e., nine criteria). In addition, a diagnosis of Caffeine Use Disorder requires that all three of the most clinically meaningful indicators of distress or impairment associated with caffeine dependence be fulfilled: (1) *persistent desire or unsuccessful efforts to cut down or control caffeine use*, (2) *continued caffeine use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by caffeine*, and (3) *characteristic caffeine withdrawal syndrome or caffeine use to relieve or avoid withdrawal symptoms*. In addition to these three primary diagnostic criteria for Caffeine Use Disorder, six other criteria are also assessed (see Table 1).

Systematic Review of Clinical Evidence for Caffeine Dependence

Summary of literature search

We conducted searches on three research databases (PubMed, Embase, and The Cochrane Library; searched July 17, 2013) using the following four search terms: “caffeine dependence,” “caffeine use disorder,” “caffeine addiction,” and “caffeinism.” In addition to literature searches conducted via electronic databases, the authors’ personal journal article collections were also searched, as well as the reference sections of review papers and studies that met inclusion criteria. After eliminating duplicates, 122 results were obtained.

Studies selected for inclusion were peer-reviewed, published in English, used experimental or observational designs, and reported prevalence of caffeine dependence or rates of endorsement of caffeine dependence diagnostic criteria. The caffeine-related substance use disorders that were evaluated, and the tools which were used to assess them varied across studies. For example, one study used only the generic *DSM-IV* diagnostic criteria for Substance Abuse applied to caffeine to assess “caffeine abuse,”⁸⁴ another study used the *DSM-III-R* diagnostic criteria for both Substance Abuse and Substance Dependence to determine the presence or absence of a “caffeine disorder,”⁸⁵ and several studies assessed caffeine dependence using various substance dependence questionnaires [e.g., Leeds Dependence Questionnaire (LDQ),²³ Shorter PROMIS Questionnaire (SPQ),¹⁹ or other surveys^{7,11}].

To be included in the present review, studies were required to evaluate *DSM-IV* Substance Dependence criteria as applied to caffeine, including, at minimum, the three most clinically meaningful indicators of distress or impairment listed in the *DSM-5* Caffeine Use Disorder diagnostic schema [i.e., (1) *persistent desire or unsuccessful efforts to cut down or control caffeine use*, (2) *continued caffeine use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by caffeine*, and (3) *characteristic caffeine withdrawal syndrome or caffeine use to relieve or avoid withdrawal symptoms*]. Two studies assessed caffeine dependence using structured interviews that were informed by the *DSM-IV* Substance Dependence criteria applied to caffeine; however, one of these studies did not assess criterion 1,¹⁵ and the other study reported rates of endorsement for criteria 1 and 3 in a manner which precluded interpretation of the results within the context of a *DSM-IV* Substance Dependence diagnosis or a *DSM-5* Caffeine Use Disorder diagnosis.¹² In addition, although two studies met all inclusion

TABLE 1. DSM-5 CAFFEINE USE DISORDER RESEARCH DIAGNOSIS^{a,b}

A problematic pattern of caffeine use leading to clinically significant impairment or distress, as manifested by at least the first three of the following criteria occurring within a 12-month period:

1. A persistent desire or unsuccessful efforts to cut down or control caffeine use.
2. Continued caffeine use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by caffeine.
3. Withdrawal, as manifested by either of the following:
 - a. The characteristic withdrawal syndrome for caffeine.
 - b. Caffeine (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.
4. Caffeine is often taken in larger amounts or over a longer period than was intended.
5. Recurrent caffeine use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated tardiness or absences from work or school related to caffeine use or withdrawal).
6. Continued caffeine use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of caffeine (e.g., arguments with spouse about consequences of use, medical problems, cost).
7. Tolerance, as defined by either of the following:
 - a. A need for markedly increased amounts of caffeine to achieve desired effect.
 - b. Markedly diminished effect with continued use of the same amount of caffeine.
8. A great deal of time is spent in activities necessary to obtain caffeine, use caffeine, or recover from its effects.
9. Craving or a strong desire or urge to use caffeine.

Instructions for specifying severity of DSM-5 Substance Use Disorders^c

Substance Use Disorders occur in a broad range of severity, from mild to severe, with severity based on the number of symptom criteria endorsed. As a general estimate of severity, a *mild* substance use disorder is suggested by the presence of two to three symptoms, *moderate* by four to five symptoms, and *severe* by six or more symptoms.

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^bThe DSM-5 proposed diagnostic criteria for Caffeine Use Disorder overlap considerably with the DSM-IV diagnostic criteria for Substance Dependence and Substance Abuse. Specifically, the DSM-IV diagnostic criteria for Substance Dependence include six of the above criteria (i.e., criteria 1, 2, 3, 4, 7, and 8) along with a seventh criterion not included in the Caffeine Use Disorder diagnostic schema (i.e., "important social, occupational, or recreational activities are given up or reduced because of substance use"). The DSM-IV diagnostic criteria for Substance Abuse include two of the above criteria (i.e., criteria 5 and 6) along with two other criteria not included in the Caffeine Use Disorder diagnostic schema (i.e., "recurrent substance use in situations in which it is physically hazardous" and "recurrent substance-related legal problems"). One Caffeine Use Disorder diagnostic criterion (criterion 9) is not listed in the DSM-IV diagnostic schemas for Substance Dependence or Substance Abuse.

^cThese DSM-5 instructions are for scoring severity of Substance Use Disorders. They are not listed with the proposed diagnostic criteria for Caffeine Use Disorder.

criteria,^{14,18} data from both of these studies were collected from subjects who participated in two other studies that met our inclusion criteria and, therefore, overlapped with data reported in these studies.^{8,13} Thus, these studies will not be discussed in detail below. A total of 9 studies are included in the following systematic review.

Prevalence of caffeine dependence diagnosis

Nine studies documented and characterized caffeine dependence in the general population and among other populations.^{8–10,13,16,17,20–22} In addition to reporting the prevalence of caffeine dependence, eight of these studies also reported rates of endorsement of caffeine dependence diagnostic criteria.^{8,10,13,16,17,20–22} For these eight studies, the rates of endorsement of the DSM-5 diagnostic criteria for Caffeine Use Disorder and the prevalence of fulfilling the research diagnosis (i.e., endorsement of all three primary criteria) are presented in Table 2. Because Buralassi *et al.*⁹ did not report rates of endorsement of each diagnostic criterion, data from this study are not included in Table 2.

General population. Hughes and colleagues¹³ characterized caffeine dependence in the general population using a random-digit-dial telephone survey of Vermont residents (see first study in Table 2). This study found that 30% of 162 current caffeine users fulfilled the DSM-IV diagnosis for Substance Dependence as applied to caffeine by indicating

that three or more of the seven diagnostic criteria were met during the past year. Hughes *et al.* also reported the percentage of participants who endorsed at least three of the four DSM-IV criteria that the researchers considered the most clinically relevant to caffeine dependence (i.e., *desire to cut down*, *use despite harm*, *withdrawal*, and *tolerance*). Nine percent of their sample endorsed at least three of these four criteria. Three of these criteria (i.e., *desire to cut down*, *use despite harm*, and *withdrawal*) are now the primary diagnostic criteria for Caffeine Use Disorder in the DSM-5 (Table 1). Thus, as shown in Table 2, the prevalence of Caffeine Use Disorder among the general population (i.e., those endorsing all three primary diagnostic criteria) should be less than or equal to 9%—a much more conservative estimate than the 30% who fulfilled the DSM-IV diagnostic criteria for Substance Dependence as applied to caffeine.

Two other studies also provided information about the prevalence of caffeine dependence in the general population.^{9,10} Both of these studies evaluated caffeine dependence in healthy subjects and in patients diagnosed with various psychiatric disorders. Ciapparelli *et al.*¹⁰ interviewed 104 healthy control subjects from the general population in Pisa, Italy (see second study in Table 2). Participants who endorsed three of the seven DSM-IV Substance Dependence criteria as applied to caffeine were considered caffeine dependent. Six percent of the control subjects received this caffeine dependence diagnosis. The prevalence of Caffeine Use Disorder among participants in this study could not be determined

TABLE 2. RATES OF ENDORSEMENT OF DSM-5 CRITERIA FOR CAFFEINE USE DISORDER AND PREVALENCE OF THE DISORDER

	Other populations					
	General population		Jones & Lejuez ¹⁶		Strain et al. ²⁰	Bernstein et al. ⁸
	Hughes et al. ¹³	Ciapparelli et al. ¹⁰	Striley et al. ²¹	Juliano et al. ¹⁷	Sovikis et al. ²²	Caffeine dependent college students (N = 30) ^b
	US Adults (N = 162)	Italian Adults (N = 104)	Adults and adolescents with history of drug use (N = 167)	Adults seeking treatment for caffeine use (N = 94)	Pregnant women (N = 44) ^a	Caffeine dependent adults (N = 16) ^c
Primary criteria						
Persistent desire or unsuccessful efforts to cut down use	56%	10%	23%	89%	45%	81%
Use despite harm	14%	7%	44%	87%	43%	94%
Withdrawal	18%	6%	26%	96%	77%	94%
Endorsed all three primary criteria (i.e., prevalence of the research diagnosis)	≤ 9% ^e	—	20%	79%	—	—
Other criteria						
Use more than intended	28%	31%	17%	38%	45%	—
Use results in role dysfunction	15%	—	—	—	—	—
Use despite interpersonal problems	2%	—	—	—	—	—
Great deal of time spent with drug	50%	3%	40%	61%	25%	—
Tolerance	8%	9%	13%	70%	50%	75%
Craving	19%	—	34%	86%	27%	—

^aData are for lifetime endorsement of diagnostic criteria (i.e., criteria were not required to be fulfilled within previous 12 months).

^bSample includes only individuals diagnosed as caffeine dependent using DSM-IV Substance Dependence criteria.

^cSample includes only individuals who were diagnosed as caffeine dependent by fulfilling at least three of the following four DSM-IV diagnostic criteria for Substance Use Disorder: *desire to cut down*, *use despite harm*, *withdrawal*, and *tolerance*.

^dSample includes only individuals who fulfilled two or more of the following four diagnostic criteria: *desire to cut down*, *use despite harm*, *withdrawal*, and *tolerance*. A subsequent study from this group was published (Oberstar et al., 2002) but is not included in this table, because it is a follow up of the same subjects.

^eValue based on results showing that 9% and 22% of volunteers in Hughes et al. (1998) and Bernstein et al. (2002), respectively, fulfilled at least three of the following four diagnostic criteria: *desire to cut down*, *use despite harm*, *withdrawal*, and *tolerance*. Thus, it is likely that less than 9% and 22%, respectively, would have fulfilled the three primary DSM-5 criteria for Caffeine Use Disorder.

from the data provided. However, Ciapparelli *et al.* reported the rates of endorsement of each diagnostic criterion. These data are shown in Table 2. Among the 104 participants in this study who were from the general population, rates of endorsement of many diagnostic criteria were considerably lower than the rates observed among those individuals who participated in the general population study that was conducted in the US.¹³ These differences may be due, in part, to cultural factors. They may also be due to differences in sampling or other study procedures. For example, Hughes *et al.*¹³ only included participants who consumed at least one caffeinated beverage per week, whereas Ciapparelli *et al.* included participants who were not regular caffeine consumers. In addition, Ciapparelli *et al.* excluded individuals with a personal or family history of substance abuse or dependence, whereas Hughes *et al.* used no such exclusion criterion. In another study, Burgalassi *et al.*⁹ interviewed 15 control subjects from the general population in Pisa, Italy (study not shown in Table 2). Participants who endorsed at least three of six *DSM-IV* Substance Dependence criteria as applied to caffeine were considered caffeine dependent. The researchers noted that a seventh criterion, *great deal of time spent with the drug*, was not included during the caffeine dependence assessment, because it was not considered applicable to caffeine use, due to the widespread availability of the drug. They found that only 2% of these participants from the general population fulfilled the caffeine dependence diagnosis.

Special populations. Eight studies investigated caffeine dependence among other populations (data from seven of these studies are shown in Table 2). Population samples in these studies consisted of patients with eating disorders,⁹ patients diagnosed with various other psychiatric disorders,¹⁰ individuals with a recent history of licit or illicit drug use,²¹ individuals who self-identified as physically or psychologically dependent on caffeine,^{20,17} adolescents and young adults who fulfilled two or more caffeine dependence diagnostic criteria,^{8,16} and pregnant women who received a lifetime (rather than previous 12-month) diagnosis of caffeine dependence.²² The prevalence of Caffeine Use Disorder and the rates of endorsement of each diagnostic criterion were typically higher among participants in these studies relative to rates among participants in the general population.^{10,13} Notably, samples from half of these studies included only participants who self-identified as caffeine dependent or met caffeine dependence diagnostic criteria.^{8,16,17,20}

Ciapparelli *et al.*¹⁰ interviewed 369 in- and outpatient psychiatric patients who were diagnosed with various mental disorders, including mood disorders, anxiety disorders, schizophrenia spectrum disorders, and eating disorders. Participants who endorsed three of the seven *DSM-IV* Substance Dependence criteria as applied to caffeine were considered caffeine dependent. Among patients in this study, 17% were diagnosed as caffeine dependent—significantly more than the 6% of control subjects who were diagnosed with the disorder. The percentage of participants who met *DSM-5* criteria for Caffeine Use Disorder could not be determined from the data provided in this study. However, rates of endorsement of several *DSM-5* diagnostic criteria that were reported in this study are shown in Table 2.

Burgalassi *et al.*⁹ interviewed 58 female patients with eating disorders (i.e., Anorexia Nervosa, Bulimia Nervosa, and

Binge Eating Disorder). Sixteen percent of these patients met the *DSM-IV* criteria for Substance Dependence applied to caffeine. The percentage of participants who met *DSM-5* criteria for Caffeine Use Disorder could not be determined from the data reported in this study, and, as mentioned earlier, rates of endorsement of each diagnostic criterion were not reported in this study.

Striley *et al.*²¹ interviewed a sample of 167 high school students, college students, pain clinic patients, and drug treatment patients with a recent history of caffeine use (previous 7 days) and other licit or illicit drug use (previous 12 months). Although 35% of their sample met the *DSM-IV* criteria for Substance Dependence as applied to caffeine by fulfilling three or more of the seven generic Substance Dependence criteria, only 20% of participants fulfilled the three primary diagnostic criteria required for a *DSM-5* diagnosis of Caffeine Use Disorder (Table 2).

Juliano and colleagues¹⁷ interviewed 94 participants seeking treatment for caffeine dependence who self-identified as physically or psychologically dependent on caffeine, or who had tried unsuccessfully to quit using the drug. Given these inclusion criteria, it is not surprising that 93% of this sample met the *DSM-IV* criteria for Substance Dependence applied to caffeine, and 79% met the *DSM-5* criteria for Caffeine Use Disorder (Table 2).

Svikis *et al.*²² interviewed 44 caffeine-using pregnant women seeking prenatal care from a private obstetrical practice in a suburban community. Fifty-seven percent of these women endorsed at least three of the seven generic *DSM-IV* criteria for a lifetime diagnosis of Substance Dependence applied to caffeine. This relatively high prevalence of caffeine dependence likely resulted from lifetime, rather than past year assessment of the diagnostic criteria. An estimate of the prevalence of the *DSM-5* diagnosis of Caffeine Use Disorder could not be determined from the data reported in this study.

A study conducted by Jones and Lejuez¹⁶ included only college students who fulfilled the *DSM-IV* diagnosis for Substance Dependence as applied to caffeine (i.e., 100% of these participants were diagnosed with caffeine dependence). Given these inclusion criteria, it is not surprising that the study showed high rates of endorsement of each diagnostic criterion relative to the rates of endorsement observed in the general population (Table 2). An estimate of the prevalence of the *DSM-5* diagnosis of Caffeine Use Disorder could not be determined from the data reported in this study.

Strain *et al.*²⁰ interviewed 27 caffeine users who self-identified as physically or psychologically dependent on caffeine. As might be expected, the majority of these participants (59%; $n = 16$) fulfilled at least three of the following four criteria: *desire to cut down*, *use despite harm*, *tolerance*, and *withdrawal*. Because only three of these four criteria are now the primary *DSM-5* diagnostic criteria for Caffeine Use Disorder (i.e., *desire to cut down*, *use despite harm*, and *withdrawal*), it is likely that less than 59% of this sample endorsed all three criteria and would have received a Caffeine Use Disorder diagnosis; especially, considering that a relatively large percentage of the sample endorsed *tolerance*, which is not one of the three primary criteria for Caffeine Use Disorder. Table 2 displays the rates of endorsement for each diagnostic criterion among only those 16 participants who fulfilled at

least three of the four diagnostic criteria assessed by Strain and colleagues.

Bernstein and colleagues⁸ characterized caffeine dependence in a sample of 36 daily caffeine consumers between 13 and 17 years of age who endorsed two or more of four *DSM-IV* diagnostic criteria for Substance Dependence as applied to caffeine (i.e., the same four criteria evaluated by Strain *et al.*²⁰ *desire to cut down, use despite harm, tolerance, and withdrawal*). They found that 22% of their sample endorsed at least three of these criteria. Thus, fewer than 22% of this sample likely endorsed all three primary criteria for the *DSM-5* diagnosis of Caffeine Use Disorder (Table 2).

Clinically meaningful indicators of distress or impairment associated with caffeine dependence

The *DSM-5* indicates that the diagnostic schema for Caffeine Use Disorder was explicitly developed to be more restrictive than that for other Substance Use Disorders to prevent over-diagnosis due to the high rate of nonproblematic caffeine use in the general population. The *DSM-5* further indicates that a key goal in including the proposed diagnostic criteria for Caffeine Use Disorder is to stimulate research that will determine the reliability, validity, and prevalence of Caffeine Use Disorder based on the new diagnostic schema, with particular attention to the association of the diagnosis with functional impairment as a part of validity testing.

In a recent survey of addiction professionals about the possible inclusion of a Caffeine Use Disorder diagnosis in the *DSM-5*, a minority of participants were concerned that the severity and clinical importance of the disorder had not been demonstrated.⁸⁶ This section summarizes data and observations that bear on the question about whether caffeine dependence is associated with clinically meaningful distress or impairment. The section is organized into three subsections based on the three primary *DSM-5* diagnostic criteria for Caffeine Use Disorder (see Table 1) that summarize information from the clinical studies included in this review (see Table 2).

A persistent desire or unsuccessful efforts to cut down or control caffeine use. Perhaps the most distinguishing feature of any Substance Use Disorder is a *persistent desire or unsuccessful efforts to cut down or control use*. In a general population survey conducted in the State of Vermont, this criterion was the most frequently endorsed diagnostic criterion for caffeine dependence, with 56% of caffeine users reporting a *desire or unsuccessful efforts to cut down*¹³ (Table 2).

In Italy, Ciapparelli *et al.* found that 10% of 104 participants from the general population endorsed this criterion.¹⁰ This rate of endorsement was significantly lower than the rate observed among psychiatric patients in the same study—20% of these patients endorsed a *desire or unsuccessful efforts to cut down*.

Striley and colleagues²¹ found that 23% of a group of licit and illicit drug users endorsed a *desire or unsuccessful efforts to cut down*.

Juliano and colleagues¹⁷ interviewed 94 participants seeking treatment for caffeine dependence who self-identified as being physically or psychologically dependent on caffeine. Participants in this study consumed 548 mg of caffeine per day (i.e., roughly twice the national average for regular caf-

feine users). As might be expected, a large proportion of these treatment seekers (89%) endorsed a *desire or unsuccessful efforts to cut down* (Table 2). Mean rating of desire to modify caffeine use on a 0 to 10 scale was 7.79 ($SD=2.18$). Many of these caffeine users did not believe that they could control their caffeine use without assistance. Sixty-five percent of participants reported that they had previously tried to stop using caffeine, and 80% reported that they had tried to cut down. In addition, 59% of 258 initial responders expressed interest in attending face-to-face counseling to receive assistance in their quit attempts. Table 3 presents three previously unpublished case histories of participants who were sufficiently distressed by their dependence on caffeine to enroll in this study, undergo diagnostic interview, maintain a detailed record of caffeine consumption, and visit a clinic several times over a 6-month period.

Among the remaining studies summarized in Table 2, Svikis *et al.*²² found that 45% of pregnant women seeking prenatal care endorsed a *desire or unsuccessful efforts to cut down* at some point in their lifetime. Jones and Lejuez¹⁶ found that, among college students who fulfilled the *DSM-IV* diagnosis for Substance Dependence applied to caffeine, 60% endorsed this criterion. Among adults who fulfilled at least three of four *DSM-IV* diagnostic criteria for Substance Dependence applied to caffeine (i.e., *desire to cut down, use despite harm, withdrawal, and tolerance*), Strain *et al.*²⁰ found that 81% endorsed *desire or unsuccessful efforts to cut down*. Finally, Bernstein *et al.*⁸ reported that, among adolescents who fulfilled two or more of the *DSM-IV* diagnostic criteria for Substance Dependence applied to caffeine, 39% endorsed this criterion (Table 2).

Continued caffeine use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by caffeine. The diagnostic criterion that may be of most concern to health care professionals is *continued caffeine use despite harm*. Caffeine consumption has been associated with a number of negative health consequences, including anxiety, insomnia, hypertension, myocardial infarction, bladder instability, gastroesophageal reflux, spontaneous abortion, and reduced fetal growth.⁸⁷

In the general population survey conducted in the United States, 14% of caffeine users endorsed *use despite harm*¹³ (Table 2). Many participants from this study (13%) reported that a physician or counselor had advised them to stop or reduce caffeine consumption within the last year. Medical and psychological problems that participants attributed to caffeine included heart, stomach, and urinary problems, and complaints of anxiety, depression, insomnia, irritability, and difficulty thinking. In addition, two-thirds of those surveyed endorsed at least one symptom associated with Caffeine Intoxication, a clinical disorder recognized by the *ICD-10* (i.e., Caffeine Acute Intoxication) and the *DSM-5* (see Table 4). For example, 39% of participants from this general population study endorsed insomnia, 30% endorsed nervousness, 24% endorsed heart pounding, 18% endorsed stomachache, and 10% endorsed muscle twitching. Seven percent of participants reported that these symptoms interfered with their performance at work, home, or school.

Ciapparelli *et al.*¹⁰ found that only 7% of participants from the general population in Italy endorsed *use despite harm*. The rate of endorsement of this criterion was significantly higher

TABLE 3. THREE CASES OF CAFFEINE USERS SEEKING TREATMENT FOR CAFFEINE DEPENDENCE

Case #1

Mr. B, a 27-year-old married man, presented with a chief complaint of severe headaches for which he took Excedrin multiple times daily. Although he had a family history of migraine headache, he believed that his headaches were rebound headaches from the caffeine withdrawal. He was a college graduate employed as a full-time elementary school teacher. He did not smoke tobacco or use illicit drugs, and he drank alcohol occasionally. Mr. B had an anxiety disorder for which he was taking prescription medication (Celexa and Clonopin daily, and Xanax as needed).

Mr. B began consuming caffeine regularly at age 18 primarily through soft drinks. At age 27, the time of his screening evaluation, his usual daily caffeine use consisted of daily consumption of three caffeinated beverages (soda, coffee, and/or hot chocolate) along with four tablets of Excedrin that he took to treat his chronic headache. He believed he was physically dependent on caffeine, and he was told by his family doctor that he should eliminate his caffeine use due to his severe headaches. Mr. B was also concerned about possible toxicity from his chronic analgesic use. His wife had also been concerned about his caffeine use. He reported waking up during the night and almost every morning with a severe headache that he attributed to caffeine withdrawal due to not having caffeine during the hours he was sleeping. He made two previous attempts to quit but in both cases, quickly relapsed because of headaches and fatigue. He contacted the caffeine dependence treatment program at Johns Hopkins after his wife saw an advertisement for a caffeine treatment study and encouraged him to participate. In the screening interview, he stated that his goal for participation was to completely eliminate caffeine from his diet.

The caffeine dependence treatment program began with an interview about caffeine use and 2 weeks of keeping a daily caffeine diary. This was followed by an individualized education and counseling session during which a gradual caffeine reduction plan was determined. Mr. B's baseline caffeine intake from his caffeine diaries was 498 mg/day. (Each Excedrin tablet contains 65 mg of caffeine, 250 mg of acetaminophen, and 250 mg of aspirin). For the caffeinated beverages, the plan consisted of gradually reducing the amount consumed before moving on to reducing his Excedrin use. He cut out his use of caffeinated beverages almost immediately. Since much of his caffeine was coming from Excedrin, he reported that it was fairly easy for him to switch to decaffeinated beverages. The treatment strategy then consisted of initially stopping the use of Excedrin and switching to the component ingredients of Excedrin, which he obtained in a local pharmacy. For the caffeine, he switched to a generic caffeine pill that he could cut using a pill cutter to obtain the desired amount of caffeine. The plan consisted of initially gradually reducing the caffeine while maintaining his usual dosing of acetaminophen and aspirin so that caffeine withdrawal would not be confounded with termination of the analgesics. He reported significant headaches only in the first few caffeine tapering weeks when he initially decreased his caffeine intake to 75% of previous levels. He was instructed to increase his caffeine again to a level that controlled his withdrawal headaches, and then to decrease more gradually over about a 10 week period. He successfully did this but departed from the treatment plan by concurrently decreasing his analgesic use after he began experiencing success in eliminating the caffeine. At the 6 month follow-up visit, he reported no regular use of caffeine or analgesics and no headaches from withdrawal. When he did get a headache, he was able to treat it with an OTC caffeine-free pain reliever.

Case #2

Ms. B, a 46 year-old married woman, presented to the caffeine dependence treatment clinic with complaints of sleep problems and occasional heart palpitations that she attributed to caffeine. She also reported fatigue, anxiety, and depressed mood when she abstained from caffeine. Ms. B was a college graduate who was employed part time. She did not smoke tobacco, drink alcohol, or use illicit drugs. The screening psychiatric diagnostic interview (SCID) indicated that she had current dysthymic disorder, bulimia nervosa, and binge eating disorder, and a past diagnosis of depression. At the time of initial evaluation she was on psychotherapy but was not taking any prescription medications.

Ms. B began consuming caffeine regularly at age 18. At the screening evaluation, her caffeinated beverages of choice were brewed coffee and green Japanese loose tea, both of which she prepared for herself at home. She would typically have two large servings of coffee, and three medium servings of tea spaced throughout the morning. Her average daily caffeine intake based on her baseline caffeine diaries was 702 mg/day. She had made numerous attempts to quit over the past 23 years, having varied success lasting anywhere from 2 weeks to as long as 4 years.

Ms. B had been advised by her family doctor to reduce her caffeine consumption to help her heart palpitations; however, she did not follow this advice because of strong cravings for coffee and tea, and because she believed that caffeine reduction would exacerbate her anxious and depressed mood. Her husband also complained that her caffeine use adversely affected their relationship.

At the time of Ms. B's counseling/treatment session, her goal was to reduce her caffeine intake from 702 mg/day to about 150 mg/day, the equivalent of about one small coffee and one cup of tea each day. She was able to reduce slightly (to about 600 mg/day by the second week) but reported that withdrawal symptoms prevented her from cutting back any further. Throughout the 6 weeks of attempting to reduce caffeine consumption, she reported various withdrawal symptoms, including feeling more depressed, tired, angry, forgetful, difficulty in concentrating, low motivation, increased appetite, and craving for caffeine. At her 6-week follow-up session, she reported a slight increase to 720 mg/day. At a 12-week follow up, she was able to reduce to 590 mg/day, and, at a 26-week follow up, she was back up to about 710 mg/day. At the 6-month follow-up visit, she continued to use caffeine at levels (710 mg/day) similar to those at enrollment. She reported that she was consuming enough caffeine to avoid withdrawal symptoms.

This case illustrates that a single one-hour counseling session is insufficient for some people to successfully reduce their caffeine intake, despite being motivated to do so. Ms. B may have had more success if a more gradual reduction plan was implemented and if additional follow-up support had been provided throughout her reduction attempt.

(continued)

TABLE 3. (CONTINUED)

Case #3

Mr. C, a 51-year-old single man, presented to a caffeine dependence treatment program with a chief complaint of sleep problems. He was a high school graduate who was employed full time doing stock work overnight at a grocery store. He enjoyed working the night shift and had done it for many years. He did not smoke tobacco, drink alcohol, or use any illicit drugs. Mr. C. had a slight heart murmur and arthritis, for which he took naproxen as needed.

Mr. C reported that he began regular use of caffeinated tea at age 8 and caffeinated soft drinks at age 12. At the time of his screening interview, he reported consuming 2-L per day of Diet Pepsi Max along with other diet soft drinks. He said that the caffeine helped him stay awake through the night, but he consumed similar amounts of caffeine on his days off from work. He attributed frequent urination and insomnia after his work shift to his caffeine consumption. He had been advised by a doctor to cut back on his caffeine use to help with his sleeping problems. He had attempted to do so but failed because he could not tolerate either the withdrawal headaches or the craving for his beverage of choice. He reported that he had made special trips to the store by bus, at 2:00 in the morning, because of strong cravings for soda.

The 2-week caffeine diary showed he was consuming ~496 mg of caffeine per day, from Diet Pepsi Max, Diet Pepsi, or Diet Coke. Mr. C's initial goal was to cut back his caffeine intake by about half. Through participation in the caffeine dependence treatment program, Mr. C successfully eliminated all caffeine use. Following a gradual caffeine reduction plan, he initially switched to Diet Coke or Diet Pepsi, which have less caffeine than Diet Pepsi Max. He then began substituting caffeine-free soda. He surpassed his goal of reducing by half and eliminated caffeine altogether in 6 weeks of gradual reduction. During the 6-week period of his reduction, he reported occasional mild or severe headaches, cravings, and a drop in energy, but at the 6-month follow up, he continued to report no caffeine use and reported no withdrawal symptoms other than occasional cravings for caffeine beverages.

among psychiatric patients participating in the study—24% of these patients endorsed *use despite harm*.

Six studies among other populations show considerable variability in the rates of endorsement of *use despite harm*. In a sample of adolescents who fulfilled two or more of the DSM-IV diagnostic criteria for Substance Dependence as applied to caffeine, Bernstein *et al.*⁸ reported that 17% of these daily caffeine users endorsed this criterion (Table 2).

Jones and Lejuez¹⁶ characterized caffeine dependence in college students who fulfilled the DSM-IV diagnosis for Sub-

stance Dependence as applied to caffeine and found that 57% of these caffeine users endorsed *use despite harm* (Table 2).

Striley and colleagues²¹ found that 44% of licit and illicit drug users endorsed *use despite harm* (Table 2). Ten percent of participants in this study reported having talked to a physician about problems associated with consuming caffeinated beverages, and 11% continued to use caffeine after learning that a health problem could be exacerbated by continued consumption. Physical and psychological problems attributed to caffeine included trouble falling or staying asleep (36%), feeling very anxious (19%), stomach problems (16%), fast or irregular heartbeat or chest pain (11%), and feeling irritable or angry (10%).

In a study of pregnant women who had been advised to quit caffeine use during pregnancy, Svikis *et al.*²² reported that 43% of these caffeine users endorsed *use despite harm* (Table 2). Twenty-one percent indicated that they had previously been told by a health care professional that they should reduce or quit caffeine because of medical conditions, including fibrocystic breast disease, headaches, pregnancy, insomnia, and stomach problems. In addition to a diagnostic assessment, Svikis *et al.* conducted a prospective study demonstrating that some of these pregnant women were unable to quit using caffeine. Participants were given written and verbal instructions by a physician to quit caffeine during their pregnancy in order to avoid adverse birth consequences. Of those who did not fulfill diagnostic criteria for caffeine dependence, none continued to consume caffeine in amounts greater than those thought to be safe during pregnancy (i.e., >300 mg/day). In contrast, 28% of women who fulfilled the caffeine dependence diagnosis continued to consume caffeine at unsafe levels. The reasons that participants provided for failing to eliminate or cut back caffeine use included cravings, headache, nervousness; migraines; need to stay awake; severe withdrawal; and inability to concentrate at work. Examples of functional impairment reported by women who attempted to reduce caffeine consumption included: "less active at work"; "flu symptoms prevented going to work"; and "it is difficult to concentrate."

TABLE 4. DSM-5 DIAGNOSTIC CRITERIA FOR CAFFEINE INTOXICATION^a

- A. Recent consumption of caffeine (typically a high dose well in excess of 250 mg).
- B. Five (or more) of the following signs or symptoms, developing during, or shortly after, caffeine use:
 1. Restlessness.
 2. Nervousness.
 3. Excitement.
 4. Insomnia.
 5. Flushed face.
 6. Diuresis.
 7. Gastrointestinal disturbance.
 8. Muscle twitching.
 9. Rambling flow of thought and speech.
 10. Tachycardia or cardiac arrhythmia.
 11. Periods of inexhaustibility.
 12. Psychomotor agitation.
- C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication with another substance.

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Not surprisingly, the rates of endorsement for *use despite harm* were highest in studies of individuals who self-identified as being psychologically or physically dependent on caffeine. In two such studies, the prevalence was 94% and 87%, respectively, in Strain *et al.*²⁰ and Juliano *et al.*¹⁷ (Table 2). In the study described by Strain *et al.*, 44% of participants reported that physical conditions such as pregnancy, palpitations, gastrointestinal problems, and acne rosacea had led physicians to recommend reduction or cessation of caffeine. All participants reported that they failed to comply with these recommendations. In the study by Juliano *et al.*, 59% of participants reported health problems or concerns as a reason for seeking treatment for caffeine dependence. Forty-three percent reported being advised by a health care professional to modify caffeine use for reasons including cardiovascular problems, fibrocystic breast disease, pregnancy, anxiety, headaches, urinary problems, gastric problems, hypoglycemia, and sleep difficulties.

Characteristic caffeine withdrawal syndrome or caffeine use to relieve or avoid withdrawal symptoms. It is well documented that habitual caffeine users can experience a well-defined withdrawal syndrome on acute abstinence from caffeine, and many caffeine dependent individuals report continuing to use caffeine to avoid experiencing withdrawal symptoms.⁵⁵ Both the *ICD-10* and the *DSM-5* recognize a clinical diagnosis of Caffeine Withdrawal. Although Caffeine withdrawal is an independent diagnosis, it can also be a feature of Caffeine Dependence Syndrome (*ICD-10*) or Caffeine Use Disorder (*DSM-5*). Table 5 shows the *DSM-5* diagnostic criteria for Caffeine Withdrawal.

In the general population study conducted in the United States by Hughes and colleagues,¹³ the rate of endorsement of *withdrawal* was 18% (Table 2), with most participants (17%) endorsing the sub-criterion of *using caffeine to relieve or avoid withdrawal symptoms* (see Table 1).

Ciapparelli *et al.*¹⁰ found that rates of *withdrawal or caffeine use to relieve or avoid withdrawal symptoms* were considerably

lower among control subjects (6%) and psychiatric patients (2%) in Italy, relative to the rates observed in the general population of the United States (Table 2).

As shown in Table 2, all six studies in other populations show considerably higher rates of endorsement of *withdrawal or caffeine use to relieve or avoid withdrawal symptoms*: 26%, 96%, 77%, 73%, 94%, and 78%, respectively, in Striley *et al.*,²¹ Juliano *et al.*,¹⁷ Svikis *et al.*,²² Jones and Lejuez,¹⁶ Strain *et al.*,²⁰ and Bernstein *et al.*⁸ (Table 2). In the two studies that provided information about the rate of endorsement of the sub-criterion, *use of caffeine to relieve or avoid withdrawal symptoms*, 24% of participants in Striley *et al.* and 92% of participants in Juliano *et al.* endorsed this sub-criterion.

Severity of withdrawal. Based on a comprehensive review of the literature, the incidence of clinically significant distress or functional impairment in prospective experimental studies of caffeine withdrawal in normal subjects varied from about 10% to 55%, with a median of 13%.⁵⁵ In the general population, withdrawal symptoms plus interference with performance was reported by 7% of caffeine users who cut down or stopped caffeine use temporarily and 24% of those who tried to stop permanently. Moreover, 33% of caffeine users reported that they needed the drug to function.¹³

Among licit and illicit drug users with a recent history of caffeine consumption, 26% reported that they needed caffeine to function.²¹ Thirteen percent of participants from this study reported that caffeine withdrawal symptoms interfered with functioning, and 13% endorsed difficulty concentrating after 12 hours without caffeine.

The incidence of functional impairment is greater among those with a caffeine dependence diagnosis. Strain *et al.*²⁰ conducted a prospective experimental assessment of the rate of functional impairment during caffeine withdrawal in 11 caffeine-dependent individuals. This double-blind study showed that 73% of participants reported significant disruptions in normal daily activities during 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.

In a survey about the effects of withdrawal in a group of caffeine dependence treatment seekers, Juliano *et al.*¹⁷ showed that 43% reported functional impairment due to withdrawal. Headache was the most frequently endorsed withdrawal symptom in this study (89%), and vomiting was the least frequently endorsed symptom (~5%). Examples of functional impairment reported by these participants included inability to work, sleeping at work, missing activities on vacation, and inability to attend church. Other studies have also reported severe withdrawal-induced functional impairment⁸⁸ as well as nausea and sickness in as many as 13% of normal subjects⁸⁹ and 33% of caffeine-dependent adolescents.¹⁸

Assessing the severity of caffeine dependence

The *DSM-5* lists nine diagnostic criteria for Caffeine Use Disorder. In addition to the three primary criteria, which are required for the diagnosis, six other criteria are also assessed (see Table 1). Among these additional criteria, Hughes *et al.*¹³ found that 28% of the general population endorsed *use more than intended*, 15% endorsed *use results in role dysfunction*, 2% endorsed *use despite interpersonal problems*, 50% endorsed *a great deal of time spent with caffeine*, 8%

TABLE 5. *DSM-5* DIAGNOSTIC CRITERIA FOR CAFFEINE WITHDRAWAL^a

-
- A. Prolonged daily use of caffeine.
 - B. Abrupt cessation of or reduction in caffeine use, followed within 24 hours by three (or more) of the following signs or symptoms:
 1. Headache.
 2. Marked fatigue or drowsiness.
 3. Dysphoric mood, depressed mood, or irritability.
 4. Difficulty concentrating.
 5. Flu-like symptoms (nausea, vomiting, or muscle pain/stiffness).
 - C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
 - D. The signs or symptoms are not associated with the physiological effects of another medical condition (e.g., migraine, viral illness) and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

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endorsed *tolerance*, and 19% endorsed *craving* (Table 2). The relatively low rate of endorsement for *use despite interpersonal problems* is not surprising given the wide availability and social acceptance of caffeine use. Likely, for similar reasons, the *DSM-IV* Substance Dependence criterion "Important social, occupational, or recreational activities are given up or reduced because of substance use" was also endorsed at only very low rates in many of the studies discussed in this review: <1% in Hughes *et al.*; 1% in Ciapparelli *et al.*¹⁰; 1% in Striley *et al.*²¹; 0% in Svikis *et al.*²²; 8% in Juliano *et al.*¹⁷; and 20% in Jones and Lejuez¹⁶ (data not shown). Nevertheless, evaluating additional diagnostic criteria such as these can contribute to an assessment of the severity of caffeine dependence.

For Substance Use Disorders, the *DSM-5* indicates that the number of diagnostic criteria endorsed can be used as a measure of severity (i.e., endorsement of two or three diagnostic criteria = mild; four or five = moderate; and six or more = severe). Although Hughes *et al.*¹³ evaluated all nine proposed *DSM-5* criteria for Caffeine Use Disorder, they did not report the proportion of participants diagnosed with Caffeine Use Disorder who also endorsed one or more of the six additional criteria. Therefore, it is not possible to estimate the severity of Caffeine Use Disorder in participants from the general population. However, data from two studies provide more information about Caffeine Use Disorder severity in other populations.

Striley *et al.*²¹ evaluated four of the six other Caffeine Use Disorder diagnostic criteria. After that study was published, Striley and Cottler conducted subsequent analyses of these data (Catherine Striley and Linda Cottler, personal communication, February 7, 2013). These analyses showed that, among licit and illicit drug users who fulfilled the three primary diagnostic criteria for Caffeine Use Disorder, 9%, 30%, 33%, and 24%, respectively, endorsed 1, 2, 3, and 4 additional criteria, with 58% endorsing *use more than intended*, 85% endorsing *a great deal of time spent with the drug*, 42% endorsing *tolerance*, and 82% endorsing *craving*. These data were also expressed in accordance with the *DSM-5* recommendations for assessing Substance Use Disorder severity. Even though Striley *et al.*²¹ evaluated only seven of the nine Caffeine Use Disorder diagnostic criteria, their data indicate that the severity of the disorder among participants who met the three primary criteria was mild in 3% (i.e., endorsed no criteria in addition to the three primary diagnostic criteria), moderate in 39% (i.e., endorsed one or two criteria in addition to the three primary criteria), and severe in 57% (i.e., endorsed three or more additional criteria).

Among treatment-seeking caffeine users, Juliano *et al.*¹⁷ evaluated the same seven criteria that were assessed by Striley and colleagues.²¹ The authors of the present review analyzed data from this study which showed that, among participants diagnosed with Caffeine Use Disorder, 12%, 24%, 31%, and 28%, respectively, endorsed 1, 2, 3, and 4 of the additional criteria, with 42% endorsing *use more than intended*, 62% endorsing *a great deal of time spent with the drug*, 74% endorsing *tolerance*, and 89% endorsing *craving*. The severity of Caffeine Use Disorder among participants who met the three primary criteria was mild in 4% (i.e., endorsed no additional criteria), moderate in 36% (i.e., endorsed one or two additional criteria), and severe in 59% (i.e., endorsed three or more additional criteria).

Future Research Directions

Although a clinical diagnosis of Caffeine Use Disorder is not recognized by the *DSM-5*, a research diagnosis may still benefit patients by providing clinicians with the diagnostic tools that are necessary to recognize an otherwise unspecified caffeine-related disorder. However, the most important function of the Caffeine Use Disorder research diagnosis is to stimulate further study of the disorder. Therefore, this section provides a discussion of important areas for future research.

Caffeine consumption and prevalence of Caffeine Use Disorder

The most recent data comprising the largest database on caffeine intake among US consumers was collected more than 15 years ago.² Thus, there is a critical need for epidemiological studies to examine caffeine consumption among US children and adults. In addition, studies should compare caffeine consumption in the United States with consumption in other countries, as some research suggests that rates of consumption vary between nations.³

There is also a critical need for studies to determine the prevalence of Caffeine Use Disorder and rates of endorsement of each diagnostic criterion in the United States and in other countries. As discussed in this review, only one general population study has been conducted in the United States, and it included just 162 regular caffeine users from the State of Vermont.¹³ Two studies conducted in Italy also included individuals from the general population.^{9,10} Notably, the prevalence of caffeine dependence was lower among participants from the general population of Italy relative to rates observed in the United States. It is not clear whether the observed difference in prevalence was due to cultural factors, different sampling procedures, or other factors. Thus, rigorous general population surveys are still needed in the United States and in other countries.

The prevalence of Caffeine Use Disorder and rates of endorsement of each diagnostic criterion should also be determined among special populations, including individuals seeking treatment for symptoms related to Caffeine Withdrawal and Caffeine Intoxication (e.g., headache, insomnia, and anxiety). Results from the studies reviewed in this article suggest that some individuals may endorse certain diagnostic criteria more or less frequently than others. For example, endorsement of *use despite harm* varied from 14% in the general population¹³ to 44% in licit and illicit drug users²¹ and 87% in caffeine users seeking treatment for caffeine dependence¹⁷ (Table 2). Some of the differences that were observed among study findings were likely due, in part, to the different sampling procedures used in each study (e.g., several studies only included participants who fulfilled caffeine dependence diagnostic criteria^{8,16,20}). Nevertheless, a diagnosis of Caffeine Use Disorder or rates of endorsement of various diagnostic criteria may vary as a function of variables such as gender, age, ethnicity, education, cultural background, or other factors. Thus, future studies should examine the prevalence of Caffeine Use Disorder and rates of endorsement of each diagnostic criterion in both the general population and among special populations to determine whether certain individuals are more susceptible to developing Caffeine Use Disorder than others.

Reliability and validity of diagnostic criteria

Studies investigating the reliability and validity of the *DSM-5* Caffeine Use Disorder research diagnosis are also needed. Factor analyses of the diagnostic criteria have not been conducted, and more test–retest evaluations are still needed. The only test–retest evaluation of caffeine dependence diagnostic criteria that has been conducted to date found high reliability for a *DSM-IV* diagnosis of Substance Dependence as applied to caffeine.¹³ However, no internal reliability studies have been conducted using the *DSM-5* criteria for Caffeine Use Disorder.

There is also a need for studies to investigate the external validity of the Caffeine Use Disorder research diagnosis. Prospective studies of caffeine reinforcement can be used to validate the diagnosis. For example, a small study of caffeine self-administration showed that subjects who had met criteria for caffeine dependence tended to be more likely to demonstrate reliable reinforcement (75%) than those who were not dependent (20%).⁴⁶

Perhaps the most important indicator of the external validity of the Caffeine Use Disorder diagnosis is its ability to predict whether an individual can quit using caffeine. To date, the only prospective study to use this clinically meaningful outcome measure showed that pregnant women with a lifetime *DSM-IV* Substance Dependence diagnosis applied to caffeine were more likely to consume caffeine at unsafe levels throughout pregnancy than those without the diagnosis.²² More studies focusing on pregnant women and other vulnerable populations are still needed. Understanding whether individuals with a diagnosis of Caffeine Use Disorder are less likely than others to quit using the drug is particularly important in populations with medical conditions that are exacerbated by caffeine consumption.

In addition to investigating the reliability and validity of the Caffeine Use Disorder diagnostic criteria, studies should compare the *DSM-5* diagnostic schema for Caffeine Use Disorder with other diagnostic schemas (e.g., the generic *DSM-5* Substance Use Disorder criteria) to determine whether the proposed Caffeine Use Disorder diagnostic schema provides a more reliable and valid assessment of caffeine dependence than other diagnostic algorithms. The research reviewed in this article suggests that the use of the Caffeine Use Disorder diagnostic schema produces relatively conservative estimates of the prevalence of caffeine dependence, but more research is needed to determine whether these estimates are more reliable or valid than those produced by other diagnostic schemas.

Objective measures of caffeine consumption

In many clinical investigations of caffeine dependence, caffeine consumption has been assessed via retrospective surveys in which participants are asked to report how many caffeinated beverages they consume on a daily basis.^{16,22} However, because caffeine concentration varies considerably within and across foods and beverages (e.g., 54 mg to 210 mg in a 6 ounce cup of brewed coffee⁸⁷), researchers should use methods to more accurately measure caffeine consumption (e.g., through the use of detailed food diaries¹⁷ or timeline follow-back approaches). Thus, future research should include studies that are designed to develop and evaluate methods to assess caffeine consumption frequently and accurately.

Functional impairment and severity

The *DSM-5* states that one key goal for the proposed research diagnosis of Caffeine Use Disorder is to stimulate research investigating the association of the diagnosis with clinically significant distress and functional impairment. Although some studies have already shown functional impairment during withdrawal,^{17,20,88} additional studies using a range of volunteer-rated, observer-rated, behavioral, and cognitive measures of impairment during withdrawal will be important.

Whether distress and functional impairment occur at times other than during caffeine abstinence should also be investigated. Thus, more prospective empirical investigations of the relationship between Caffeine Use Disorder and functional impairment during chronic caffeine administration are needed. Future research should also include surveys administered in medical settings to patients and health care providers (e.g., primary care physicians) to assess the prevalence, severity, and functional impairment of Caffeine Use Disorder among patients who present with symptoms of the disorder.

As discussed earlier, the *DSM-5* indicates that the severity of Substance Use Disorders should be estimated based on the number of criteria scored (two or three criteria = mild, four or five = moderate, and six or more = severe). To date, the only information on the severity of Caffeine Use Disorder is presented in this article based on re-analyses of data from two previously published studies that collected data on only seven of the nine *DSM-5* diagnostic criteria.^{17,21} Thus, it will be important for future researchers to attempt to validate the proposed *DSM-5* severity scoring approach by scoring all criteria and by comparing *DSM-5* severity scores with other measures of addiction severity.

Genetics

Further research investigating the role of genetic determinants in the development of Caffeine Use Disorder is needed. Although heritabilities for some markers of Caffeine Use Disorder have been demonstrated,^{60–63} no studies have examined the heritability of Caffeine Use Disorder *per se* nor the heritability of the primary diagnostic criteria of *desire to cut down or use despite harm*. In addition, given that genetic polymorphisms in the *ADORA2A* gene have been shown to predict the subjective effects of caffeine,^{67,68} future research should investigate the role of specific polymorphisms in Caffeine Use Disorder.

Comorbidity with nondrug psychiatric disorders

Because drug dependence diagnoses are frequently associated with nondrug psychiatric disorders,⁹⁰ more studies are needed to examine the relationship between Caffeine Use Disorder and nondrug psychiatric disorders. Ciapparelli *et al.*¹⁰ showed that psychiatric patients were more likely than healthy controls to fulfill *DSM-IV* Substance Dependence diagnostic criteria as applied to caffeine. Other research has shown an association between various comorbid conditions and excessive caffeine consumption. For example, excessive caffeine consumption is common among psychiatric patients, particularly those diagnosed with schizophrenia.^{91–95} In addition, some features of caffeine dependence, including tolerance and withdrawal, have been associated with

major depression, adult antisocial disorder, panic disorder, and generalized anxiety disorder.^{64,96} Moreover, excessive caffeine consumption is believed to exacerbate chronic psychiatric conditions, including anxiety.⁹⁷⁻¹⁰¹ Thus, future research should investigate whether a diagnosis of Caffeine Use Disorder predicts or exacerbates other nondrug psychiatric disorders.

Relationship between Caffeine Use Disorder and other Substance Use Disorders

Although comorbidity among Substance Use Disorders is common, only a few studies have examined the relationship between caffeine dependence and other drug dependencies. Among a group of pregnant women, Svikis *et al.*²² found that those who received a lifetime diagnosis of caffeine dependence were nearly nine times more likely than those without the diagnosis to report a history of cigarette smoking (44% vs. 5%). Further, women with both caffeine dependence and a family history of alcoholism were six times more likely to have a lifetime diagnosis of alcohol abuse or dependence. Among licit and illicit drug users, Striley *et al.*²¹ found a non-significant trend ($p < 0.10$) in the proportion of caffeine-dependent participants who were also alcohol dependent (i.e., 42% of caffeine-dependent alcohol users were also alcohol dependent, and 28% of caffeine-dependent alcohol users were not alcohol dependent; $n = 142$). They also found a non-significant trend ($p < 0.10$) in the proportion of caffeine-dependent participants who were nicotine dependent (i.e., 37% of caffeine-dependent nicotine users were also nicotine dependent, and 19% of caffeine dependent nicotine users were not nicotine dependent; $n = 120$). Among individuals from the general population, Hughes and colleagues¹⁴ found a weak correlation between the severity of caffeine dependence and alcohol dependence, but they found no correlation between caffeine dependence and nicotine dependence. In addition, some twin studies examining caffeine use, alcohol use, and cigarette smoking found that a common genetic factor (i.e., polysubstance use) underlies the use of these three substances, with 28% to 41% of the heritable effects of caffeine use (or heavy use) shared with alcohol and smoking.^{63,102} However, other twin studies suggest that caffeine and nicotine use and dependence are substantially influenced by genetic factors unique to these drugs.^{64,65} Thus, much more clinical, epidemiological, and genetic research is needed to determine the relationship between Caffeine Use Disorder and other Substance Use Disorders.

In addition to further investigations of comorbidity, studies that directly compare Caffeine Use Disorder with other Substance Use Disorders are also needed. To our knowledge, only two such studies have been conducted to date. In a group of 148 licit and illicit drug users who used caffeine, nicotine, and alcohol, Striley *et al.*²¹ compared the proportion of participants who endorsed the seven *DSM-IV* diagnostic criteria for Substance Dependence as applied to caffeine with the proportion who endorsed the criteria as applied to alcohol and nicotine. The proportion endorsing each criterion for caffeine was generally lower than the proportion endorsing each criterion for nicotine and for alcohol, consistent with the finding that the prevalence of caffeine dependence (about 28%) was lower than that for nicotine (80%) and alcohol (50%) in this group of drug users. Miyata and colleagues¹⁰³ compared

individuals who met the *DSM-IV* Substance Dependence diagnosis for either caffeine or nicotine before they experienced a controlled 7-day abstinence from their respective drug of dependence. The results showed no differences between nicotine and caffeine in craving or social functioning. Although the incidence of irritability was higher with nicotine than caffeine, there were no differences in irritability on a well-being questionnaire. The authors concluded that, overall, there were no meaningful differences between nicotine and caffeine in the difficulties of abstaining. Additional qualitative and quantitative comparisons of Caffeine Use Disorder with other Substance Use Disorders are needed.

Future research is also needed to determine whether the development of Caffeine Use Disorder is predictive of the development of subsequent licit or illicit Substance Use Disorders. If this is the case, such research could have important implications for the early identification and treatment of subpopulations that are vulnerable to the development of more harmful substance abuse.

Caffeine Use Disorder among energy drink consumers

Future research should investigate the prevalence and severity of Caffeine Use Disorder among consumers of caffeinated energy drinks. Although energy drinks often contain a variety of compounds, including taurine, glucuronolactone, and B-vitamins, research suggests that the effects of these additives contribute little beyond the effects of caffeine on physical and cognitive performance.^{104,105} However, more research is needed to evaluate the independent subjective and behavioral effects of these ingredients and the effects of the additives when combined with caffeine.

The primary psychoactive ingredient in energy drinks is caffeine. The amount of caffeine contained in energy drinks can range from 50 mg to 505 mg.¹⁰⁶ Therefore, these beverages allow consumers to drink large quantities of caffeine in a relatively small number of servings. Research suggests that this level of consumption can produce Caffeine Intoxication⁸⁷ (see Table 4), resulting in serious adverse health consequences and, in rare cases, death.¹⁰⁷

Due to recent increases in the popularity of caffeinated energy drinks, there is growing concern among health professionals about the short- and long-term negative health consequences associated with energy drink consumption, especially among children, adolescents, and young adults.¹⁰⁸⁻¹¹⁰ Indeed, these concerns may be warranted, considering that a 2013 report from the Drug Abuse Warning Network (DAWN) showed that emergency room visits involving energy drinks doubled in the United States from 2007 to 2011.¹¹¹ In addition, some research has shown that energy drink consumption is associated with increased marijuana use, alcohol consumption, and alcohol-related risky behavior, including riding with an intoxicated driver, taking advantage of another sexually, and being physically hurt or injured.¹¹²⁻¹¹⁴ Moreover, studies have found that energy drink consumption is associated with an increased risk for alcohol dependence¹¹⁵ and predicts subsequent nonmedical prescription drug use.¹¹⁶ Thus, researchers should explore whether a diagnosis of Caffeine Use Disorder among adolescents and adults who consume energy drinks is associated with increased energy drink consumption, subsequent licit and illicit drug dependencies, or negative health consequences.

Course and treatment

No studies have investigated the course and history of Caffeine Use Disorder. However, similar to other Substance Use Disorders, Caffeine Use Disorder appears to be a chronic relapsing condition. For example, studies have shown that caffeine-dependent participants report frequent relapses due to failed efforts to quit caffeine.^{17,20}

The research discussed in the present review shows that some individuals desire to quit using caffeine but are unable to do so. Moreover, some caffeine users are sufficiently distressed by their caffeine use to seek assistance to quit or reduce caffeine consumption. For example, Juliano and colleagues¹⁷ reported that 47% of 258 individuals seeking treatment for caffeine use were interested in one-on-one counseling, 12% were interested in group counseling, 25% were interested in a self-help booklet, and 4% were interested in phone-based assistance. Future research should determine the extent of the demand for Caffeine Use Disorder treatment.

Unfortunately, few treatments for Caffeine Use Disorder are currently available. To date, only a handful of studies have examined individuals receiving treatment for problems related to caffeine use.^{117–121} More research on this population is needed to determine what methods work best to promote caffeine reduction and cessation, ideally, so that brief, inexpensive interventions can be developed to assist caffeine users with their quit attempts.

Summary and Conclusion

The literature reviewed in this article shows that caffeine produces behavioral and physiological effects similar to those produced by other drugs of dependence. Indeed, an abundance of evidence from controlled laboratory studies with human and nonhuman animal subjects demonstrates the biological plausibility of caffeine dependence. Further, a number of recent clinical studies show that a nontrivial proportion of caffeine users develops clinically meaningful features of caffeine dependence, including a persistent desire or unsuccessful efforts to cut down or control caffeine use, continued use despite harm, and a characteristic withdrawal syndrome.

Although the World Health Organization already recognizes a diagnosis of Caffeine Dependence Syndrome in the *ICD-10*, the American Psychiatric Association has indicated that more research is needed to determine the clinical significance of Caffeine Use Disorder before the diagnosis may be recognized in the *DSM* as a clinical disorder. Indeed, there is a critical need for more clinical, epidemiological, and genetic research on caffeine dependence. To date, no national population-based study has been conducted to investigate the prevalence and severity of caffeine dependence in the general population, and most studies that have characterized caffeine dependence in the general population and among special populations relied on relatively small sample sizes. Nevertheless, several recent reports have shown that caffeine dependence can result in clinically significant distress and functional impairment, and many individuals are sufficiently distressed by their caffeine dependence to seek treatment. Due to this new evidence, Caffeine Use Disorder is now recognized by the *DSM-5* as a condition in need of further study.

The inclusion of Caffeine Use Disorder in the *DSM-5* should help stimulate more research on caffeine dependence. More studies are needed to determine the prevalence of

Caffeine Use Disorder and the severity of functional impairment associated with the disorder. In addition, research is needed to evaluate the reliability and validity of the Caffeine Use Disorder diagnostic schema and the relationship between Caffeine Use Disorder and other behavioral and mental disorders. Most importantly, however, more research is needed to determine which methods work best to treat individuals who are currently distressed by this clinically important health problem.

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