Caffeine dependence: fact or fiction?

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INTRODUCTION

Caffeine is the most widely consumed psychoactive substance in the world[1], with consumption occurring in different forms (e.g., drinking coffee, tea, maté, and soft drinks; chewing kola nuts; consuming cocoa and guarana products), and in widely different but culturally well-integrated social contexts (e.g., the coffee break in the USA; teatime in the UK; kola nut chewing in Nigeria). As shown in Figure 1, the per capita consumption of caffeine varies widely between countries. The average caffeine content for some common caffeine-containing foods and medications is presented in Table 1.

Studies of the acute effects of low to moderate doses of caffeine show caffeine tends to produce a profile of positive subjective effects such as alertness, increased feelings of well-being, and energy[2,3], while studies of adverse effects or physical illnesses associated with caffeine consumption have generally failed to find significant morbidity or mortality associated with moderate caffeine use[4]. Thus, the wide use and acceptability of caffeine may be understood in the context of this combination of positive subjective effects and no marked adverse effects.

The acute ingestion of a large dose of caffeine can produce the distinct clinical syndrome of caffeine intoxication. However, the existence of other syndromes associated with caffeine use such as caffeine dependence has been less well established, as exemplified by their absence in the most recent edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM)[5,6].

The purpose of this paper is to address the question of whether caffeine dependence is fact or fiction. The omission of caffeine dependence as a diagnostic category in the DSM, and the wide availability and acceptability of caffeine use, suggest both clinicians and the lay public may view an official recognition of a caffeine dependence syndrome (equivalent to dependencies on other drugs such as nicotine and heroin) as a trivialization of the concept of dependence, or an inappropriate use of the term. However, before considering the evidence supporting caffeine dependence as a meaningful concept, an important semantic clarification pertinent to a discussion of drug dependence should be made.

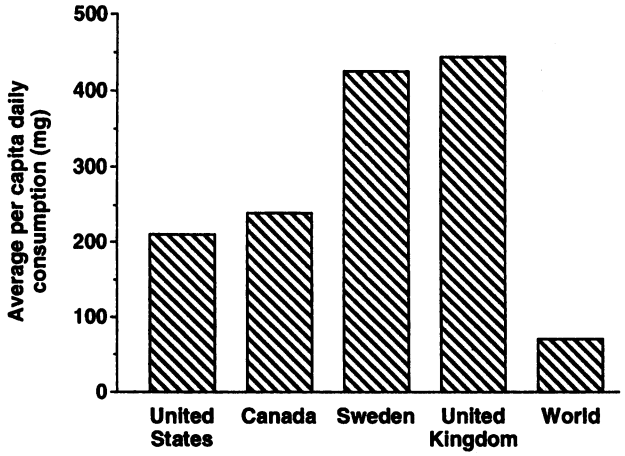

Figure 1 **The 1981 or 1982 average per capita daily caffeine consumption in milligrams for selected countries. Estimates are based upon production data, and should be considered tentative. (From Gilbert RM. Caffeine consumption. In: Spiller GA, ed. *The Methylxanthine Beverages and Foods: Chemistry, Consumption and Health Effects*. New York: Alan R Liss Inc, 1984:185–213)**

The term 'dependence' may be used to describe *physical* dependence upon a psychoactive substance (typically indicated by the presence of a distinct withdrawal syndrome upon cessation of consumption of the substance), or it may be used to describe a *clinical syndrome* of dependence upon a psychoactive substance (typically diagnosed using a number of signs and symptoms from a clinical assessment, one component which may be evidence of physical dependence). These two meanings of dependence create confusion, particularly because some people may be physically dependent upon a substance without having a clinical syndrome of dependence (such as a patient with cancer who is prescribed opioids chronically for analgesic treatment), and some people may have a clinical syndrome of dependence without evidence of physical dependence (such as episodic binge alcohol use). Thus, a discussion of drug dependence requires clarification of the context in which the term 'dependence' is being used.

This paper will, first, briefly review the large body of preclinical and clinical studies demonstrating that physical

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Table 1 **Typical caffeine content of foods and medications**

Substance	*Caffeine content*
Coffee	
Brewed	100 mg/cup (177 ml)
Instant	70 mg/cup (177 ml)
Decaffeinated	4 mg/cup (177 ml)
Tea	40 mg/cup (177 ml)
Caffeinated soda	45 mg/can (355 ml)
Cocoa beverage	5 mg/cup (177 ml)
Chocolate	
Chocolate milk	4 mg/cup (177 ml)
Dark chocolate	20 mg/bar (29 g)
Milk chocolate	6 mg/bar (29 g)
Medications	
Caffeine-containing cold remedies	25–50 mg/tablet
Caffeine-containing analgesics	25–65 mg/tablet
Stimulants	100–350 mg/tablet
Weight-loss aids	75–200 mg/tablet

dependence upon caffeine can occur. This will be followed by an evaluation of the more limited evidence showing some people can manifest a clinical syndrome of caffeine dependence similar to other drug dependence syndromes. The paper will conclude by examining the implications of the establishment of a diagnosis of a clinical syndrome of caffeine dependence, and some of the future directions research on caffeine dependence may take.

CAN CAFFEINE PRODUCE PHYSICAL DEPENDENCE?

Caffeine physical dependence has been demonstrated in both preclinical animal studies as well as in clinical studies with humans by showing that cessation of caffeine use produces a distinct, time-limited withdrawal syndrome. Preclinical animal studies have demonstrated caffeine withdrawal produces decreases in locomotor activity, operant responding, and the reinforcement threshold for electrical brain stimulation, as well as changes in sleep patterns and the avoidance of a preferred flavour when the flavour is paired with caffeine abstinence[7–14]. Such caffeine withdrawal has been shown in rats, cats and monkeys[7–14], and can occur following a wide range of doses over variable periods of time[7,8]. The severity of withdrawal in animals appears to be dependent upon the maintenance dose of caffeine, with higher doses associated with more severe withdrawal[10,11]. Withdrawal onset in animals typically occurs within the first 24 h after caffeine cessation, and peaks within the first 48 h.

Caffeine withdrawal has also been demonstrated in a number of clinical studies. The following most usual signs and symptoms of caffeine withdrawal have been reported:

(i) Headache
(ii) Drowsiness/sleepiness
(iii) Impaired concentration/fatigue/work difficulty
(iv) Depression
(v) Anxiety
(vi) Irritability
(vii) Nausea/vomiting
(viii) Muscle aches/stiffness

The most common symptom of caffeine withdrawal is headache. Over 100 years ago Bridge reported that the abrupt termination of coffee drinking could result in a severe headache, and he recommended 'reducing the rations of coffee gradually through a week or more of time'[15]. Caffeine withdrawal headache generally occurs 12–24 h after the last dose of caffeine, and usually resolves within 2–4 days, although some people may report sporadic headaches for as long as 11 days after caffeine use[16,17]. Other features of caffeine withdrawal include sleepiness/drowsiness, impaired concentration/lassitude/work difficulty (distinct from drowsiness or sleepiness), anxiety/depression, and flu-like symptoms (including headache, fatigue, muscle aches and stiffness, hot or cold spells, nausea and vomiting). Other signs and symptoms of caffeine withdrawal can include impairments in psychomotor performance (usually one detected through the use of specific tests), irritability, rhinorrhoea, confusion, diaphoresis, blurred vision, and craving for caffeine[17]. While it may seem that symptoms of caffeine withdrawal simply represent sequelae of headache, non-headache symptoms of caffeine withdrawal do not necessarily correlate with the presence of headache, and can occur in the absence of headache[17]. As has been demonstrated in preclinical studies, the severity of caffeine withdrawal appears to be a function of the dose of caffeine[18–21], although caffeine withdrawal has been demonstrated in low to moderate caffeine consumers[21]. In fact, caffeine withdrawal has been shown to occur with doses as low as 100 mg per day—the equivalent of about one cup of brewed coffee or two to three caffeinated sodas per day[17].

Thus, converging lines of evidence from both preclinical and clinical studies have shown that caffeine withdrawal is a discrete syndrome associated with the cessation of caffeine use. While several further questions regarding caffeine withdrawal remain, such as its features in special populations (e.g., children, the elderly), whether a relative decrease in caffeine use can produce caffeine withdrawal, and the optimal parameters under which caffeine can be discontinued without the appearance of withdrawal, the overwhelming evidence suggests caffeine can produce *physical* dependence.

CAN CAFFEINE PRODUCE A CLINICAL SYNDROME OF DEPENDENCE?

While there is considerable pre-clinical and clinical evidence supporting physical dependence on caffeine, there is markedly less evidence for a clinical syndrome of caffeine dependence. There are two studies which have attempted to address this issue. The first was a random telephone survey of residents of the state of Vermont (USA) conducted by Hughes and colleagues[22]. The investigators applied the generic criteria for DSM–III–R substance dependence to 166 current caffeine users, and found 27% had mild caffeine dependence (3–4 criteria), 14% had moderate dependence (5–6 criteria), and 3% had severe dependence (7–9 criteria). The most commonly reported symptom was a persistent desire or one or more unsuccessful efforts to cut down or control caffeine use. While there were several limitations to this study (e.g., a telephone survey, a relatively small sample size), these results suggest there may be a large number of people who demonstrate symptoms consistent with a DSM-based diagnosis of caffeine dependence.

The second study was a diagnostic evaluation of people who reported problems with their caffeine use[23]. In this study 16 cases of caffeine dependence were diagnosed based upon DSM–IV criteria applied through the use of a standardized psychiatric interview. A conservative approach to making diagnoses was used, as only four of the seven DSM–IV criteria were applied (since not all criteria are appropriate for a licit substance that is generally socially accepted). The four criteria were: (1) tolerance; (2) withdrawal; (3) use continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance use; and (4) a persistent desire or unsuccessful efforts to cut down or control substance use. Subjects were diagnosed only if they fulfilled at least three of the four criteria. The median daily caffeine dose for the 16 caffeine dependent subjects was 360 mg, and 38% of the subjects consumed approximately 300 mg or less on a daily basis. The primary vehicle used by subjects was coffee, tea, or soft drinks. Surprisingly, for over 40% of subjects, the primary vehicle was soft drinks. Interestingly, the 16 people with caffeine dependence had high rates of other psychiatric disorders, including other substance use disorders and mood disorders, and the average time in remission for these diagnoses was several years. Thus, employing a narrow set of diagnostic criteria applied by a psychiatrist using a standardized structured interview, cases of a clinical syndrome of caffeine dependence were identified. However, there were limitations to this study, such as the use of a small, relatively select population of self-identified problematic caffeine users, and the lack of information about the prevalence of caffeine dependence in the community.

Thus, evidence for a clinical syndrome of caffeine dependence is relatively limited, although the two studies described above suggest a clinical syndrome of caffeine dependence can occur for some consumers of caffeine, and the syndrome may be more common than is generally recognized.

IMPLICATIONS OF A CLINICAL SYNDROME OF CAFFEINE DEPENDENCE

It is not unusual for physicians to recommend patients to reduce or discontinue caffeine use because of conditions such as anxiety, insomnia, arrhythmias, palpitations and tachycardia, and oesophagitis/hiatal hernia[24]. If there is a recommendation to quit caffeine, then it is important to recognize that patients with caffeine dependence may not be compliant with a simple instruction to stop. However, the presence of caffeine dependence should not necessarily be grounds in and of itself for recommending a person to discontinue caffeine use.

A concern with the establishment of a diagnosis of caffeine dependence is that the diagnosis should not be used to trivialize forms of drug dependence associated with serious health risk, such as tobacco use, intravenous drug use, and heavy alcohol use. The similarities between nicotine dependence and caffeine dependence are particularly striking. Both caffeine and nicotine are licit, culturally-integrated substances that do not produce marked intoxication at typical doses. Furthermore, chronic consumption of both nicotine and caffeine does not generally lead to dose escalation, they both can function as reinforcers, and both can produce tolerance and physical dependence[25,26]. However, unlike caffeine there clearly is morbidity and mortality associated with nicotine dependence, resulting in significant health risks with the regular use of nicotine-containing substances. Thus, when comparing caffeine dependence to classic drug dependence syndromes it is important to recognize the relative safety of caffeine use as a unique feature of caffeine dependence.

There are compelling research and clinical reasons for continued study of caffeine dependence. From a research perspective, caffeine may serve as a useful model of drug abuse, permitting a better understanding of the common physiological and psychological components underlying psychoactive drug use. For example, the co-occurrence of certain disorders such as mood disorders with a clinical syndrome of caffeine dependence is an intriguing observation, and suggests caffeine dependence may serve as a clinical marker for detecting other psychiatric disorders. Finally, from a clinical perspective, recognition of caffeine dependence is important because there are people who are distressed by their caffeine use, and feel they cannot control or stop their use. Such people are in need of treatment, and

it is important to recognize them as patients requiring the compassionate care of clinicians.

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