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# Caffeine challenge test and panic disorder: a systematic literature review

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This systematic review aimed to examine the results of studies that have investigated the induction of panic attacks and/or the anxiogenic effect of the caffeine challenge test in patients with panic disorder. The literature search was performed in PubMed, Biblioteca Virtual em Saúde and the ISI Web of Knowledge. The words used for the search were caffeine, caffeine challenge test, panic disorder, panic attacks and anxiety disorder. In total, we selected eight randomized, double-blind studies where caffeine was administered orally, and none of them controlled for confounding factors in the analysis. The percentage of loss during follow-up ranged between 14.3% and 73.1%. The eight studies all showed a positive association between caffeine and anxiogenic effects and/or panic disorder.

**KEYWORDS:** anxiety disorder • caffeine • caffeine challenge test • coffee • panic attacks • panic disorder

## The metabolic properties of caffeine

Chemically, caffeine is 1,3,7-trimethylxanthine, which means that it is a molecule of xanthine with methyl groups replacing the three hydrogens attached to nitrogens in the xanthine ring. After absorption, caffeine is metabolized (demethylated) in the liver by cytochrome P450 1A2 (CYP1A2) and excreted in urine. Caffeine has a half-life of 3–5 h in adults. As caffeine is a liposoluble alkaloid, it is easily absorbed by the GI tract. Nicotine increases the elimination of caffeine, and antibiotics, especially quinolones, increase serum levels of caffeine. The lethal dose of caffeine for humans is approximately 10 g (for reference, a cup of coffee contains ~125 mg of caffeine) [1–3].

Biotransformation of caffeine is complex and leads to the formation of three main groups of metabolically active methylxanthines: 84% paraxanthine (1,7-dimethylxanthine), 12% theobromine (3,7-dimethylxanthine) and 4% theophylline (1,3-dimethylxanthine). CYP1A2 is responsible for approximately 90% of the primary metabolism of caffeine [4], but other enzymes, such as cytochrome P450 2A6 (CYP2A6), cytochrome P450 2E1 (CYP2E1), *N*-acetyltransferase (NAT2) and xanthine oxidase (XO), are also involved in caffeine metabolism (FIGURE 1) [5].

Caffeine is a psychoactive substance that acts as a stimulant on the CNS. Caffeine antagonizes adenosine receptors present in nervous tissue

while maintaining a state of arousal. Adenosine is a cellular component formed by one adenine and one ribose, and its levels are primarily governed by metabolism of ATP and other adenine nucleotides. Adenosine acts as a messenger that regulates brain activity and modulates wakefulness and sleep. Through this mechanism, caffeine improves the ability to make physical and mental effort before the onset of fatigue.

Caffeine binds with high affinity at both the A1 and A2a adenosine receptors, the two subtypes known to be responsible for many of caffeine's behavioral effects [6]. Both of these adenosine receptor subtypes are expressed in the human brain, with A1 receptors being widely distributed throughout the brain and A2a receptors mainly concentrated in the dopamine-rich basal ganglia areas of the brain [7]. In addition, caffeine contributes to the release of catecholamines, which leads to constriction of blood vessels. This mechanism is important in relieving the pressure of migraines and headaches, which explains why many analgesics contain caffeine [8–10].

## Caffeine sources & its concentration in coffee

Caffeine is present in approximately 60 plant species and numerous food items, such as tea, chocolate, cola soft drinks, guarana and cocoa (TABLE 1).

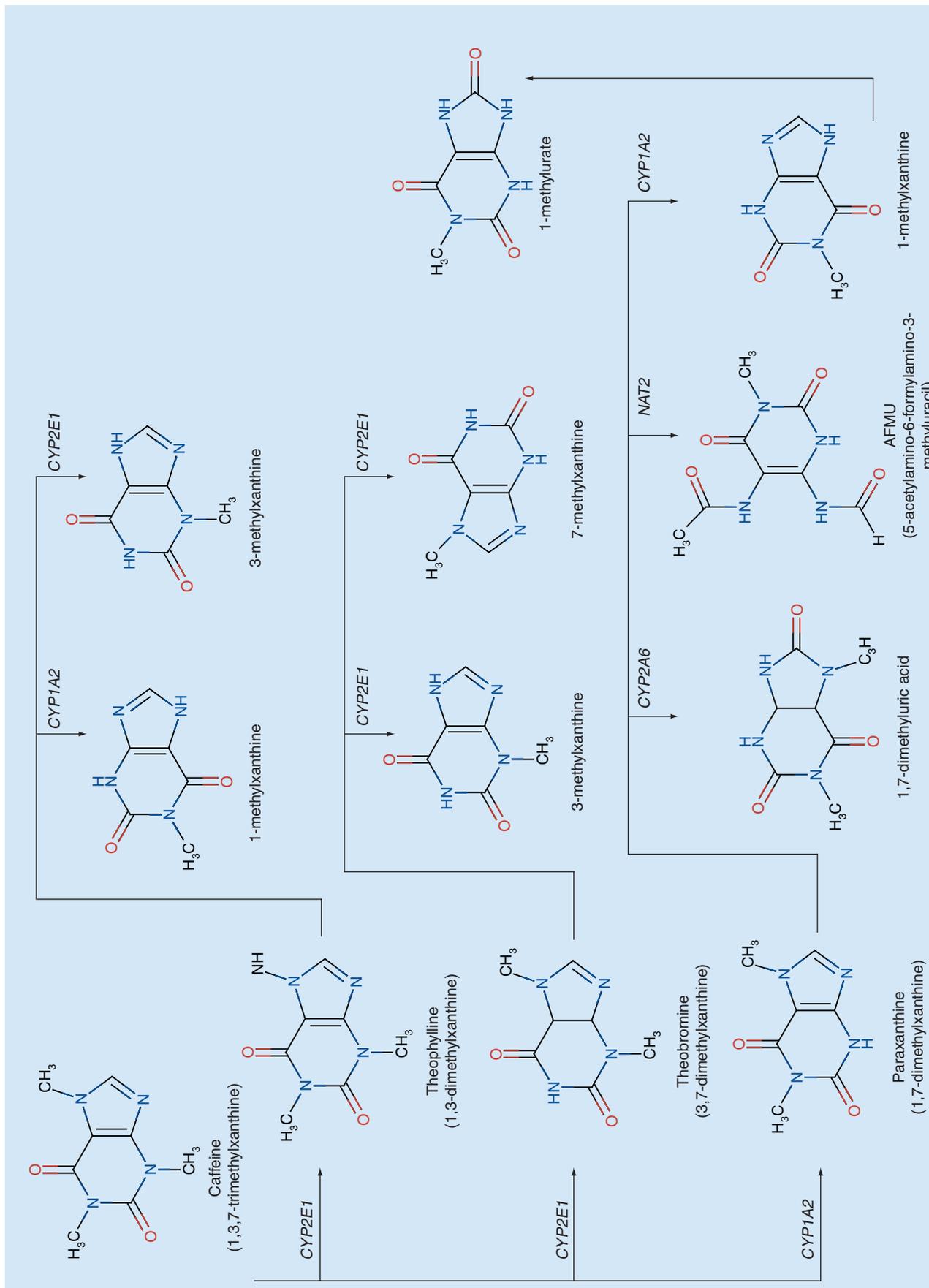


Figure 1. Action of enzymes cytochrome P450 1A2 (CYP1A2), cytochrome P450 2A6 (CYP2A6), cytochrome P450 2E1 (CYP2E1), N-acetyltransferase (NAT2) and xanthine oxidase (XO) in the metabolism of caffeine.

Caffeine is also present in medicines, such as analgesics, and appetite suppressants [11,12]. In Brazil, in drugs such as paracetamol, dipyrrone and acetylsalicylic acid, the amount of caffeine per dose is between 15 and 100 mg.

In foods, caffeine content can vary greatly, and coffee is the food source that accounts for the majority of caffeine intake. The amount of caffeine in coffee depends on a number of factors, including the variety of plant, method of cultivation, growth conditions and genetic and seasonal aspects. In the case of brewed coffee, the amount of ground bean, the type of product (roasted or instant, decaffeinated or regular) and the process used in its preparation also influence caffeine levels [13,14]. Caffeine content can vary from 29 to 176 mg/cup in coffee, 8–107 mg/cup in tea, 50–10 mg/cup in chocolate and 32–65 mg/360 ml in cola [15].

### Caffeine intake

As a range of foods and medicines contain caffeine, caffeine consumption is common throughout the world. Indeed, caffeine intake has been estimated to be approximately 120,000 tons per year [13]. Approximately 80% of the world's population consumes caffeine daily [1].

In the USA, which is the largest consumer of caffeine in the world, the average consumption of caffeine is approximately 200 mg, or the equivalent of two cups of coffee per day. However, 10% of the population ingests more than 1000 mg per day [16]. Approximately 90% of the US population consumes caffeine daily [17].

In Europe, the average consumption of caffeine among adults is approximately 200 mg per day. In the Nordic countries (Denmark, Finland, Norway and Sweden), the average consumption of caffeine is 400 mg daily [1,18].

The Latin countries have traditionally been accustomed to drinking concentrated coffee with high levels of caffeine. Between November 2009 and October 2010, the per capita consumption of coffee in Brazil was 6.02 kg of raw coffee beans, or 4.81 kg of roasted coffee, which equates to almost 81 l per person per year. These data approximate the Brazilian per capita consumption to be similar to that of Germany (5.86 kg per person per year). Moreover, Brazil has already exceeded the rates of consumption of Italy and France, which are big consumers of coffee. The Nordic countries (Finland, Norway and Denmark), however, are still the leaders in consumption, with a volume of approximately 13 kg per capita per year [101].

Although there is no evidence that caffeine intake at moderate doses (approximately 300 mg/day) is harmful to the health of a normal individual, higher doses of this substance may increase the risk for gastrointestinal cancers, heart disease, miscarriage, reduction in fetal weight and potentiation of teratogenic agents. Caffeine can also exacerbate anxiety and contribute to sleep disorders. In addition, there have been reports of poisoning and suicide

**Table 1. Caffeine content of some drinks and food.**

Amount of caffeine in drinks and food	Service size	Caffeine (mg)
Coffee, generic brewed	8 oz	133 (range: 102–200)
Coffee, generic instant	8 oz	93 (range: 27–173)
Coffee, generic decaffeinated	8 oz	5 (range: 3–12)
Tea, brewed	8 oz	53 (range: 40–120)
Nestea®	12 oz	26
Coke Red, regular or diet	12 oz	54 (20 oz = 90)
Pepsi®	12 oz	38 (20 oz = 63)
Red Bull®	8.3 oz	80
Hot cocoa	8 oz	9 (range: 3–13)
Hershey's® Special Dark Chocolate Bar	1.45 oz	31
Hershey's® Chocolate Bar	1.55 oz	9

Data taken from [102].

attempts with caffeine. Caffeine intoxication, which can present with vomiting, abdominal cramps, convulsions and arrhythmias, requires intensive care [1,19,20].

Numerous studies have documented the safety of caffeine in typical daily doses, but there are some anxiety symptoms that can be associated with its use. In panic disorder (PD) patients, oral administration of caffeine produces significant increases in subject-rated anxiety, nervousness, fear, nausea, palpitations, restlessness and tremors [21]. In sensitive individuals, high doses of caffeine can induce symptoms of a condition called 'caffeinism', which include anxiety, agitation, nervousness, dysphoria, insomnia and rambling flow of thoughts and expressions [22,23].

After a prolonged period of high caffeine use, a person can manifest withdrawal symptoms that vary from one person to another. Indeed, some individuals may be highly sensitive and present symptoms after exposure to lower doses of caffeine. The reinforcing effect of caffeine and withdrawal symptoms has led to repeated intake of this substance, which can characterize a cycle of abuse [18].

Like nicotine, caffeine is a legal stimulant that causes dependence and it has been widely discussed. While not including caffeine dependence or abuse as a diagnosis in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV because of insufficient clinical evidence of caffeine dependence and abuse is medically correct [24,25], this approach may be disappointing for primary care physicians and psychiatrists because it may deprive consumers of the awareness of the issues associated with caffeine use, particularly for individuals who consume large quantities [26].

### Panic disorder

Panic disorder has a lifetime prevalence of approximately 1.5–2% of the population and PD is associated with increased psychiatric morbidity (e.g., depression, alcoholism and suicide risk) [27]. The diagnosis of PD is based on the existence of three major clinical syndromes: panic attacks, anticipatory anxiety and phobic avoidance.

Panic attacks are among the most common diagnoses that lead patients to seek care from emergency medical services. Thus, the diagnosis and management of panic attacks are of interest to psychiatrists and general practitioners. According to Ballenger, 90% of PD patients believe they have a physical problem, rather than a psychiatric or psychological problem [28].

According to McLean *et al.*, the lifetime occurrence of PD is 7.1% for women and 4.0% for men [29]. Women with a lifetime diagnosis of an anxiety disorder are more likely than men to also be diagnosed with another anxiety disorder, bulimia nervosa and major depressive disorder. There are no gender effects in the mean age of onset for PD [30]. Men and women have differences in physiological response to stressors. For example, women show greater cardiovascular reactivity to stress [31]. Men and women also appear to use internal sensory information and external environmental cues differently in perceiving emotions such as fear. Men appear to more accurately perceive physiological changes, whereas women are more expert at assessing situational cues [32]. These differences in reactivity and appraisal strategy could contribute to the cognitive differences observed in PD [33].

Several types of panic attacks can occur. The most common is the spontaneous panic attack, which is not associated with any known precipitating situation. Another type is the situational panic attack, which occurs when an individual faces certain situations, such as traffic or crowds. Another type is triggered by certain emotional contexts, such as family disagreements or the threat of divorce. There are also panic attacks with limited symptoms, which refer to attacks when patients have three or fewer symptoms during a somatopsychic anxiety attack [34]. There are also nocturnal panic attacks, which are characterized by sudden awakening, terror and hypervigilance. Interestingly, approximately 40% of PD patients have panic attacks during sleep [35].

Klein formulated a phenomenological three-phase model for PD [36,37]. A panic attack, which is the most important feature of PD, is characterized by the sudden onset of anxiety, increasing autonomic symptoms and a subjective sense of terror, which lasts 10–30 min. The second feature of PD is anticipatory anxiety. At this stage, the patient develops a concern that a panic attack will occur again and appears to be in a chronic state of anxiety. The anticipatory anxiety occurs in the interval between panic attacks and becomes a constant and diffuse anxiety. This form of anxiety has many features of anxiety found in generalized anxiety disorder, such as increased focus on somatic sensations, seizures and hyperactivity. The anticipatory anxiety leads to avoidance behavior (i.e., the phobia).

Some patients (30–60%) may develop a third phase of PD (i.e., a phobic avoidance). They are so scared of suffering a new panic attack that they avoid being in places or situations where it is difficult or embarrassing to escape or get help if they suffer from a panic attack. Agoraphobia is often associated with psychological symptoms of anxiety, such as fear of losing control, fear of going crazy or being embarrassed, and fear of fainting or dying. This leads an individual to avoid a series of situations, such as being home alone or going out alone into the street, being in crowded places, traveling, using public transportation (e.g., bus or subway), driving a car or crossing a bridge [38].

In clinical practice, especially in centers specializing in treatment of PD, the occurrence of multiple psychiatric diagnoses in patients with PD has been more like the rule than the exception. Uncomplicated PD is more likely to exist independently, but even this disorder is found alone less than 50% of the time. Generalized anxiety disorder and social phobia are the most frequent comorbid diagnoses [39].

Panic disorder is often associated with other anxiety disorders and depression. In the National Comorbidity Survey – NCS Replication [40], one or more comorbid conditions were found in 71.9% of cases of panic attack without PD and without agoraphobia, and 83.1% of cases of PD without agoraphobia. In the case of comorbidity with other anxiety disorder and major depression, with agoraphobia odds ratios (ORs; 4.4–24.0) were consistently higher than the PD without agoraphobia ORs (2.0–5.4) and often as high as the PD with agoraphobia ORs (2.5–25.8) [27]. Alcohol/substance dependence or abuse and personality disorders are often associated with PD [41].

Cognitive-behavioral therapy (CBT) is a psychotherapeutic approach that proposes to treat a variety of psychological problems based on theoretical assumptions derived from experimental studies. One of the basic assumptions is that our feelings and behaviors are largely determined by how we think.

One of the objectives of CBT is identifying the core beliefs of the patient and submitting them to tests of validity (i.e., contrast them with reality and see whether they are true). The psychotherapeutic work within the CBT approach can be divided into three phases: research, case formulation and treatment. Techniques used for the management of panic attacks are respiratory training, distraction and cognitive restructuring. In addition, interoceptive exposure has been shown to be effective in the treatment of PD, and it can be implemented with the help of these three techniques [42]. Pharmacological treatments, including tricyclic antidepressants, selective serotonin-reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs) and benzodiazepines, associated with psychotherapy have shown success in the treatment of PD [43].

### Anxiogenic tests

There are only a few epidemiological studies that have demonstrated the effects of caffeine on PD. Some of these studies reported that PD patients were likely to suffer panic attacks in response to challenge tests, such as caffeine administration. Oral administration of caffeine has been shown to significantly increase anxiety, nervousness, fear, nausea, palpitations, agitation and/or tremors in humans [44,45].

Animal models of anxiety have been used in preclinical research to select new drugs with therapeutic potential for anxiety disorders. In addition, animal models are useful for examining mechanisms of action and testing hypotheses about the pathophysiology of anxiety disorders [46].

There are two ways to produce experimental anxiety in humans: chemical means (e.g., caffeine, cholecystokinin-tetrapeptide [CCK-4] and CO<sub>2</sub>) and psychological means. Chemically induced anxiety results from challenge (provocative testing)

**Table 2. Year of publication, origin, sample size and age of participants of the selected studies concerning the association between caffeine and panic disorder from 1991 to 2009.**

Study (year)	Country	Sample (n)	Age	Ref.
Klein <i>et al.</i> (1991)	USA	10	30–57 years	[55]
Beck & Berisford (1992)	USA	21	The mean age was 33.9 years	[63]
Bruce <i>et al.</i> (1992)	UK	12	NI	[64]
Nardi <i>et al.</i> (2007)	Brazil	143	29 panic disorder patients with a mean age of 34.2 years; 27 patients with current major depression with panic attacks with a mean age of 43.9 years; 25 patients with current major depression with a mean age of 39.7 years; and 28 subjects with no family history of anxiety or mood disorder with a mean age of 35.2 years	[57]
Nardi <i>et al.</i> (2007)	Brazil	83	The mean age of the responsive group was 36.9 years, and the mean age of the nonresponsive group was 39.2 years	[58]
Nardi <i>et al.</i> (2008)	Brazil	93	25 panic disorder patients with a mean age of 33.9 years; 27 of the panic disorder patients' first-degree relatives had a mean age of 37.2 years; and 22 healthy subjects with no first-degree relatives with a history of moderate or severe anxiety or mood disorder had a mean age of 31.7 years	[54]
Masdrakis <i>et al.</i> (2008)	Greece	23	The mean age was 27 years	[45]
Nardi <i>et al.</i> (2009)	Brazil	98	28 panic disorder patients with a mean age of 37.4 years; 25 generalized social anxiety disorder patients with a mean age of 41.5 years; 19 performance social anxiety disorder patients with a mean age of 38.2 years; and 26 subjects for the control group with a mean age of 35.5 years	[44]

NI: Not informed.

with chemicals used to induce panic attacks. Psychologically induced anxiety results from environmental stimuli or contexts that represent some kind of threat [47].

Cholecystokinin-tetrapeptide is a synthetic analog of the endogenous neuropeptide cholecystokinin [48,49], which has been found in different brain regions [50]. Particularly high concentrations of CCK have been detected in regions that have been implicated in the mediation of panic attacks. Moreover, there is increasing evidence that CCK acts there as a neurotransmitter [51].

Klein suggested that panic attacks result from the triggering of a –hypersensitive in PD patients– ‘suffocation alarm monitor system’ and that the increased rate of endogenous CO<sub>2</sub> accumulation is one of the most potent asphyxia-relevant cues that trigger this biological system [52]. Breath-holding (BH) test increases endogenous CO<sub>2</sub> and, presumably, lower BH duration indicates a greater CO<sub>2</sub> sensitivity and, by the same token, a lower threshold of the suffocation alarm monitor. Thus, BH test was introduced as a simple probe to test the sensitivity of the suffocation alarm monitor system [53].

This article examined the results of studies that investigated the induction of panic attacks and/or anxiogenic effects by the oral caffeine challenge test in patients with PD.

## Methods

We performed a systematic review of the literature, which consisted of retrospective searches of scientific articles related to the association between caffeine consumption and PD. We performed our searches in PubMed, BVS (Virtual Health Library [VHL]) and the ISI Web of Knowledge (ISIWEB), and the selected studies were published between 1991 and 2009.

To set the exposure ‘caffeine challenge test’ for the outcome ‘panic attack and/or anxiogenic effect’, we used the following keywords in our searches: caffeine, caffeine challenge test, PD, panic attacks and anxiety disorder. Another strategy was a manual search in reference lists of identified articles selected by our electronic search. The studies that we chose did not include pregnant women or individuals younger than 18 years of age.

Using our established strategy, the bibliographic search resulted in 1349 articles. However, only eight articles were selected to compose the current article. The others were excluded for several reasons (i.e., they did not fit into any of the criteria, they were literature reviews, they were repeats from one of the other databases or the articles were not available in their entirety).

The criteria used to select articles for review were a randomized double-blind study design, written in English, Portuguese or Spanish, and using an oral administration of caffeine. Selected articles were then compared with the following axes: the year of publication, country of origin, sample size, participants' age, rate of loss during follow-up, amounts of caffeine and placebo offered, measures of effect size/strength of association, disorders/symptoms evaluated, scales used to measure PD, panic attacks and/or anxiety, and main results observed.

## Results

In total, 410 papers were found in PubMed, 245 in BVS and 694 in ISIWEB. A total of 33 abstracts were reviewed in the searches. Marina Machado Vilarim planned, reviewed the literature, analyzed the results and developed the final version of the article.

**Table 3. Losses, placebo/caffeine offered and measures of effect size/strength of association in the selected studies concerning the association between caffeine and panic disorder.**

Study (year)	Losses (%)	Placebo/caffeine offered	Measures of effect size/strength of association	Ref.
Klein <i>et al.</i> (1991)	30	NI; 480 mg of caffeine in capsules	ANOVA, Bonferroni t-tests	[55]
Beck & Berisford (1992)	14.3	Chilled juice containing placebo; chilled juice containing 250 mg of anhydrous caffeine	ANOVA	[63]
Bruce <i>et al.</i> (1992)	0	NI; white capsules of 250 or 500 mg of anhydrous caffeine	$\chi^2$	[64]
Nardi <i>et al.</i> (2007)	23.8	Caffeine-free solution in the form of instant coffee; 480 mg of caffeine in the same form	$\chi^2$ , ANOVA	[57]
Nardi <i>et al.</i> (2007)	15.7	Caffeine-free solution in the form of instant coffee; 480 mg of caffeine in the same form	$\chi^2$	[58]
Nardi <i>et al.</i> (2008)	73.1	Caffeine-free solution in the form of instant coffee; 480 mg of caffeine in the same form	$\chi^2$ , ANOVA	[54]
Masdrakis <i>et al.</i> (2008)	0	NA; 200 mg and 400 mg of caffeine in the form of instant coffee	Odds ratio	[45]
Nardi <i>et al.</i> (2009)	0	Caffeine-free solution in the form of instant coffee; 480 mg of caffeine in the same form	$\chi^2$	[44]

ANOVA: Analysis of variance; NA: Not available; NI: Not informed.

Daniele Marano Rocha Araujo planned, analyzed the results, guided and reviewed the article. Antonio Egidio Nardi planned, guided and reviewed the article.

Of the eight studies selected, four were from Brazil, one was from England, one was from Greece and two were from the USA. Sample sizes ranged between ten and 143 individuals. In terms of age, six studies reported the average age, one study reported the minimum and maximum ages and one study did not mention the participants' ages (TABLE 2).

The percentage of subjects lost during follow-up varied between 14.3% and 73.1% (TABLE 3). However, the eight studies showed a positive association between caffeine and anxiogenic effects and/or PD (TABLE 4).

## Discussion

We were interested in investigating the association between caffeine and anxiety because caffeine challenge tests can give researchers control of the expression of panic attacks. This control enables investigations of the mechanism of action of PD and stimulates the development of pharmacological interventions.

As for the percentage of patient loss during follow-up, only two studies reported a loss  $\geq 30\%$  [54,55]. According to Araujo *et al.*, this percentage can cause a reduction in the validity of the results [56]. Indeed, some of the associations found in the selected studies may be hampered by the fact that none of the studies quantified the loss or controlled for important confounding factors.

Among the selected studies, 62.5% had administered doses of 480 mg of caffeine [44,54–58]. The justification for more than half of studies administering 480 mg of caffeine was that it was

a safe dose that had been tested in the laboratory to demonstrate the significant increase of anxiety in PD patients compared with normal controls [59,60].

With regard to the measurement scales, various types of instruments were used to assess PD, panic attacks and/or anxiety. Although no scale alone has been able to make a psychiatric diagnosis, they may offer a suggestive diagnosis of PD. As the scores can be confused with a number of clinical diseases, the validity of these scales is generally measured by their concordance with a 'gold standard' [61,62].

In the eight studies selected, the most frequently used rating scales for PD were the DSM, Structured Clinical Interview and the Subjective Units of Disturbance Scale. All of the selected studies found a positive association between panic attacks and/or anxiogenic effects of a caffeine challenge test in patients with PD. This agreement may be attributed in part to the type of study design and the standard amount of caffeine offered.

None of the studies controlled for confounding factors in the analysis. The small sample size was a limitation for four studies [45,55,63,64] and two did not use sophisticated measurements of cognitive factors associated with PD [45,64]. As a suggestion for future studies, the use of alcohol, cigarettes and medicines should be controlled because they can enhance or suppress the action of caffeine, both at the metabolic level and at the level of receptor interaction.

The vulnerability of anxiety disorder patients to the caffeine challenge test is also demonstrated by a study conducted by Nardi *et al.* where 16% of generalized social anxiety disorder (GSAD) patients and 52.6% of performance social anxiety disorder (PSAD) patients had a panic attack during the caffeine test [44].

**Table 4. The disorders/symptoms evaluated and the scales and results of the selected studies concerning the association between caffeine and panic disorder.**

Study (year)	Disorders/symptoms evaluated	Scales	Results	Ref.
Klein <i>et al.</i> (1991)	Panic disorder with or without agoraphobia	DSM-III, HDRS, NIMH panic attack inventory, NIMH rating scales for anxiety, depression and global impairment, and Zung SAS	Demonstrated that patients with panic disorder responded to caffeine with increased anxiety and panic attacks	[55]
Beck & Berisford (1992)	Panic disorder	ADIS-R, DSM-III-R	Although panic disorder patients in both caffeine and placebo conditions endorsed a significant number of panic symptoms and reported greater symptom severity relative to the normal controls, only the panic disorder/caffeine sample reported a significant increase in subjective anxiety	[63]
Bruce <i>et al.</i> (1992)	Panic disorder and generalized anxiety disorder	BSS, MRS, STAI	Patients with panic disorder showed different reactivity than normal patients, but were less reactive than patients with generalized anxiety disorder	[64]
Nardi <i>et al.</i> (2007)	Panic disorder, major depression and major depression with panic attacks	DSM-IV, DSQ, SCID, SUDS	Suggested that there is an association between panic attacks in panic disorder or major depression with panic attacks and hyper-reactivity to an oral caffeine challenge test	[57]
Nardi <i>et al.</i> (2007)	Panic disorder with agoraphobia	DSM-IV, SCID, SUDS	Suggested that there is an association between respiratory panic disorder subtype and hyperreactivity to an oral caffeine challenge test	[58]
Nardi <i>et al.</i> (2008)	Panic disorder	DSM-IV, DSQ, SCID, SUDS	Suggested that there is a genetic association between panic attacks after the intake of caffeine in panic disorder patients and their healthy first-degree relatives	[54]
Masdrakis <i>et al.</i> (2008)	Panic disorder with or without agoraphobia	DSM-IV, HDRS, SCID, SCLR-90-R, STAI	Indicated that patients with panic disorder who experience a panic attack after a 200 mg or a 400 mg caffeine challenge (compared with those patients with panic disorder who do not panic after both of these caffeine challenges) may present significantly higher nonspecific general psychopathology at baseline	[45]
Nardi <i>et al.</i> (2009)	Panic disorder, generalized social anxiety disorder and performance social anxiety disorder	DSM-IV, SCID, SUDS	Suggested that there is an association between panic disorder and an oral caffeine challenge test	[44]

ADIS-R: Anxiety Disorders Interview Schedule-Revised; BSS: Bodily Symptom Scale; DSM-III: Diagnostic and Statistical Manual of Mental Disorders III; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders III-Revised; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders IV; DSQ: Diagnostic Symptom Questionnaire; HDRS: Hamilton Depression Rating Scale; MRS: Mood Rating Scale; NIMH: National Institutes of Mental Health; SAS: Self-rating Anxiety Scale; SCID: Structured Clinical Interview; SCLR-90-R: Symptom Checklist-90-Revised; STAI: State-Trait Anxiety Inventory; SUDS: Subjective Units of Disturbance Scale.

Masdrakis *et al.* assessed the BH duration in PD patients in relation to panic attacks induced by caffeine intake [65]. Their findings indicate that in PD patients, caffeine-induced panic attacks are strongly associated with a significant reduction of BH duration both pre- and post-challenge. Jointly, these findings suggest that in a subgroup of PD patients, sensitivity to endogenous CO<sub>2</sub> accumulation may underlie both the lower BH durations and the caffeine-induced panic attacks. In this subgroup of PD patients, caffeine might exert its panicogenic properties through the exacerbation of patients' already

pathological hypersensitivity to CO<sub>2</sub> accumulation, as indicated by both the significant decrease of their BH duration post-challenge and by their significantly lower baseline BH duration, respectively.

Experimental evidence qualifies the dorsal periaqueductal gray (PAG) as the main substrate of aversion in the brain [66]. Symptomatically, the acute type of aversion/anxiety elicited in man by dorsal PAG stimulation seems in many aspects reminiscent of the acute anxiety characterizing a panic attack in humans. Neurosurgical PAG stimulation has been used for pain

relief in the clinic [67] and, when applied to the dorsal part of the PAG, likewise elicits short-lived, intense unpleasant subjective emotional responses and signs of autonomic arousal in the subjects. Drugs known to acutely reduce (alprazolam and clonazepam) or precipitate (caffeine) panic attacks in patients were found to acutely and dose-dependently reduce or enhance, respectively, aversion induced by dorsal PAG stimulation in rats [68].

Alsene *et al.* demonstrated that an adenosine receptor gene polymorphism that has been associated with PD is also associated with anxiogenic responses to an acute dose of caffeine [69]. While the reason for the interindividual variability in responses to caffeine is not clear [70–73], there is evidence that some of the variability in acute responses to caffeine may have a genetic basis. Polymorphisms in the A1 and A2a adenosine receptor genes may account for variations in subjective responses to caffeine [69].

However, some studies have demonstrated the benefits of caffeine consumption. A prospective study of more than 17,000 Dutch men and women found that the risk of developing Type 2 diabetes mellitus was 50% lower in those who consumed at least seven cups of coffee daily compared with those who drank two cups or less [74].

A 10-year study of more than 128,000 men and women participating in a California health plan found that the relative risk of suicide decreased by 13% for every cup of coffee consumed daily. Similarly, a 10-year study of more than 86,000 women found that those who drank at least two cups of coffee daily had a risk of suicide that was 50% lower than those who did not drink coffee [8,75]. Another study of more than 8000 Japanese–American men found that those who did not drink coffee were three to five times more likely to develop Parkinson's disease over the next 24–30 years than those who drank at least 28 oz daily [76].

Methylxanthines also produce bronchodilation. In addition to this effect on the airway smooth muscle, these agents inhibit antigen-induced release of histamine from lung tissue. This bronchodilation action is a very important therapeutic action in asthma [77].

Issues surrounding the concept of comorbidity in anxiety and mood disorders are complex and have not been fully defined [78]. What is worrying from a biological standpoint is the real possibility of an organic comorbidity that could alter the pathogenesis of some disorders and affect their diagnosis, treatment and prognosis. We want to mention that the use of challenge tests like the caffeine test does not enhance the ability to evaluate these processes at different points in time.

Panic disorder has been the primary focus of research dealing with the neurochemistry of anxiety disorders. Achieving a greater understanding of the nature and diversity of PD is important for investigations into the control of panic attacks. More experimental models that induce anxiety should be developed to help achieve a breakthrough in the understanding of PD.

### Expert commentary

The induction of panic attacks and/or anxiogenic effects by the caffeine challenge test in patients with PD has received attention from the scientific community. However, caffeine use is also associated with other psychiatric disorders, such as symptoms of depression and worsening of psychotic symptoms in schizophrenic patients. In addition, the consumption of toxic doses of caffeine can induce psychosis in normal individuals [79]. The evidence for the potential exacerbation of the anxiogenic effect by caffeine is an important finding for the treatment of patients with PD who are more sensitive to caffeine.

Although human experiments are more difficult than animal studies because of cost and ethical issues, experiments that induce anxiety in humans are extremely important to stimulate the development of drug therapies for the control of psychiatric disorders. Through recognition, education and patient care, research should aim to prevent the psychiatric symptoms induced by the consumption of caffeine.

### Five-year view

Several studies demonstrate the possible effect that caffeine alone and/or associated with other psychostimulants have on numerous disorders, including PD. However, the real knowledge of

### Key issues

- Caffeine is a psychoactive substance that acts as a stimulant on the CNS to maintain a state of arousal. In addition, caffeine antagonizes adenosine receptors present in nerve tissue.
- Caffeine is present in coffee, tea, chocolate, cola soft drinks, guarana and cocoa, and is also found in medicines.
- Approximately 80% of the world's population consumes caffeine daily.
- Finland, Norway and Denmark are leaders in the consumption of coffee, with a total volume of approximately 13 kg per capita per year.
- There are two ways to produce experimental anxiety in humans: chemical means and psychological means. Chemical means involve challenges (provocative testing) with chemicals used to induce panic attacks, and psychological means involve environmental stimuli or contexts that represent some kind of threat.
- The percentage of subjects lost during follow-up varied between 14.3 and 73.1%. However, the eight studies analyzed showed a positive association between caffeine and anxiogenic effects and/or panic disorder.
- Caffeine challenge tests can give researchers control of the expression of panic attacks, which enables investigations of their mechanisms of action. This knowledge stimulates the development of pharmacological interventions.
- More research needs to be carried out to prevent the psychiatric symptoms induced by caffeine consumption, and scientists and doctors should also focus on recognition, education and patient care.

the mechanism that this component has on the human body, as well as the amount of caffeine required to produce beneficial effects on these patients with PD, remains scarce [80]. For these reasons, in 5 years, we expect that studies with the following characteristics will be designed: longer period for the consumption of caffeine; similar dosages between studies; specific dosages for each age group and sex; and standardization of types of coffee (decaffeinated/toasted).

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