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Caffeine: Cognitive and Physical Performance Enhancer or Psychoactive Drug?

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Abstract: Caffeine use is increasing worldwide. The underlying motivations are mainly concentration and memory enhancement and physical performance improvement. Coffee and caffeine-containing products affect the cardiovascular system, with their positive inotropic and chronotropic effects, and the central nervous system, with their locomotor activity stimulation and anxiogenic-like effects. Thus, it is of interest to examine whether these effects could be detrimental for health. Furthermore, caffeine abuse and dependence are becoming more and more common and can lead to caffeine intoxication, which puts individuals at risk for premature and unnatural death. The present review summarizes the main findings concerning caffeine's mechanisms of action (focusing on adenosine antagonism, intracellular calcium mobilization, and phosphodiesterases inhibition), use, abuse, dependence, intoxication, and lethal effects. It also suggests that the concepts of toxic and lethal doses are relative, since doses below the toxic and/or lethal range may play a causal role in intoxication or death. This could be due to caffeine's interaction with other substances or to the individuals' pre-existing metabolism alterations or diseases.

Keywords: Abuse, caffeine, coffee, dependence, energy drinks, safety doses, toxicity.

INTRODUCTION

The use of caffeine to stay awake and alert is a long-standing habit. Coffee is the most popular beverage after water and is consumed worldwide in daily amounts of approximately 1.6 billion cups, which is quite an impressive figure.

There is some uncertainty about the etymology of the word "coffee". The botanical name of the plant from which coffee is derived is *Coffea Arabica*: it finds its origins in Ethiopia and is an exceptionally hardy self-pollinating plant. The Persian physician Rhazes was the first to mention it in his manuscripts. Yemen was the first country to cultivate the coffee plants, whilst Turkey was the first country to roast the green coffee beans. So it is not surprising that the word "coffee" finds its roots in Arabia, where it was called "qahwah". Although there is no doubt about the origin of the word, researchers do not agree on how the language process led the English word "coffee". It is likely that the latter found its way into European languages in the 17th century from the Italian word "caffé", stemming, in turn, from the word "kahveh", which was the Turkish way to pronounce "qahwah". Over the centuries, the habit of drinking coffee spread from Arabia to all the world.

Caffeine is contained in more than sixty plants, which is a remarkable number, thus it has been hypothesized that caffeine was originally a minor nutrient, not essential for the plant, but extremely useful as a pesticide. In fact, caffeine is toxic for several insects and animals, especially herbivores. Through caffeine the plant may defend itself and have a better chance of survival: in this view, caffeine can be considered as a "co-evolutionary protecting agent" [1].

"The Canon of Medicine", written in 1025 by the Persian physician Avicenna, is the first text mentioning coffee as a medication. At the time, coffee was used to "clean the skin, dry up the humidities that are under it, and give a better odor to the body". In the 15th century, the diffusion of coffee, initially employed by Muslim dervishes for providing energy, had remarkably increased and countless coffee houses had opened in Arabia. In the late 17th and in the 18th century, as sea shipping had expanded, the use of coffee became common in Europe [2].

The stimulant effects of caffeine on the central nervous system have been known for centuries [3]. In the 19th century a well-known consumer was Honoré De Balzac. Saying that he loved the coffee is not enough. He was completely dependent on it and in the period in which he wrote "The Human Comedy" he went on to drink up to 50 cups a day. In 1830, he published an article in a French magazine called "Pleasures and pains of coffee", which recounted: "coffee slips into the stomach and you immediately feel a general commotion. Ideas begin to move like the battalions of the Grand Army on the field of the battle and the battle takes place. Memories come at a gallop, carried by the wind". Nowadays, caffeine is believed to be the most frequently consumed psychostimulant worldwide, being ingested predominantly as coffee. Many other caffeine-containing

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beverages and products exist and contain significant amounts of the substance, for example, tea, chocolate, cocoa beverages, soft drinks, and energy drinks. Coffee and caffeinated beverages are part of the diet in all countries.

With regard to cognitive functions, caffeine's properties have been investigated in both human and animal studies. In epidemiological reports, a link between chronic caffeine consumption and a significantly lower risk of developing neurodegenerative diseases, such as Alzheimer's disease, has been described [4]. Likewise, chronic treatment with caffeine has been shown to be effective in preventing β-amyloid (Aβ) production and memory deficits in experimental models of Alzheimer's disease [5, 6]. While caffeine seems to prevent or restore memory impairment due to disturbances in brain homeostasis [7], its cognition-enhancing properties are still a matter of debate [8, 9]. Besides, moderate-to-high consumers develop tolerance to caffeine and only low or nonconsumers can eventually benefit from an acute administration [10].

In addition, in epidemiological reports [11] and experimental models [12, 13], caffeine has been found to have a role in the prevention of motor symptoms and loss of dopaminergic neurons in Parkinson's disease.

With regard to physical activity, it should be noted that until 2004 the International Olympic Committee listed caffeine in its prohibited substances list. Professional athletes who tested positive for more than 12 μg/l of urine – which corresponds to drinking about 5-6 cups of coffee in a day – were banned from the Olympic games [14].

In the past years, a relationship between coffee consumption and several types of cancers, such as colon, bladder, and pancreatic ones, has been postulated. Yet, the recent literature has provided no evidence of this relationship [15, 16].

METHODS

Eligibility Criteria

The present conceptual review was performed by including retrospective, prospective, and transversal (i.e., cross-sectional) studies examining caffeine's mechanisms of action, use, abuse, dependence, and intoxication, which may lead to death.

Search Criteria and Critical Appraisal

As regards the search strategy, an electronic search of Pubmed, INFORMA healthcare, Excerpta Medica Database (EMBASE), and PsycINFO from the inception of these databases to July 20, 2014 was performed. The search included publications in any language. Search terms were caffeine AND "pharmacokinetics" OR "pharmacodynamics" OR "heart" OR "brain" OR "abuse" OR "dependence" OR "intoxication" OR "death" in title, abstract, and key-words. Reference lists of all located articles were further searched for the detection of still unidentified literature and its evaluation.

Search Results and Included Studies

From each electronic database, we read all titles and selected those promising ones to be relevant, which were 29,421. Through a hand search of reference lists 20 other potentially eligible articles were singled out.

Risk of Bias

No evidence of language bias was found, as the search was not limited to English language studies. This limited the possibility of missing relevant studies. Moreover, no proof of significant publication bias was found. The database search produced no unpublished study, initiating, ongoing, or finished.

RESULTS

Pharmacokinetics and Pharmacodynamics

After ingestion, caffeine is quickly absorbed from the gastrointestinal tract into the circulatory system [17, 18]. The maximum plasma concentration is reached after 30-60 minutes from consumption. However, maximum plasma concentrations reached between 15 and 120 min have been reported, due to inter-individual differences and delayed gastric emptying. Caffeine is widely distributed through the body. The pre-systemic (i.e., first-pass) metabolism takes place in the liver, since orally ingested substances are absorbed through the small intestine into the portal circulation, before entering the systemic one. Caffeine's pre-systemic metabolism is negligible [17] and, once caffeine is absorbed, it promptly gets into all the body tissues and crosses the blood-brain, blood-placenta, and blood-testis barriers [17, 19]. The hepatic microsomal enzyme system is in charge of caffeine metabolism in the liver. The main enzyme responsible for caffeine metabolism is cytochrome P450 1A2 (CYP1A2), which accounts for about 95% of caffeine clearance. Caffeine metabolism rate is controlled not only by CYP1A2, but also by xanthine oxidase and N-acetyltransferase 2 (NAT2) [20]. Only from 0.5% to 2% of ingested caffeine is excreted as such in the urine, as it undergoes an almost complete tubular reabsorption [17]. Caffeine's half-life in humans ranges from a minimum of 2 to a maximum of 12 hours [21, 22], mainly due to the inter-individual variability in absorption and metabolism. When levels of intake are higher, a prolonged duration of action can be observed, possibly because of a delay in caffeine clearance and an accumulation of paraxanthine and other xanthines. In fact, caffeine is subjected to demethylation, resulting mostly in the release of paraxanthine (84%), followed by theobromine (12%) and theophylline (4%). The chemical structure of the xanthines theobromine and theophylline is very similar to that of caffeine [23]. These metabolites are further transformed in the liver through demethylation and oxidation, resulting in the production of urates [24].

Paraxanthine, the key metabolite of caffeine, has a similar chemical structure and half-life to those of caffeine and is easily measured in serum and urine. About 60% of orally ingested paraxanthine is excreted unmodified. Compared to caffeine, paraxanthine's production and degradation rates are similar, but serum concentration is more stable throughout the day, even if it reflects only recent consumption [25]. Paraxanthine's plasma levels decrease more slowly, even after accounting for inter-individual metabolism variations, and they become higher after 8-10

hours from ingestion [17]. Paraxanthine is then metabolized through two alternative pathways: the former produces 8-hydroxyparaxanthine, the latter, consisting in the 7-demethylation of paraxanthine, produces three metabolites, i.e., 5-acetylamino-6-formylamino-3-methyluracil (AFMU), 1-methylxanthine, and 1-methylurate [26]. AFMU makes up for 67% of paraxanthine metabolites [17] and is converted to 5-acetyl-6-amino-3-methyluracil (AAMU), which can be measured in the urine without any difficulty. The paraxanthine metabolites are excreted in the urine almost as rapidly as they are produced, as a result of an active renal tubular secretion [26]. Because of the high caffeine doses and the repeated consumption of coffee that are typical of the daily caffeine consumer, paraxanthine accumulates in the plasma and this process reduces caffeine elimination. Paraxanthine, as mentioned above, has many similar effects to those of caffeine and, consequently, daily caffeine consumption generates high levels of both caffeine and paraxanthine, which are biologically active.

Theobromine constitutes the higher proportion of the biologically active metabolites [27]. It is rapidly absorbed and about 50% is excreted through the urine in 8-12 hours [28]. Its effects include diuresis induction, cardiovascular system stimulation, smooth muscle relaxation, and glandular secretion [29]. CYP1A2 and, to a smaller extent, CYP2E1, are responsible for theobromine's metabolism, as they determine 86% of its demethylation [30]. Theobromine's half-life is approximately 7-11 hours [28, 31] and plasma and renal clearance are about 46% and 67%, respectively [32]. Plasma clearance is influenced by smoking: smokers show a 30% higher clearance than nonsmokers [33].

Theophylline and caffeine share a similar chemical structure, however theophylline lacks one N-methyl group and determines more potent effects than caffeine and theobromine. Its half-life is quite unpredictable, varying from 3 to 9 hours [34]. Theophylline is subjected to hepatic and renal clearance. Hepatic clearance is mediated essentially by CYP1A2, *via* an N-demethylation that leads to the production of monomethylxanthines and an 8-hydroxylation that leads to the production of 1,3-dimethyl-uric acid.

In conclusion, there are significant inter-individual differences in the metabolism, clearance, and elimination of caffeine and its metabolites. Several extrinsic factors influence metabolic and excretion rates, such as smoking, food intake, gastric emptying speed, pregnancy, hepatic and cardiovascular diseases, viral infections, and concomitant drug use.

In particular, smokers are characterized by a metabolism rate that is almost twice the one of nonsmokers [35]. Cigarettes contain polycyclic aromatic hydrocarbons that promote a greater liver enzyme activity, thereby increasing caffeine metabolism [26, 36]. Smoking may accelerate the pre-systemic (i.e., first-pass) and systemic (i.e., second-pass) metabolism of caffeine, with the hepatic microsomal oxidative enzymes causing a faster demethylation [37, 38].

Pregnancy decreases the clearance and excretion of caffeine, thus the latter and its metabolites, such as theophylline, can accumulate in the body [34]. Variations in enzyme activity, especially with regard to CYP1A2, are reported. As a result, there is a growing effort to identify genetic polymorphisms influencing caffeine metabolism [26, 39].

Mechanisms of Action

The potential effects of caffeine, at the cellular level, can be explained by three mechanisms of action: the antagonism of adenosine receptors, especially in the central nervous system; the mobilization of intracellular calcium storage; the inhibition of phosphodiesterases.

Antagonism of Adenosine

Caffeine blocks adenosine receptors, mainly A_1 and A_{2A} subtypes, competitively antagonizing their action [40, 41] and causing an increased release of dopamine, noradrenalin, and glutamate [42, 43]. Caffeine is able to reduce cerebral blood flow [44]. It is also able to reduce myocardial blood flow, by inhibiting A_1, A_{2A} and A_{2B} adenosine receptors in blood vessels and limiting adenosine-mediated vasodilation [45]. A_1 receptors can be found in almost all brain areas. The highest concentration is in the cerebral and cerebellar cortices, the hippocampus, and a number of thalamic nuclei [46, 47], whereas only a modest concentration is found in the corpus striatum, i.e. the caudate and putamen, and the nucleus accumbens. Pre-synaptic A_1 receptors inhibiting the release of neurotransmitters are present in almost all types of neurons.

There is significant evidence of a relationship between adenosine A_{2A} and dopamine D_1 receptors [42]. Adenosine A_{2A} and D_2 receptors show a high concentration in the dopamine-rich areas of the brain, i.e., the corpus striatum, the nucleus accumbens, and the tuberculum olfactorium, where they are co-localized. There is little evidence supporting their presence outside these areas, even if, according to recent functional neuroimaging studies, they may be present in the cerebral cortex and the hippocampus. The blockade of A_{2A} receptors in the basal ganglia, i.e., the corpus striatum and globus pallidus, appears to be fundamental for the stimulatory effects of caffeine [48]. These effects largely depend on an intact dopaminergic neurotransmission. Finally, it has been shown that the effects of caffeine in low doses can be replicated by a selective A_{2A} receptor antagonist, but not by a selective A_1 receptor antagonist [49]. These findings suggest that the interaction between caffeine in high doses and dopaminergic transmission finds its roots in the increase of post-synaptic D_2 receptor transmission. The antagonistic effects of caffeine on the A_{2A} adenosine receptors in the corpus striatum are in line with the reduced risk of developing Parkinson's disease when caffeine consumption is increased [9].

The ability of caffeine to block adenosine receptors can be observed also at low doses, such as those contained in a single cup of coffee.

Other mechanisms of action, such as the mobilization of intracellular calcium and the inhibition of phosphodiesterases, require higher doses of caffeine, unlikely to be obtained with the common daily dietary sources of caffeine.

Mobilization of Intracellular Calcium

Caffeine can induce calcium release from the sarcoplasmic reticulum [50] and can also inhibit its reuptake [51]. Through these mechanisms, caffeine can increase contractility during submaximal contractions in habitual and nonhabitual caffeine users. Intracellular calcium determines the activation of endothelial nitric oxide synthase (eNOS), with the production of higher quantities of nitric oxide [47]. Therefore, some of the effects induced by caffeine might be partly mediated by neuromuscular function modulation and contractile force increase in the skeletal muscles [52, 53].

A potential counter effect of caffeine is represented by diuresis stimulation, accountable for ergolytic effects in endurance athletes during prolonged workouts and competitions [54].

Inhibition of Phosphodiesterases

Caffeine acts as a nonselective competitive inhibitor of phosphodiesterases [55]. These enzymes hydrolyze the phosphodiester linkages in molecules, such as cyclic adenosine monophosphate (cAMP), inhibiting their degradation. cAMP stimulates lipolysis by triggering the activity of the hormone-sensitive lipase (HSL) and has a vital role in the adrenaline cascade [56]. It also activates protein kinase A, which in turn phosphorylates several enzymes implicated in glucose and lipid metabolism [57]. These mechanisms of action require very high doses of caffeine, unlikely to be present in the standard diet, which contains moderate amounts of caffeine.

Further mechanisms of action describe the use of caffeine in sport activities and as a dietary supplement that are described below.

Increase of Post-exercise Muscle Glycogen Accumulation

Faster recovery following intense exercise, mediated by a higher rate of glycogen resynthesis, has been described [58]. It has been maintained that caffeine ingestion has no effect on glycogen stacking during recovery from exercise in recreational athletes [59]. However, a recent study has found that caffeine (8 mg/kg body weight), coingested with carbohydrates, is responsible for higher rates of post-exercise muscle glycogen stacking in comparison to the ingestion of carbohydrates alone in well-trained athletes after the depletion of glycogen that follows exercise [60]. Although this finding deserves further investigation in broader population samples (recreational and professional athletes, untrained individuals) and occasions (during exercise or recovery), caffeine in addition to post-exercise carbohydrates consumption seems to be able to stimulate glycogen resynthesis.

Increase of Fatty Acid Oxidation

The increase of lipolysis determines a decreased dependence from glycogen use [61]. Caffeine switches the substrate preference from glycogen to lipids by stimulating HSL activity and inhibiting glycogen phosphorylase activity [62].

Effects on the Cardiovascular System

Caffeine has several effects on the cardiovascular system, which have been examined thoroughly with conflicting result. Many mechanisms have been suggested in relation to caffeine toxicity, which primarily affects the cardiovascular system.

In the heart, adenosine acts through specific receptors and is a negative inotropic and chronotropic agent. The blockade of cardiac adenosine receptors inhibits adenosine's effects and can cause tachycardia and arrhythmias through intense β_1-receptor activity.

High caffeine doses induce adenosine antagonism and phosphodiesterases inhibition, interacting with the sympathetic nervous system and inducing β_1-receptor activation. This results in positive inotropic and chronotropic effects, accountable for an augmented heart rate and conductivity [63]. In fact, higher concentrations of caffeine increase intracellular cAMP and cyclic guanosine monophosphate (cGMP) by a nonspecific phosphodiesterases inhibition, which affects cardiac contractility secondary to calcium release. The latter mechanism may increase the susceptibility for arrhythmias. Other caffeine's mechanisms of action with indirect effects on the cardiovascular system have been reported, such as the stimulation of the sodium-potassium-ATPase, which is an integral membrane protein responsible for a decrease in the plasma levels of potassium and the ion's transfer from the circulation to intracellular compartments, rendering the membrane potential more negative. This determines an increased risk of ventricular arrhythmias [64]. According to the aforementioned mechanisms, arrhythmic episodes have been hypothesized to be responsible for death in cases of lethal intoxication. Caffeine, especially at high doses, leads to palpitations and arrhythmias, such as atrial fibrillation and supraventricular and ventricular ectopic beats (the latter also known as premature ventricular contractions, PVCs) [65]. It must be underlined that the positive inotropic effects of caffeine are reinforced by the positive chronotropic effects of guarana, a substance that is frequently added to energy drinks and contains caffeine, theobromine, and theophylline [66]. Berger *et al*. [67] reported ventricular fibrillation after overconsumption of a caffeinated energy drink in a 28-year-old healthy young man who was hospitalized and subsequently discharged after six days in healthy conditions.

Caffeine's pro-arrhythmic effects at high doses are supported by animal studies [65, 68], which have been performed with higher doses of caffeine and evaluation by invasive techniques. Numerous physiological and epidemiological human studies have investigated the link between caffeine and both atrial and ventricular arrhythmias [69], but their results are not always in agreement.

The first human studies were carried out using invasive electrophysiology. Gould *et al*. [70] and Dobmeyer *et al*. [71] found a refractory period shortening of the atrio-ventricular node and of the right atrium and ventricle after coffee intake: both effects were attributed to catecholamine release. Opposite results were found in the left atrium, whose refractory period paradoxically increased with caffeine intake.

As regards the effects of caffeine on the human electrocardiogram [69] after the intake of moderate amounts

of caffeine [72] or high-caffeine energy drinks [73], it was noticed that caffeine does not acutely induce any statistically and clinically significant changes in P-wave indices, i.e., PR interval, QRS duration, corrected QT interval (QTc), and RR interval [74]. Donnerstein *et al*. [75] observed a modest, but statistically significant prolongation of approximately 1 ms of signal-averaged QRS complexes in 12 individuals given a 5 mg/kg body weight dose of caffeine *vs.* placebo.

In addition, studies of individuals performed with continuous electrocardiographic monitoring suggested that caffeine has a limited effect on the circuits underlying ventricular arrhythmias [69, 76, 77]. Therefore, despite increases in adrenaline levels, caffeine appears to have no proarrhythmic effect even in patients with clinical ventricular arrhythmias; caffeine showed no capacity of modifying the inducibility or severity of arrhythmias in patients with malignant ventricular arrhythmias [77] and did not induce an increase of cardiac ectopy, neither atrial nor ventricular, in patients with a high prevalence of baseline ectopy [69]. Furthermore, in high-risk patients with recent myocardial infarction no increase in the frequency or severity of PVCs or arrhythmias was found [69]. It is interesting to note that although adrenaline concentration increases with caffeine ingestion, the degree of the release is six times lower than the boost noted during exercise [78].

Larger-scale epidemiological studies found no increased risk of development of atrial arrhythmias after caffeine intake in healthy subjects [69]. A recent meta-analysis [79] suggested that it is unlikely that the chronic consumption of caffeine causes or contributes to atrial fibrillation. It was also demonstrated that in habitual caffeine consumers, caffeine's adrenergic effects were greatly attenuated and acute proarrhythmic effect was somewhat reduced [80]. Furthermore, as atrial fibrosis is an important substrate for atrial fibrillation and caffeine has antifibrotic properties [81-84], this finding might encourage the search for effective antifibrosis agents or the use of caffeine to prevent atrial fibrillation.

Prineas *et al*. [69] found that nine cups of coffee were associated with twice the risk of PVCs after adjusting for other risk factors. The same authors found a very significant association between heavy coffee intake (10 cups per day) and increased risk of sudden cardiac death in 117 patients with a history of coronary artery disease who suffered from sudden cardiac arrest *vs.* controls with coronary artery disease (odds ratio=55.7) [69]. However, a possible limitation may be represented by the fact that only two of the controls drank more than 10 cups of coffee per day

Some researchers have conjectured that caffeine is a vasoconstrictive substance [80, 85, 86]. *In vitro* studies have found that the concentration of intracellular calcium in vascular smooth muscle is modified by caffeine and this phenomenon could directly determine variations of coronary artery tone [67]. Caffeine has been shown to elevate blood pressure in both normotensive and hypertensive prone men, partly by inhibiting adenosine action, leading to elevated noradrenalin release and vasoconstriction [87, 88]. A number of studies have demonstrated that acute caffeine ingestion increases blood pressure and catecholamine levels and decreases heart rate [74, 89]. A study of caffeine's ability to interfere with pharmacologic cardiac stress testing, showed *in vivo* increases in coronary vascular resistance and ascribed them to the antagonism of A_2 receptors or to the induction of an α2-adrenoreceptor-mediated vasoconstriction consequent to the increase in catecholamine release [90]. It is well known that adenosine causes vasodilation, thus, the antagonization of adenosine receptors may induce vasoconstriction.

By contrast, caffeine also augments endothelium-dependent vasodilation by agonist stimulation of endogenous nitric oxide production in young, healthy individuals. A double-blind, randomized study [55] showed that caffeine ingestion produced an increase in systolic and diastolic blood pressures in the brachial artery, in agreement with previous studies that highlighted how acute caffeine ingestion elevated peripheral blood pressure [80, 86, 91] and augmented the forearm blood flow response to acetylcholine, an endothelium-dependent vasodilator. It has been reported that caffeine stimulates nitric oxide synthesis in the endothelium *via* the release of calcium from the endoplasmic reticulum by activating the ryanodine-sensitive calcium channel and inhibiting the breakdown of cGMP in the aorta: this results in the caffeine-induced increase of endothelium-dependent vasodilation [92]. A balance between the vasodilatory effect of caffeine as an endothelium-dependent vasodilator and its vasoconstrictive effect as an adenosine receptor antagonist may control vascular function. High caffeine concentrations may cause marked hypotension secondary to vasodilation and, thus, ventricular fibrillation, which could be a possible mechanism of cardiovascular collapse [93].

Blood pressure changes induced by acute caffeine ingestion need to be further investigated. Karatzis *et al*. [94] observed, after the acute administration of caffeine, an increase of central blood pressure, but not of peripheral systolic blood pressure. Therefore, there seems to be a relevant acute effect of caffeine ingestion on central hemodynamics, but not on peripheral pressure.

Several factors, such as age, exercise-induced stress, and hypertension, have been reported to influence blood pressure changes induced by caffeine [86]. Forman *et al*. [95] suggested that high doses of caffeine and low estrogen levels may act in a synergistic way to induce coronary arteries vasoconstriction.

These observations highlight the importance of keeping fairly constant any confounding factor when carrying out experimental studies, in order to assess correctly the blood pressure changes during caffeine administration.

Similarly, case-control and prospective studies have shown differing result with regard to the risk of myocardial infarction among patient with high coffee intake. A potential role of caffeine in promoting the development on cardiac ischemia has been suggested, taking into account the higher oxygen demand deriving from increased cardiac work levels and, in addition, caffeine's direct effect on the coronary arteries [95]. There are case reports [67, 96] of coronary artery vasospasm induced by caffeine-containing energy drinks, but there is not enough evidence to support a relationship between caffeine and vasospasm. *In vitro*, caffeine has

physiological effects on the concentration of intracellular calcium in the vascular smooth muscle and could induce coronary vasospasm; *in vivo*, caffeine reduces myocardial blood flow during exercise [97]. Benjo *et al*. [98] reported left main coronary artery acute thrombosis related to caffeinated energy drinks intake, but it is difficult to single out which compound – e.g., caffeine, glucoronolactone, taurine, or vitamins – is responsible for the effect on platelet aggregation and endothelial function. Caffeine has not been shown to affect platelet function by itself, and no studies of the other compounds are available [99].

Finally, extensive studies performed in cohorts of both healthy and diabetic subjects have demonstrated minimal or no effect of caffeine on coronary artery disease, myocardial infarction, and stroke [100-102]. A study of patients with coronary artery disease, in which exercise stress tests were carried out, showed that caffeine at a dose of 250 mg had no effect on exercise duration, time to onset of angina, and time to onset of ST-segment depression, although peak blood pressure increased by 7 mmHg [103]. Another study speculated that the regular intake of caffeinated beverages could provide protection against the risk of cardiovascular disease mortality in nonhypertensive elderly patient [104].

Effects on the Central Nervous System

Caffeine, besides influencing cognitive performance, increases the perception of alertness and wakefulness [105, 106] and sometimes induces anxiety, especially at high doses [107-109]. Furthermore, antagonism of A_1 and A_2 receptors can cause seizures and cerebral vasoconstriction.

Even if caffeine seems to prevent or restore memory losses or other disorders due to disturbances in brain homeostasis [7], its cognitive enhancement properties are still under discussion [8, 110]. A wide range of studies in humans suggest that the cognitive benefits of caffeine are associated with relief from withdrawal symptoms, rather than with improvement in cognitive functions [9, 111, 112]. In 2001, the Institute of Medicine Food and Nutrition Board Committee on Military Nutrition Research reported that the ingestion of caffeine at a dose of 150 mg enhances cognitive performance for at least 10 hours [113].

While the benefits of caffeine on cognitive functions remain under debate, the anxiety-inducing effects are well documented in both animals and humans [114-117]. Caffeine actions are dose-related and divided into two broad categories: at lower concentrations, caffeine stimulates the locomotor activity [118], at higher concentrations it induces an anxiogenic-like effect [117, 119, 120].

Caffeine is studied in relation to the possible treatment of neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. In epidemiological reports, caffeine consumption was associated with a significantly lower risk of developing them [4, 11, 12, 120-122, 124]. Recent experimental evidence suggests that the primary target of the neuroprotective effects of caffeine [124, 125] is either the activation or the inhibition of the A_1 and A_{2A} adenosine receptor subtypes [126, 127] (Table **1**; findings not discussed in this review). The use of adenosine receptor antagonists, such as caffeine, has shown its usefulness not only in the treatment, but also in the protection against the aforementioned diseases [128-131]. Experimental evidence supports the use of caffeine and other adenosine receptor antagonists, as well as adenosine receptor agonists, in the reduction of hyperalgesia, excitotoxicity, inflammatory response, dyskinesia, akinesia, sensory and motor deficits, and neuronal cell death related to the pathophysiology of the discussed neurodegenerative diseases [132, 133].

Caffeine has several effects on pain. It has been employed as a coadjuvant in the treatment of pain for many years. However, the analgesic effects of caffeine have not been properly studied until 1984, when it was demonstrated

Table 1. Findings of caffeine effects on main neurodegenerative diseases.

Drug Type (Adenosine Receptor Subtype)	Known Effects on Neurodegenerative Diseases	
	Parkinson's Disease	*Alzheimer's Disease (AD)*
Caffeine (adenosine receptor antagonist)	Improves motor activity [7, 134].	Prevents the accumulation of amyloid-β- peptide (Aβ) in and around cerebral blood vessels [135].
	Down-regulates neuroinflammatory responses and nitric oxide (NO) production [136, 137].	Reverses cognitive impairment and decreases brain Aβ levels in AD mice [138].
	Reduces both motor and nonmotor early onset symptoms [139].	Consumption of 3-5 cups/day of coffee at midlife is associated with a decreased risk of dementia/AD by about 65% in later life [129].
	Prevents the loss of nigral dopaminergic neurons [140].	Protects against oxidative stress and AD-like pathology in rabbit hippocampus [141].
	Protects against disruptions of the blood-brain barrier in animal models [142].	Increases mitochondrial function and blocks melatonin signaling to mitochondria [143].
		Men in the highest quartile of caffeine intake are less likely than men in the lowest quartile to have any lesion type [144].

that the use of the compound as an additive reduced the amount of acetaminophen necessary to obtain the same effect by about 40% [145]. *In vitro* and *in vivo* pharmacological studies provided evidence that caffeine could have an antinociceptive action through the blockade of adenosine receptors and the inhibition of cyclooxygenase-2 enzyme synthesis. Nevertheless, these actions occur only occasionally: it is hypothesized that the doses of analgesics and caffeine used nowadays can influence the analgesic adjuvant effect of caffeine, but doses that are either too low or too high determine no analgesic enhancement.

A number of headache studies have reported that acute caffeine ingestion produces an intrinsic analgesic effect [146, 147]. Caffeine in high doses, of about 300-500 mg, soothed post-dural puncture headaches [148], but repeated administration of lower doses did not produce such an effect [149]. The vasoconstrictor action of caffeine, secondary to adenosine receptor antagonism, is implicated in headache relief [150]. After chronic caffeine ingestion, cessation of intake was shown to cause a withdrawal syndrome dominated by headache and fatigue; symptoms manifested themselves after 12-24 hours, reached a peak at 24-48 hours, and persisted for about one week [151]. Headaches were originally documented as part of withdrawal symptoms after high intake levels that went beyond 600 mg/day, but they occurred even after moderate intake levels, equal to 100 mg/day [152].

Tolerance and Safety Doses

The extent of the development of tolerance towards caffeine's effects is unclear [153, 154]. The uncertainty regarding this issue may be partly due to methodological limitations. The majority of studies compare caffeine "naïve" individuals to habitual caffeine users, or habitual users before and after caffeine abstinence. As 80% of the population report regular use of caffeine, nonusers are much selected, atypical subpopulation. Response differences may merely reflect genetic differences between nonusers and habitual users, or an atypical response to caffeine that might have led to nonusers' caffeine avoidance. Furthermore, very few studies compare individuals subjected to repeated caffeine administration *vs*. controls taking placebo. The recent literature suggests that the development of caffeine tolerance is partial and may differ with regard to caffeine's central *vs*. peripheral effects.

As for central effects, a study assessed human brain metabolic response to caffeine using rapid proton echo-planar spectroscopic imaging in regular caffeine users [154]. In the hour following caffeine intake (10 mg/kg body weight) brain lactate was increased in caffeine "naïve" individuals compared to regular caffeine users. In the regular caffeine users, after a 4-8 weeks abstinence, caffeine reexposure incremented brain lactate to a similar level to that of the caffeine "naïve" individuals. Thus, most of the studies suggest either complete or partial tolerance to caffeine's central effects.

The peripheral effects of caffeine and the possible development of tolerance towards them have been more extensively analyzed because of concerns regarding dietary caffeine intake and cardiovascular status [155]. A study employing the same caffeine administration methodology as the one of the above cited study, which regarded the central effects of caffeine, found that caffeine elevated peripheral blood pressure *vs.* placebo and the blood pressure response was not abolished after five days of caffeine doses of 600 mg/day. The sympathetic nervous system has an important role in regulating blood pressure [156]. A study assessed sympathetic nerve activity and blood pressure in habitual and nonhabitual coffee drinkers [80]. In comparison with placebo, caffeine at a dose of 250 mg elevated blood pressure in nonhabitual drinkers, but not in habitual ones. In contrast, the activity of the sympathetic nervous system was similarly increased in both groups. Most importantly, plasma caffeine concentrations did not differ between the two groups. Therefore, tolerance to the peripheral effects of caffeine may be variable, depending on the response system assessed, but it appears to be less consistent than tolerance to its central effects.

Caffeine-containing Products

The most common dietary source of caffeine is coffee, but cocoa beverages, soft drinks, energy drinks, medications, and specialized sports foods and supplements also contribute to regular intake. Since the introduction of Red Bull in Austria in 1987 and in the US in 1997, the energy drink market has enormously expanded. Countless brands can now be found, with caffeine content ranging from a modest 50 mg to an alarming 500 mg per can or bottle. The regulation of energy drinks, including their labeling, permissible maximum caffeine levels, and health warnings, has been rather complex in most countries, with one of the most lax normative frameworks in the US. Because of the varying amounts of caffeine consumed in each country, it is difficult to set an international standard. This has resulted in aggressive marketing of energy drinks, targeted primarily at young individuals, for physical performance enhancing and psychostimulatory effects. Furthermore, several studies suggest that energy drinks may serve as a gateway to other forms of substance dependence. In the recent years, to limit this phenomenon, regulatory upper limits have been set for those beverages in which caffeine is not contained naturally, but added either from a natural or a synthetic source.

As already mentioned, caffeine consumption has been linked with a number of health issues. There are increasing reports of caffeine abuse, dependence, and withdrawal syndromes, and it seems likely that caffeine intoxication will also increase. In children and adolescents who are not habitual caffeine users, vulnerability to caffeine intoxication is significantly higher due to the absence of pharmacological tolerance. Genetic factors may also contribute to an individual's vulnerability to caffeine-related disorders.

In sports, caffeine use is very common. A moderate dose of caffeine (3-5mg/kg body weight) taken an hour before a hard training or competition, has been found to significantly increase performance as compared to placebo, with the athletes affected by minimal side effects. Prior to 2004, caffeine was included in the World Anti-Doping Agency (WADA) Prohibited List of substances and methods, with a

legal urinary concentration limit of 12μg/ml; however, it was subsequently removed, allowing athletes who compete in sports compliant with the WADA code to consume caffeine within their usual diets or for specific purposes of performance. This revision was based on the acknowledgment that caffeine enhances performance at doses that are impossible to differentiate from daily caffeine use and that the practice of monitoring caffeine use *via* urinary concentration is not completely reliable. However, the WADA continues to measure caffeine levels through urinary concentration testing within its Monitoring Program, in order to investigate patterns of misuse of substances in sport. Differently from the WADA, the National Collegiate Athletic Association (NCAA), a nonprofit association that regulates the athletes of 1,281 institutions and associations, and organizes the athletic programs of many colleges and universities in the US and Canada, has a urinary concentration limit of 15μg/ml; thus, athletes in the NCAA must take into account that caffeine is still on the list of controlled substances.

The amount of caffeine contained in a cup of coffee can vary greatly, depending on its origin or the composition of the blend, the brewing method, and the strength of the brew. Instant (also known as soluble) coffee generally contains less caffeine than roast and ground coffee, but is usually consumed in greater volumes. Robusta coffees contain about twice as much caffeine than arabicas. A cup is usually assumed to contain 180 ml of coffee, but an espresso may contain as little as 40 ml [157].

Decaffeinated coffee, regardless of the method of decaffeination, must contain less than 0.1% caffeine by dry weight to comply with regulations. This corresponds to about 3-5 mg of caffeine in a cup of decaffeinated coffee.

Tea contains more caffeine than coffee by dry weight, but less weight is used, in general, to brew a cup of tea. Both the type of tea and the infusing time can affect the amount of caffeine. The caffeine content of a cup of tea is usually less than 60 mg, but a strong cup of tea may contain more caffeine than a weak cup of regular coffee (Table **2**).

Cocoa and chocolate drinks contribute to the diet with 4-5 mg of caffeine per cup, dark chocolate and cooking chocolate with 0.7-0.9 mg per gram.

Numerous soft drinks, including colas and peppers, contain caffeine, which, as well as being present in cola nuts, is often added as a flavoring agent. About 180 ml of a soft drink contain 30-70 mg of caffeine. The major brands of cola sold in Europe contain about 120 mg of caffeine per liter (Table **2**).

Caffeine is present in many prescription and nonprescription (i.e., over-the-counter) medications, including some taken for headache, pain relief, cold, appetite control, staying awake, asthma, and fluid retention. The caffeine content of drugs varies from 16 mg to 200 mg per tablet (Table **2**).

Energy drinks contain high concentrations of caffeine, as well as other performance-enhancing substances, such as guarana, taurine, and B vitamins. They claim to provide its consumers with extra energy (Table **2**).

Caffeine consumption has been classified as follows:

- low caffeine users: <200 mg/day
- moderate caffeine users: 200-400 mg/day
- high caffeine users: >400 mg/day

Caffeine use, Abuse, and Dependence

Reissig *et al*. [159] have described several negative effects of excessive caffeine consumption. Throughout their lives, individuals can consume high quantities of caffeine only for some periods of time, but more often on a regular basis. Moreover, some individuals go on to abuse caffeine to enhance their concentration and memory or to improve their physical performance, and in some cases develop a dependence syndrome. Caffeine use becomes "abuse" when an uncontrolled urge to consume caffeine arises, even if it is detrimental for health; it becomes "dependence" when tolerance and abstinence mechanisms occur and there are some habits of chronic use that render caffeine even more harmful. In caffeine dependence, individuals start to consume extremely high doses, ignoring all safety issues; they take a combination of two or more different sources of caffeine, for example, coffee and energy drinks, although the combination is not proven to have any added desirable effects; they consume caffeine almost continuously for years, reaching an excessive cumulative duration of use.

The effects of caffeine dependence are still under investigation. One issue in studying caffeine dependence has been the uncertainty regarding the products that contain caffeine and their respective concentration of caffeine, thus the existing studies, mainly observational, have often found difficulties in verifying the exact nature or amounts taken. Moreover, many individuals who consume caffeine simultaneously consume other substances, such as nicotine or alcohol, which may have overlapping effects. Another issue has been the application of appropriate criteria. A "substance dependence disorder" was coded by the American Psychiatric Association (APA) in 1989 [160]. Over the years, the existing literature has applied DSM-IV-TR [161] or previous criteria to assess dependence among populations of users. A problem that has arisen is that the standard DSM-IV-TR substance dependence criteria are difficult to apply to some compounds, such as caffeine, since they were designed largely to apply to intoxicating drugs. For example, even if caffeine causes the classic withdrawal syndrome, mediated by neuroendocrine and cortical neurotransmitter systems, it is a cumulatively acting substance that produces little or no acute intoxication, unless taken in large doses. Hence it does not usually compromise daily functioning in the manner of intoxicating drugs. In an attempt to address this problem, the DSM-5 [162] suggested the code "substance use disorder", where the specific substance has to be indicated, i.e., caffeine, nicotine, alcohol, cannabis, hallucinogen (phencyclidine and others), inhalant, opioid, sedative, hypnotic, anxiolytic, or stimulant categories. Substance use disorder in DSM-5 combines the DSM-IV-TR categories of substance abuse and substance dependence into a single disorder measured on a continuum from mild to severe. Each specific substance is addressed as a separate

Table 2. Average caffeine content in foods, beverages, and medications (adapted from Cherniske, 1998 [158]).

Servings per day	Item	Total Caffeine (in mg)
Coffee (180 ml cup)	Drip brewed	100 mg per 180 ml
	Percolated	120 mg per 180 ml
	Instant	90 mg. per 180 ml
	Brewed decaffeinated	5 mg per 180 ml
	Instant decaffeinated	3 mg per 180 ml
Tea (180 ml cup)	Green	35 mg per 180 ml
	Black	70 mg per 180 ml
	Canned ice tea	35 mg per 360 oz can
Cocoa	Cocoa beverages	13 mg per 180 ml
Chocolate	Milk chocolate	6 mg per 30 ml
	Baking chocolate	35 mg per 30 ml
	Small candy bar	25 mg per bar
Soft drinks (360 ml can)	Leading colas (regular and diet)	45 mg
	Dr. Pepper	40 mg
	Mello Yello	53 mg
	Mountain Dew	54 mg
	Mr. Pibb	41 mg
	OK Soda	40 mg
	Jolt Cola	72 mg
Medications (per tablet)	Anacin	32 mg
	Dristan (i.e., acetylsalicylic acid+caffeine)	16 mg
	Dexatrim (i.e., phenylpropanolamine+caffeine)	16 mg
	Excedrin (i.e., acetaminophen+acetylsalicylic acid+caffeine)	200 mg
	Midol (i.e., acetaminophen+pyrilamine maleate+caffeine)	32 mg
	Nodoz (i.e., caffeine)	100 mg
	Vivarin (i.e., caffeine)	200 mg
	Vanquish (i.e., acetaminophen+acetylsalicylic acid+caffeine)	33 mg
Energy drinks	28 Energy Drink	80 mg
	6 Hour Power	125 mg
	BANG Energy Drink	357 mg
	Biggby Iced Coffee	192 mg
	Caffeine Energy Drink	140 mg
	Chameleon Cold Brew Coffee	2160 mg
	Cocaine Energy Drink	280 mg
	Diablo Energy Drink	95 mg
	Guayaki Empower Mint	140 mg

Table 2. contd….

Servings per day	Item	Total Caffeine (in mg)
Energy drinks	Hardcore Energize Bullet	300 mg
	Java Monster	188 mg
	Liquid Lightning	200 mg
	Monster Energy Drink	160 mg
	Neurofuel Energy Drink	128 mg
	Octane Energy Drink	225 mg
	Potencia Energy Drink	250 mg
	Rage Inferno	375 mg
	Red Bull	80 mg
	Speed Energy Drink	186 mg
	Starbucks Tall Coffee	260 mg
	Ubermonster Energy Brew	160 mg
	Venom Black Mamba	160 mg
	Zun Energy Drink	100 mg

disorder, but nearly all substances are diagnosed based on the same overarching criteria. These criteria have not only been combined, but strengthened. Whereas in the past a diagnosis of substance abuse required only one symptom, substance use disorder in the DSM-5 requires at least two symptoms from a list of eleven. Substance craving was added to the list and problems with law enforcement were eliminated because of cultural considerations that made the criteria difficult to apply internationally. The revised substance use disorder, a single diagnosis, better matches the symptoms that individuals experience. Furthermore, in the past the diagnosis of dependence caused much confusion. Most people linked dependence with addiction, when in fact dependence can be a normal body response to a substance. DSM-5 diagnostic criteria for dependence are listed in Table **3**.

The disorder can occur in a broad range of severity, basing on the number of symptom criteria endorsed: mild, if 2 to 3 symptoms are present, moderate if 4 to 5 symptoms are present, and severe if 6 or more symptoms are present.

As said before, it can be noted that the DSM-5 includes the craving criteria. Craving is a key element in the genesis of substance addiction and relapse that often individuals with abuse or dependence encounter. Initially, the term was used to describe, in opiate addicts, a strong and irresistible urge arising during withdrawal. Subsequently, it has come to indicate a desire to make use of any psychotropic substance in any situation. The WHO [163] describes craving as an "intense and compulsive desire to experience the effects of a psychoactive substance used in the past", which, in simpler terms, indicates a strong urge to use the substance. Once considered a manifestation of the withdrawal syndrome, craving appears to be essentially the result of a stimulus evoking the substance, but sometimes its onset is not apparently linked with any stimulus; it tends to diminish with time, but it can appear even after years of abstinence. This urge can become compelling and may increase in the presence of internal and external stimuli (i.e., "triggering events") and the perception of the availability of the substance. It is characterized by a behavior aimed at obtaining the substance and by intrusive thoughts that focus on the substance, such as intrusive thoughts about caffeine. In the field of psychiatry two types of craving are distinguished [164]: 1) physical craving that occurs in substance addicts or alcoholics who stop taking drugs or drinking after a long period of excessive consumption; this type of craving is mostly associated with physical symptoms of the withdrawal type, such as increased heart rate, sweating, nausea, agitation, tremors, etc.; 2) psychological craving that occurs during abstinence and often leads to relapse. It is related to the activation of the reward system, located in the brain in the medial forebrain bundle, which includes the dopaminergic meso-cortico-limbic pathway.

Finally, individuals – both adults and adolescents – who consume high doses of caffeine frequently report psychiatric symptoms and disorders, mainly anxiety and mood disorders, but also behavioral alterations. Some disorders are typically linked to recreational and professional athletes who consume caffeine to face fatigue and intense workouts. An example is muscle dysmorphia. This disorder, also known as reverse anorexia or bigorexia or Adonis complex, is a subtype of body dysmorphic disorder generally affecting men, with its onset in adolescence or early adulthood, characterized by obsessiveness and compulsivity directed

Table 3. DSM-5 diagnostic criteria for dependence. At least two of the following criteria must be met over a 12-month period.

Criteria
The substance is often taken in larger amounts or over a longer period than was intended
There is a persistent desire or unsuccessful efforts to cut down or control use of the substance
A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
Craving, or a strong desire or urge to use the substance
Recurrent use of the substance resulting in a failure to fulfill major role obligations at work, school, or home
Continued use of the substance despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of its use
Important social, occupational, or recreational activities are given up or reduced because of use of the substance
Recurrent use of the substance in situations in which it is physically hazardous
Use of the substance is 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
Tolerance, as defined by either of the following: a) a need for markedly increased amounts of the substance to achieve intoxication or the desired effect b) a markedly diminished effect with continued use of the same amount of the substance
Withdrawal, as manifested by either of the following: a) the characteristic withdrawal syndrome for the substance b) the substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms

toward achieving a lean and muscular physique, even at the expense of health. This raises the issue of whether caffeine use causes these disorders in athletes, by inducing neuroadaptive changes within the reward neural circuit and affecting mechanisms of resilience to stress, or, *vice versa*, athletes with pre-morbid abnormal personalities or a history of psychiatric disorders are attracted to caffeine use, encouraged by an extrinsic motivation for exercise focused on appearance and weight control.

Caffeine Toxicity

Caffeine intoxication is a recognized clinical syndrome included in the DSM-5 [162] and the World Health Organization's International Classification of Diseases (ICD-10) [165]. Caffeine toxicity is defined by specific symptoms that arise as a direct consequence of caffeine consumption.

Common features of caffeine intoxication, also known as "caffeinism" (i.e., a state of chronic toxicity from excessive caffeine consumption), include anxiety, agitation, restlessness, insomnia, gastrointestinal disturbances, tremors, tachycardia, psychomotor agitation, and, in some cases, death (see Table **4**). Symptoms of caffeine intoxication can mimic those of anxiety and other affective disorders [166]. Energy drink consumption may increase the risk of caffeine overdose in caffeine abstainers, as well as habitual caffeine users.

Caffeine intake at very high doses, exceeding 500-600 mg, which are equivalent to 4-7 cups per day, can cause anxiety, tremor, and tachycardia. This mechanism of action requires higher concentrations of caffeine, unlikely to be reached with the common amount of caffeine contained in dietary sources. The acute toxic level of caffeine is not well established, but for adults it is approximately 10 g/day, which is comparable to a consumption of approximately 100 cups of coffee [167].

Generally, life-threatening caffeine overdoses entail the ingestion of caffeine-containing medications, rather than caffeinated foods or beverages [168], and have been associated with blood concentrations in excess of 80 mg/l [169].

In the majority of lethal cases, caffeine was introduced as a dietary supplement or with other substances, such as stimulant drugs and alcohol.

Only in one lethal case, described by Chaturvedi *et al*. [174], the concentration of caffeine was below the fatal levels and above the toxic levels: this was a case of multi-chemical death involving caffeine and nicotine. It appears that the interaction between the two substances in the body tissues played a role, due to the rapid onset of the toxicity leading to an early death [165, 186-189].

DISCUSSION

In recent years caffeine use has increased, especially among young people, due to the wide diffusion of caffeinated beverages advertised as energy drinks. Despite the wide diffusion of caffeine in the form of drinks, foods, and medications, death from acute intoxication is relatively rare and is mostly caused by voluntary or involuntary ingestion of tablets containing pure caffeine in high concentrations. In fact, although variable amounts of

Table 4. Lethal cases of caffeine intoxication.

Author (Year)	Caffeine Blood Level (mg/L)	Age	Manner of Death	Route of Administration (Source)
Dimaio *et al*. (1974) [170]	158.5	5-year-old	Accidental	Oral (pills)
	1040	15-month-old	Accidental	Oral (pills)
	79	45-year-old	Accidental	Oral (pills)
Turner *et al*. (1977) [171]	106	34-year-old	Uncertain	Oral (pills)
McGee (1980) [172]	181	19-year-old	Accidental	Oral (pills)
Bryant (1981) [173]	113.5	42-year-old	Suicide	Oral (pills)
Chaturvedi *et al*. (1983) [174]	62	21-year-old	Suicide	Oral (pills)
Garriott *et al*. (1985) [175]	129.9	19-year-old	Suicide	Oral (pills)
	147	21-year-old	Suicide	Oral (pills)
	343.9	21-year-old	Suicide	Oral (pills)
	184.1	23-year-old	Accidental	Oral (pills)
	251	21-year-old	Suicide	Oral (pills)
Winek *et al*. (1985) [176]	240	21-year-old	Suicide	Oral (pills)
Morrow (1987) [177]	117.3	14-month-old	Child abuse	Oral (pills)
Mrvos *et al*. (1989) [178]	1560	22-year-old	Accidental	Oral (pills)
Riesselmann *et al*. (1999) [179]	220	19-year-old	Accidental	Oral (pills)
	190	81-year-old	Suicide	Oral (pills)
Holmgren *et al*. (2004) [180]	173	54-year-old	Uncertain	Oral (pills)
	210	21-year-old	Suicide	Oral (pills)
	153	31-year-old	Suicide	Oral (pills)
	200	47-year-old	Uncertain	Oral (pills)
Kerrigan *et al*. (2005) [181]	192	39-year-old	Accidental	Intravenous
	567	29-year-old	Accidental	Oral (pills)
Thelander *et al*. (2010) [182]	90	43-year-old	Uncertain	Not reported
	105	53-year-old	Suicide	Not reported
	170	47-year-old	Uncertain	Not reported
	86	26-year-old	Uncertain	Not reported
	210	25-year-old	Suicide	Not reported
	230	40-year-old	Uncertain	Not reported
	210	21-year-old	Suicide	Not reported
	153	31-year-old	Suicide	Not reported
	173	54-year-old	Uncertain	Not reported
	200	47-year-old	Uncertain	Not reported
	180	18-year-old	Suicide	Not reported
	166	20-year-old	Suicide	Not reported
	140	72-year-old	Suicide	Not reported

Table 4. contd….

Author (Year)	Caffeine Blood Level (mg/L)	Age	Manner of Death	Route of Administration (Source)
Thelander *et al*. (2010) [182]	80	24-year-old	Suicide	Not reported
	160	46-year-old	Suicide	Not reported
	113	73-year-old	Uncertain	Not reported
	138	66-year-old	Accidental	Not reported
	190	84-year-old	Suicide	Not reported
	192	79-year-old	Suicide	Not reported
	310	33-year-old	Suicide	Not reported
Jabbar *et al*. (2013) [183]	350	39-year-old	Accidental	Oral (pills)
Jantos *et al*. (2013) [184]	141	25-year-old	Suicide	Oral (pills)
Bonsignore *et al*. (2014) [185]	170	31-year-old	Suicide	Oral (pills)
Banerjee *et al*. (2014) [93]	220	57-year-old	Suicide	Oral (pills)
	320	50-year-old	Uncertain	Oral (pills)
	90	39-year-old	Uncertain	Oral (pills)
	320	43-year-old	Suicide	Oral (pills)
	74	44-year-old	Uncertain	Oral (pills)

caffeine are contained in coffee, tea, and other drinks, it is difficult to reach lethal doses of caffeine exclusively through one of these products.

On the basis of the known mechanisms of action, caffeine can be considered as a psychostimulant, since its main effects are correlated to the interfering action on the neuroendocrine control systems.

Caffeine's psychological effects are also responsible for its widespread use, as they can provide energy and improve cognitive skills; they are a direct result of the caffeine-induced chemical activation of different neuronal pathways through alterations in neurotransmitters' release. These effects can cause both psychological and physical dependence. It has been demonstrated that caffeine is able to induce an abstinence syndrome during withdrawal after prolonged use and can lead to addiction and tolerance mechanisms, which on the one hand may determine a reduction of the "dangerous" cardiovascular effects, but on the other hand may increase frequency and amounts of consumption.

The effects of caffeine use on the cardiovascular system taken into account to evaluate the risk of acute and chronic cardiovascular diseases are also the result of the direct and/or indirect actions of caffeine on the neuroendocrine control systems of vascular resistance, cardiac function, and electrolyte balance.

Although cases of lethal intoxication have been mainly associated with the occurrence of arrhythmic events induced by caffeine, human studies provided scarce evidence to support the substance's ability to induce arrhythmias in healthy subjects and in subjects predisposed to such events. These findings, however, even if provided by studies differing in sample sizes and methods, should not be considered in disagreement with the findings of those studies reporting cases of lethal intoxication, as the former take into account caffeine doses below the ones considered toxic for humans.

Furthermore, it should be considered that the concepts of toxic and lethal doses in humans are relative, as doses below the toxic and/or lethal range may play a causal role in inducing intoxication or death. This could be due to:

- interactions with other substances that have a synergistic effect when consumed with caffeine or are capable of increasing caffeine's blood levels;
- individuals' pre-existing conditions or diseases that can potentiate caffeine' mechanisms of action;
- inter-individual differences, mostly genetically determined, that can affect caffeine metabolism in both directions (i.e., increase or reduction), contributing to a different individual "sensibility" to the substance's effects.

CONCLUSION

Ultimately, the dangers of caffeine are related to the wide diffusion of the substance, which results in an only partially conscious high consumption, due to the difficulty of ascertaining the actual amount of caffeine ingested daily and the inability to predict specific effects in relation to the triggering role that caffeine may have – even at doses considered to be "safe" – on underlying and not necessarily known cardiovascular conditions.

Caffeine, like other psychoactive substances, can induce abuse and dependence. Furthermore, caffeine, like alcohol and tobacco, is legally used, but, unlike the last two, its sale in the form of high concentration drinks or tablets is not controlled or restricted.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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