FOOD STANDARDS Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

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Supporting document 1 – Safety assessment of caffeine

P1056 – Caffeine review.

Executive summary

The purpose of Proposal P1056 is to review the permissions for caffeine in sports foods and general foods, with consideration of the risk it poses to sensitive sub-populations.

Pharmacokinetics

Caffeine is rapidly and completely absorbed, and widely distributed in the body. The half-life is in the range 3 to 7 hours. Caffeine is metabolised primarily by hepatic cytochrome P450 1A2 (CYP1A2). Elimination is a first-order process at intakes of up to 10 mg/kg bw, while at higher levels zero order kinetics are observed. Excretion of caffeine and its metabolites occurs primarily in the urine.

In pregnant women, the half-life of caffeine increases to approximately 10 hours by 17 weeks of gestation and up to 18 hours by the end of pregnancy, resulting in increased exposure to caffeine for both mother and fetus. Caffeine crosses the placenta by passive diffusion and the fetus and placenta lack enzymes to metabolise caffeine. Milk:serum concentration ratios ranging from 0.52 to 0.81 have been reported for lactating women.

The half-life of caffeine in neonates is much longer than in adults, at up to 100 hours, due to immaturity of the CYP1A2 enzyme system. The system then matures rapidly, and caffeine clearance reaches or exceeds adult levels by 5 to 6 months of age.

Pharmacodynamics

The effects of caffeine are mediated through adenosine receptor antagonism at plasma concentrations achieved through normal dietary intake levels. Antagonism of adenosine receptors promotes the release of several neurotransmitters in the brain associated with the positive effects of caffeine, including glutamate, serotonin, acetylcholine, noradrenaline, and dopamine. Other mechanisms of action such as phosphodiesterase inhibition, GABA receptor modulation and activation of ryanodine-sensitive calcium channels become more relevant at toxic levels of intake.

Caffeine has been reported to interact with a range of medicines. For example, caffeine is contraindicated in pregnant women taking phenobarbital, because there is evidence that the combination of caffeine and phenobarbital is teratogenic, although neither xenobiotic is a significant human teratogen alone. Potential for interactions with prescription medicines should be managed by the medical care provider and in the medicine product information.

Acute toxicity (single doses) of caffeine

Single intakes of caffeine of up to 210 mg (approximately 3 mg/kg bw) are not generally associated with any adverse effects. Above that dose, caffeine intake is associated with an

increase in blood pressure, plasma catecholamines and anxiety. FSANZ and other regulatory agencies (EFSA; US FDA; IOM) have previously identified 400 mg/day as safe for most adults. At or above 1200 mg more serious effects such as tachycardia, ventricular arrhythmia or seizures may develop, and urgent medical attention may be required. Death of an adult has been reported following a single dose of 3000 mg, however it is more commonly associated with doses of around 5000 to 10,000 mg caffeine. The direct cause of death in caffeine poisoning is usually ventricular fibrillation.

Chronic (habitual) consumption of caffeine

Adult population, excluding pregnant and lactating women

Chronic moderate consumption of caffeine at up to 400 mg/day (5.7 mg/kg bw/day based on a 70 kg bodyweight) is not associated with significant adverse effects in the general adult population. This is based on extensive epidemiological evidence, including systematic reviews and meta-analyses.

Caffeine consumption is typically self-limiting and is generally considered to have little potential for abuse. That is, consumers generally learn to regulate their intake to achieve the beneficial effects of caffeine while avoiding the adverse effects.

Evidence from premature infants and psychiatric patients indicates that chronic high consumption of caffeine does not have adverse physical effects. Protracted use of extremely high doses of caffeine in premature infants, as therapy for apnoea of prematurity, has been found to have no adverse physical or psychological sequelae up to 11 years later. In addition, psychiatric patients typically consume seven times as much caffeine as the general population, and although this level of consumption may have adverse psychological effects in some psychiatric disorders, there is a lack of evidence of adverse physical effects.

Pregnant women

Findings of a systematic review with dose-response meta-analysis show positive associations between caffeine consumption and miscarriage, stillbirth, preterm delivery, low birthweight and small for gestational age (SGA) infants. The authors were not able to identify a threshold for these adverse effects, but the associations are generally modest within the range of usual dietary intake, and the results suggest that a maximum of 200 mg caffeine/day is appropriate for pregnant women.

Lactating women

There is very little information on the effects of caffeine exposure via breastmilk on infants. EFSA (2015) concluded that caffeine at up to 200 mg per day consumed by lactating women do not give rise to safety concerns for the breastfed infant, based on a calculation that caffeine intake by the infant would not exceed 0.3 mg/kg bw.

Children

Caffeine poses a risk of acute toxicity in infants and small children, due to their low bodyweights.

The FSANZ Expert Working Group (2000); EFSA (2015) and BfR (2019), have previously recommended a maximum caffeine intake of 3 mg/kg bw/day for children. The FSANZ Expert Working Group based this value on increased anxiety at that level.

A recent systematic review also reported negative effects of caffeine in children at moderate

(~3 mg/kg bw/day) and high (~5 mg/kg bw/day) intake including alteration of the sleep cycle and alterations in affective states including anxiety and depression. EFSA identified a reference point of 1.4 mg caffeine/kg bw/day for sleep disturbance in children. The American Academy of Pediatrics discourages the use of caffeine by children and adolescents due to the adverse effects of sleep disturbance on academic performance.

Adolescents

There is a lack of new information on which to base a quantitative estimate of safe levels of caffeine in adolescents. Caffeine clearance in adolescents is likely to be at least that of adults, so the recommended level for adults (i.e., 5.7 mg/kg bw/day) is also applicable to adolescents.

Athletes

Caffeine has positive effects on physical exertion, and the purported risks of dehydration or acute mountain sickness from the diuretic effect of caffeine appear to be unfounded. In fact, caffeine may be more beneficial than harmful at high altitude. However, athletes are at elevated risk of caffeine toxicosis. Reasons for this include misleading labelling of sports supplements, failure to follow the recommended daily dose, deliberate or inadvertent 'stacking' by consuming caffeine from multiple sources, and a general lack of appreciation of the risks of high caffeine consumption. Caffeine may exacerbate body dysmorphia in bodybuilders.

A maximum level of 400 mg/day is considered safe for athletes.

There is a lack of information on potential interactions between caffeine and the other chemicals commonly included in energy drinks and other sports supplements.

Other potentially sensitive subpopulations

Caffeine consumption is generally self-limiting in adults, due to consumers' familiarity with its adverse effects. This self-limiting mechanism is likely to be applied to a number of susceptible subpopulations identified in this review, including insomniacs, patients with anxiety disorders or panic disorder, migraineurs in whom caffeine is a trigger, people with genetic polymorphisms that make them unusually susceptible to the adverse effects of caffeine, people allergic to caffeine, and people experiencing changes in caffeine clearance due to commencing oral contraceptives or quitting smoking.

Most potentially sensitive subpopulations identified in this review may be expected to be managed by the medical profession or by prescribing pharmacists. These include antagonistic, additive, potentiating or synergistic effects with prescription medications, and a number of specific contraindications of caffeine including familial long QT syndrome, Brugada syndrome, mitral valve prolapse, left ventricular hypertrophy, cardiomyopathy (or history of cardiomyopathy), Tetralogy of Fallot, aortic aneurysm, epilepsy being treated with phenobarbital during pregnancy, migraine being medicated with triptans, history of ocular hypertension or glaucoma, some psychiatric disorders (such as anxiety disorders and panic disorder), and adrenergic urticaria. The medical profession may also advise patients with a history of migraine to consume less than 200 mg caffeine per day and to be consistent in the time/s of consumption; prescribe long-acting pain relievers to migraineurs who consume coffee and undertake periods of fasting; and advise people at risk of Huntington's disease to limit caffeine intake to ≤ 190 mg caffeine/day.

Additional comments

Epidemiological evidence indicates that habitual coffee consumption is neutral to beneficial regarding the risks of hypertension, coronary heart disease, congestive heart failure, arrhythmias, and stroke. Habitual coffee consumption is inversely related to risk of type 2 diabetes, several types of cancer, hepatic fibrosis and cirrhosis, development of gallstones and kidney stones, and risk of Parkinson's disease, Alzheimer's disease, and general age-related cognitive decline. The beneficial effects of coffee may not be entirely attributable to caffeine, and therefore may not be applicable to products in which pure caffeine is an ingredient, such as energy drinks or other sports supplements.

There is some evidence of a lack of understanding of the hazards of caffeine in athletes and adolescents, and caffeine consumption poses a risk of acute toxicity to infants and small children.

Conclusions

Chronic moderate consumption of caffeine at up to 400 mg/day is not associated with significant adverse effects in the general adult population. The caffeine intake of pregnant women should be limited to ≤ 200 mg caffeine/day. There is a lack of information on which to base recommendations for breastfeeding women. Safe levels of caffeine for children and adolescents in the range 2.5 to 3.0 mg/kg bw/day have previously been extrapolated from adults based on bodyweight. However, 3.0 mg/kg bw/day has been associated with adverse effects on affective states in children, and > 1.4 mg/kg bw/day has been associated with sleep disturbance in children. The rate of clearance of caffeine in adolescents is comparable to that of adults, so caffeine intake up to 5.7 mg/kg bw/day is considered to be safe for this age group.

Most of the contraindications of caffeine identified in this review may be expected to be managed by consumers, by the medical profession, or through advice provided by pharmacists. Subpopulations at potential risk that are not managed through these avenues include users of supplements that are not accurately labelled, infants and pre-schoolers, and athletes. There is evidence of a lack of understanding of the hazards of caffeine, particularly in athletes and adolescents, and caffeine consumption poses a risk of acute poisoning to infants and small children.

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1. Introduction

1.1. Background

Caffeine (1,3,7-methylxanthine; synonyms include guaranine and mateine) occurs naturally in more than 60 plants (IOM 2014) and has been described as the most widely consumed psychoactive agent in the world (van Dam et al 2020). Plants from which dietary caffeine is commonly sourced include *Coffea arabica* (coffee), *Coffea robusta* (coffee), *Camellia sinensis* (tea), *Theobroma cacao* (cocoa, chocolate, tejate), *Paullinia cupana* (guarana), *Ilex paraguariensis* (yerba mate), *Ilex guayusa* (guayusa tea), *Ilex vomitoria* (yaupon tea), *Paullinia yoco* (yoco bark), and *Cola* species (Kola nuts, cola) including *Cola acuminata* and *Cola nitida.* In plants, caffeine may protect the plant from predators. Another hypothesis is that the release of caffeine from seed coats inhibits germination of the seeds of competing species (Singh et al 2018). Caffeine may also be produced synthetically. Purified caffeine is added to a variety of products including soft drinks, energy drinks, and sports supplements.

1.2. Previous assessments by FSANZ and other agencies

1.2.1. FSANZ

FSANZ has considered caffeine previously. In 2000, a FSANZ Expert Working Group analysed the available literature on caffeine and concluded that there was evidence of increased anxiety levels in both adults and children at doses of about 3 mg/kg bw/day of caffeine. This level was considered to be equivalent to a caffeine dose of 95 mg per day (approximately two cans of cola) in children and about 210 mg per day (approximately three cups of instant coffee) for adults.

Standard 2.6.4 – Formulated Caffeinated Beverages was gazetted in 2001, the outcome of A394. This Standard states that a formulated caffeinated beverage must contain no less than 145 mg/L and no more than 320 mg/L of caffeine.

FSANZ considered caffeine most recently in 2019 in P1054, an urgent proposal to prohibit the retail sale of pure and highly concentrated caffeine food products. FSANZ noted that EFSA and the US FDA have concluded that a total caffeine intake of 400 mg/day (5.7 mg/kg bodyweight/day) is safe for most adults. The outcome of P1054 was to prohibit the retail sale of foods in which total caffeine is present in a concentration of 1% (1000 mg/100 mL, liquid form) or 5% (5000 mg/100g, powder and gel form) or more in the product presented at retail sale, unless that sale or presence was expressly permitted by the Code.

1.2.2. Health Canada

Health Canada published their risk assessment of caffeine in 2003. They concluded that for the healthy adult population, caffeine consumption at up to 400 mg day is not associated with adverse effects. Women of reproductive age, and children, were identified as ‘at risk’ subpopulations. Health Canada recommended that women of reproductive age should consume ≤ 300 mg caffeine/day, and children should consume ≤ 2.5 mg/kg bw/day. Endpoints considered included acute toxicity, cardiovascular effects, effects on bone and calcium balance, effects on behaviour, mutagenicity, genotoxicity, carcinogenicity, and effects on reproduction and development. The recommendation for women of reproductive age was based on adverse effects on pregnancy and fetal development, and the recommendation for children was based on behavioural effects (Nawrot et al 2003).

1.2.3. European Food Safety Authority (EFSA)

EFSA published a Scientific Opinion on the safety of caffeine in 2015, in which they concluded that a single dose of caffeine of 200 mg (approximately 3 mg/kg bw), or a total caffeine intake of 400 mg/day (5.7 mg/kg bw/day) is safe for most adults, but pregnant women should not consume more than 200 mg/day (approximately 3 mg/kg bw/day) based on a risk of adverse effects on fetal growth and on birthweight at higher levels of maternal consumption. EFSA concluded that there is insufficient information to determine safe levels of caffeine for children or adolescents, but that the acute (single dose) intake of no concern to adults (3 mg/kg bw) may be used to derive acute and daily caffeine consumption values for those groups. EFSA noted that caffeine consumption ≥1.4 mg/kg bw/day may disrupt sleep in children (EFSA 2015).

1.2.4. US Food and Drug Administration (USFDA)

The US FDA[1] has also concluded that 400 mg/day of caffeine is not associated with adverse effects. They warn that some medical conditions, and some medications, may increase individual sensitivity to caffeine, and advise pregnant and breastfeeding women to seek the advice of their healthcare provider. The US FDA has not set a level of caffeine for children but noted that the American Academy of Paediatrics discourages the consumption of caffeine by children and adolescents. The US FDA estimated that severe adverse effects, such as seizures, may occur with rapid consumption of 1200 mg caffeine or more, and has identified products consisting of or containing only pure or highly concentrated caffeine as 'a significant public health threat'. The US FDA issued guidance stating that it considers certain types of such products to be adulterated and, therefore, prohibited under US food law because they present a significant or unreasonable risk of illness or injury[2].

1.2.5. Institute of Medicine (IOM)

The US-based Institute of Medicine (renamed the National Academy of Medicine in 2015) convened a workshop on caffeine in August 2013 to review available science on safe levels of caffeine consumption in foods, beverages, and dietary supplements, and to identify data gaps. A summary of the workshop was published in 2015 (IOM 2015). The conclusions of the workshop were summarized by McGuire (2014). The workshop noted that industry stakeholders rely on the "generally regarded as safe" determination process of the FDA which suggests that intakes up to approximately 400 mg caffeine/day should be safe. The workshop cited Health Canada as identifying children and women of reproductive age as vulnerable subpopulations, with the recommendation that children should consume no more than 2.5 mg caffeine/kg bw/day. Health Canada was further cited as recommending a daily limit of 300 mg/day for pregnant women, but it was also noted that the American College of Obstetrics and Gynecology recommends that pregnant women limit their caffeine intake to 200 mg caffeine/day. The workshop advised that children with cardiac conditions may be a sensitive subpopulation and should be discouraged from consuming energy drinks. The workshop considered that the evidence concerning the risk of caffeine to individuals with cardiac arrhythmia is inconsistent, and that caffeine may pose a risk to some of these individuals but not to others. The workshop considered the question of whether chronic caffeine intake can lead to addiction to be a matter of debate. The lack of rigorous research on interaction of caffeine with other components in foods or beverages was noted. The workshop participants noted the need for additional clinical and animal studies, especially

[1] https://www.fda.gov/consumers/consumer-updates/spilling-beans-how-much-caffeine-too-much
[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-highly-concentrated-caffeine-dietary-supplements

during vulnerable periods of the lifespan.

1.2.6. German Federal Institute for Risk Assessment (BfR)

The Bundesinstitut für Risikobewertung (BfR) published their Opinion on the risks to children and adolescents of the consumption of caffeinated energy drinks in May 2019. They cited the EFSA (2015) conclusion that children and adolescents should not consume any more than 3 mg caffeine/kg bw/day. BfR reviewed data published since the EFSA review, and concluded that acute, moderate consumption of energy drinks, with caffeine intake levels regarded as of no concern by EFSA, does not lead to undesirable effects in healthy young adults. However, they noted that acute consumption of copious amounts of energy drinks by young people were associated with palpitations, shortness of breath, uncontrolled muscle tremors, severe nausea, anxiety, nervousness, and changes in the electrocardiogram (ECG), particularly extension of the QTc interval.

According to Regulation (EU) No. 1169/2011, energy drink products containing more than 150 mg of caffeine per litre must bear the warning: “High caffeine content. Not recommended for children or pregnant or breastfeeding women” in the same field of vision as the name of the beverage, followed by an indication in brackets of the caffeine content expressed in mg per 100 millilitres (mL). Despite this mandatory labelling, the BfR found that a substantial proportion of children and adolescents consume substantial amounts of energy drink on occasion, exceeding the limit recommended by EFSA, and that these events may be accompanied by alcohol consumption and strenuous physical exercise, which could exacerbate adverse effects on the cardiovascular system. BfR considered that children and adolescents may lack awareness of the risks, and that greater education was indicated.

In 2012, the BfR published an assessment of sports and weight loss products containing both synephrine and caffeine. They concluded that both substances increase heart rate, possibly leading to arrhythmia, and both also increase blood pressure. Consuming both substances together may result in synergy.

1.2.7. Norwegian Scientific Committee for Food and Environment (VKM)

The Vitenskapskomiteen for mat og miljø (VKM) published its risk assessment of energy drinks and caffeine in 2019. The assessment was conducted in response to a request from the Royal Norwegian Ministry of Health and Care Services to assess potential adverse health effects of energy drinks and caffeine in children and adolescents. The assessment was limited to children and adolescents aged 8 to (and including) 18 years. The literature search included the interval 2013 to 2018.

The VKM Panel applied the two following toxicological reference points set by EFSA (2015); 3 mg /kg bw/day for general adverse health effects, and 1.4 mg /kg bw/day for sleep disturbance. Four scenarios were considered: all energy drinks contain 15 mg caffeine/100 mL; all energy drinks contain 32 mg caffeine/100 mL; all energy drinks contain 40 mg caffeine/100 mL; all energy drinks contain 55 mg/100 mL. Based on dietary exposure data, the Panel concluded that there is a risk of sleep disturbance for children aged 8 to 12 years if there is high chronic intake of energy drinks containing ≥ 40 mg caffeine/100 mL, and for adolescents in the 13-15 years and 16-18 years cohorts if there is high chronic intake of energy drinks containing ≥ 32 mg caffeine/100 mL.

For adverse health effects other than sleep disturbance, for the age group 13-15 years, high chronic intake of energy drinks may represent a risk if all consumed energy drinks contain ≥40 mg caffeine/100 ml. The Panel also concluded that individuals with predispositions to certain heart conditions represent a sensitive subpopulation for which the reference point of 3

mg/kg bw/day may not be protective.

1.2.8. National Institute for Public Health and the Environment (RIVM)

The Rijksinstituut voor Volksgezondheid en Milieu (RIVM) which is an independent agency of the Dutch Ministry of Health, Welfare and Sport, published their risk assessment of caffeine in food supplements in 2020. They concluded that people using caffeinated food supplements can consume levels of caffeine that lead to adverse effects including high blood pressure, headaches, or restlessness. The RIVM based their assessment on the maximum limits established by EFSA (2015). They noted that the risk of adverse effects is increased if a person combines caffeinated food supplement use with the consumption of other products that contain caffeine such as coffee, tea, and chocolate.

RIVM noted that there is no legal limit for the maximum amount of caffeine present in food supplements in the European Union.

Summary
There is a consensus among regulatory agencies that caffeine consumption of up to 400 mg/day is not associated with serious adverse effects in healthy adults, but that sensitive subpopulations exist, and include children, adolescents, pregnant women, and people with certain pre-existing cardiac disorders. The effects of energy drinks were also of concern. The acute and daily intakes are summarized in Table 1.

Table 1: Summary of Opinions of Regulatory Agencies		
Non-pregnant adults		
3 mg/kg bw single dose		EFSA
400 mg/day	5.7 mg/kg bw/day	EFSA; US FDA; IOM; FSANZ (P1054)
210 mg/day	3 mg/kg bw/day	FSANZ Expert Working Group
Pregnant women		
300 mg/day		Health Canada
200 mg/day	3 mg/kg bw/day	EFSA; ACOG
Children		
	3 mg/kg bw/day	FSANZ Expert Working Group; EFSA; BfR
	2.5 mg/kg/day	Health Canada; IOM
Recommendations		
Children and adolescents should be discouraged from using caffeine		American Academy of Pediatrics
Children with cardiac conditions should be discouraged from consuming energy drinks		IOM
Energy drinks containing more than 150 mg caffeine/L must bear the warning: “High caffeine content. Not recommended for children or pregnant or breastfeeding women”		European Union
Risk of sleep disturbance for children aged 8 -12 if there is high chronic intake of energy drinks containing ≥ 40 mg caffeine/100 mL		VKM
Risk of sleep disturbance for adolescents aged 13-18 years if there is high chronic intake of energy drinks contain ≥32 mg caffeine/100 mL.		
3 mg caffeine/kg bw/day may not be protective to individuals predisposed to certain heart conditions		

1.3. Purpose and scope of current review

The purposes of the current review include the following:

- To establish the acute and chronic intake levels of caffeine that pose health risks to adults
- To determine the risks of caffeine intake to vulnerable subpopulations including:
  - Children
  - Adolescents
  - Pregnant and lactating women
- To identify any other vulnerable subpopulations and where possible, to determine the risks of caffeine intake to these subpopulations

1.4. Literature search terms

A literature search was carried out using PubMed as the primary database, but also using EBSCO as a secondary database and Google Scholar as an auxiliary database. The PubMed search was limited to papers and chapters published since 1 January 2003, and the limit 'human' was also applied. Search terms included sports AND supplement AND safety; sports AND supplement AND toxic; caffeine AND safety; caffeine AND toxic; caffeine AND interaction; caffeine AND pregnancy; methylxanthine AND safety; methylxanthine AND toxic; methylxanthine AND interaction. Related searches were carried out for theobromine, theophylline, pentoxifylline, 3-methylxanthine, paraxanthine, doxofylline, and aminophylline. Additional searches of PubMed and EBSCO were conducted as required to investigate specific issues.

2. Safety Assessment

2.1. Kinetics and metabolism of caffeine

Absorption

Absorption of an oral dose of caffeine from caffeinated beverages is rapid and practically complete (≥99%) in humans. Approximately 20% is absorbed from the stomach, and the balance in the small intestine, within 45 minutes of ingestion. Following an oral dose of 5 mg/kg caffeine, mean time to peak plasma concentration (T_{max}) in healthy male volunteers was 29.8 ± 8.1 minutes. Comparison of the area under the curve (AUC; a measure of total systemic exposure) following intravenous and oral exposure has shown that the bioavailability of oral caffeine is 100%, which indicates that there is no significant hepatic first-pass effect.

The rate of consumption of caffeinated beverages, the temperature of the beverage and the vehicle (coffee versus energy drink) appear to have negligible effect on caffeine pharmacokinetics (Montiero et al 2018). Relative to absorption of caffeine from caffeinated beverages, caffeine absorption from chocolate may be delayed, with a T_{max} at 1.5 to 2 hours (Arnaud 2011).

Distribution

Caffeine is widely distributed in the body and can be found in all body fluids including

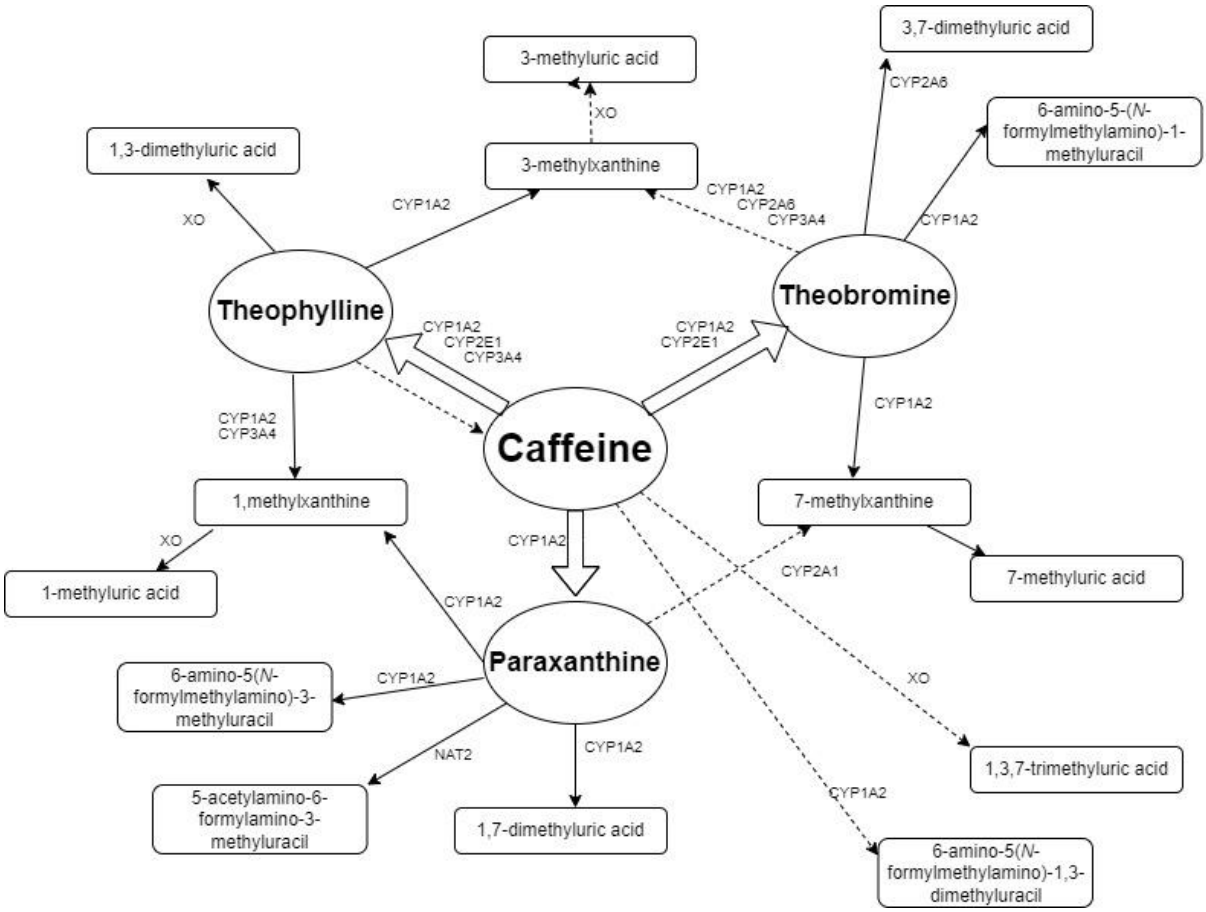
plasma, cerebrospinal fluid, saliva, bile, semen, breast milk and umbilical cord blood (Arnaud 2011). The blood-to-plasma ratio of caffeine is close to 1, reflecting limited binding of caffeine to plasma proteins (Nehlig et al 2018). Autoradiography studies in animals following administration of radiolabelled caffeine have shown that there is no bioaccumulation of caffeine or its metabolites in any tissue. Intravenous studies in rabbits have shown that the tissue:blood concentration ratio is approximately 1.0 for most tissues, with the exceptions of adipose tissue, adrenal glands, liver, and bile, for which the ratios were 0.2, 0.6, 1.5 and 2.7, respectively. Caffeine readily crosses the blood-brain barrier and readily crosses the placenta. *Ex vivo* studies have established that caffeine crosses the placenta by passive diffusion. Caffeine and its metabolite paraxanthine distribute nearly homogeneously in tissues of 29-day rabbit fetuses, and are also found in amniotic fluid. Both caffeine and paraxanthine accumulate in fetal hair and can be assayed in the hair of newborn babies, with the quantities showing a high correlation with maternal caffeine consumption in the last trimester of pregnancy (Lehtonen et al 2021). Caffeine is excreted in milk, with interspecies differences. In the rabbit, the concentration of caffeine in the milk is significantly lower than in the maternal plasma whereas in the cow, the concentration in milk is similar to that in plasma between 1.5 to 24 hours after administration. In lactating women, milk: serum concentration ratios of 0.52 to 0.81 have been measured. It appears that there is some binding of caffeine to the lipid fraction of milk (Arnaud 2011).

It has been estimated than an oral dose of 1 mg/kg bw caffeine typically produces a peak plasma concentration in the range 5-10 µM. A linear dose-response relationship has been demonstrated in the oral dose range 1 to 10 mg/kg, although there is considerable interindividual variation in plasma concentrations. Saliva caffeine concentration is typically approximately 80% of plasma concentration. At oral doses up to 250 mg, caffeine reaches a steady-state volume of distribution (V_D) between 500 and 800 mL/kg bodyweight (Magkos and Kavouras 2005). The half-life of caffeine in the circulation is usually within the range 3 to 7 hours in adults (Sharif et al 2017; Temple et al 2017) but tends to be longer in obese people than lean people (Arnaud 2011).

Metabolism

Caffeine is metabolized in the liver to three primary metabolites, paraxanthine (~84%), theobromine (~12%) and theophylline (~4%) (Singh et al 2018) (**Figure 1**). These metabolites are further metabolized to a range of methylurates and substituted uracil derivatives, and some paraxanthine also undergoes glucuronidation.

Figure 1 Metabolism of caffeine



NAT2 = *N*-acetyltransferase-2
XO = xanthine oxidase

CYP1A2 is responsible for more than 90% of caffeine metabolism (Arnaud 2011). Other enzymes in the cytochrome P450 family, including CYP2E1, CYP2C8, CYP2C9, and CYP3A4, have minor roles in caffeine metabolism (Jabir et al 2018). Some metabolic pathways, notably demethylation to paraxanthine, can be saturated in adults in the dose range 1-4 mg/kg caffeine. (Arnaud 2011).

Whether caffeine induces upregulation of CYP1A2 activity in humans is a matter of debate. Vaynshteyn and Jeong (2012) found that caffeine caused a nine-fold increase in CYP1A2 in rat hepatocytes *in vitro*, but did not alter CYP1A2 expression at a concentration attained by ordinary coffee drinking (50 μM). The expression of CYP1A2 was modestly (2.3-fold) increased only at the highest concentration tested, 400 μM. However, Urry et al (2016) found, in a study of CYP1A2 activity and caffeine consumption in humans, that participants who habitually consumed more caffeine than the population average showed higher CYP1A2 activity than participants with lower than average caffeine consumption. Urry et al (2016) interpreted this finding as suggesting that caffeine induces CYP1A2 upregulation, although an alternative explanation would be that people who can rapidly metabolise caffeine, can tolerate more caffeine, and may consume more caffeine to get similar effects to those reached by lower doses in people with lower CYP1A2 activity.

Puri et al (2020) found no sex-related difference in salivary caffeine clearance in 213 healthy adults.

The half-life of caffeine in the first trimester of pregnancy is comparable to that in nonpregnant women but increases to approximately 10 h by 17 weeks' gestation and up to 18 h by the end of pregnancy, resulting in increased caffeine exposure to both mother and fetus. Maternal activities of both CYP1A2 and N-acetyltransferase are downregulated during pregnancy, while both the fetus and the placenta lack the enzymes required to metabolize methylxanthines (Ådén 2011). Tracy et al (2005) measured CYP1A2 activity in 25 women at 14 to 18 weeks of gestation, 24 to 28 weeks of gestation, and 36 to 40 weeks of gestation and again at 6 to 8 weeks after delivery, and found mean changes in activity of -32.8% (±22.8%), -48.1% (±27%), and -65.2% (±15.3%), at the first, second and third measurements respectively, when compared to the fourth, postnatal measurement.

Absorption and distribution of caffeine in premature and term infants is similar to that in adults, but the half-life of caffeine in neonates is much longer than in adults, at up to 100 hours, due to immaturity of the CYP1A2 enzyme system. However, the system matures rapidly, and caffeine clearance reaches or exceeds adult levels by 5 to 6 months of age (Turnbull et al 2016).

Genetic variability in *CYP1A2*, the gene that encodes CYP1A2, represents a major cause of interindividual variability in CYP1A2 activity. The clearance of caffeine can vary 40-fold between individuals. More than 150 single nucleotide polymorphisms (SNPs) have been identified for *CYP1A2* (Yang et al 2010). One SNP that has attracted particular attention, because it affects inducibility of the enzyme and the speed of caffeine metabolism, is an A to C substitution at position 163 (rs762551). Individuals with the AA genotype are characterised as fast metabolisers of caffeine whereas individuals with CA and CC genotypes are slow metabolisers (Muñoz et al 2020).

Excretion

In the dose range of 2 to 10 mg/kg bw, caffeine elimination in healthy adult humans is a first-order process[3], described by a one-compartment open model (Arnaud 2011). However, at high doses metabolic pathways become saturated and excretion becomes zero-order[4] (Jones 2017).

Caffeine and its metabolites are predominantly excreted by the renal route. Both caffeine and the primary dimethylxanthine metabolites are extensively reabsorbed in the renal tubules and renal clearance is highly dependent on urine flow. Reabsorption of caffeine by the renal tubules is approximately 98% (Arnaud 2011). While in adults only slightly over 1% of caffeine is excreted in urine as the parent compound rather than as metabolites, in neonates 80 to 90% of a dose of caffeine is excreted as the parent compound, with the balance comprising small amounts of a wide variety of demethylated metabolites (Ginsberg et al 2004).

After oral administration of radiolabelled caffeine to human volunteers, faecal excretion over 48 hours was between 2 to 5% of the administered dose. Metabolites found in the faeces were 1,7-dimethyluric acid, 1-methyluric acid, 1,3-dimethyluric acid, 1,3,7-trimethyluric acid, and caffeine, representing 44, 38, 14, 6 and 2% respectively of the total radiolabel found in the faeces (Arnaud 2011).

Summary

Caffeine is rapidly and completely absorbed, and widely distributed in the body. It can be found in all body fluids. The half-life is generally in the range 3 to 7 hours. CYP1A2 is

[3] In a first-order process, a consistent proportion of the xenobiotic is eliminated per unit time
[4] In a zero-order process, a consistent amount of the xenobiotic is eliminated per unit time

responsible for more than 90% of the first step in caffeine metabolism, other enzymes in the cytochrome P450 family have minor roles in caffeine metabolism. Up to a dose of 10 mg/kg bw, caffeine elimination is a first-order process described by a one-compartment open model. Caffeine and its metabolites are primarily excreted in the urine.

2.2. Pharmacodynamic mechanisms of caffeine

The effects of caffeine are mediated through adenosine receptor antagonism at plasma concentrations achieved through normal dietary intake levels (<100 mM). Other effects such as phosphodiesterase inhibition, GABA receptor modulation and activation of ryanodine-sensitive calcium channels are relevant at toxic levels.

Blockade of adenosine A_1 and A_2 receptors occurs when caffeine is present at a serum concentration between 0.2 to 2 mg/L (0.001 to 0.01 mM (Ådén 2011). Adenosine inhibits the release of several neurotransmitters in the brain, including glutamate, serotonin, acetylcholine, noradrenalin, and dopamine, and therefore adenosine receptor antagonists promote the release of these neurotransmitters.

Recently, caffeine has been shown to act *in vitro* as both an agonist and, at higher doses, an ion channel blocker on nicotinic acetylcholine receptors. The agonist effect occurs at micromolar concentrations consistent with typical exposure (Fabiani et al 2018).

In reviewing the literature concerning caffeine, it is important to distinguish the effects of caffeine from those of the vehicle in which it is consumed. Animal studies are usually conducted using pure caffeine, and short-term clinical trials may also be conducted using pure caffeine. However, in some short-term clinical trials, coffee with a known caffeine content is used as the test article, and epidemiological studies generally reflect consumption of coffee or tea, often with the assumption that observed effects are attributable to caffeine. This is not a safe assumption, because coffee is a complex food that contains thousands of chemicals, of which over 100 are pharmacologically active (Ranheim and Halvorsen 2005). Chemicals in coffee include polyphenols (e.g., chlorogenic acid, lignin), the alkaloid trigonelline, and magnesium, potassium, and niacin. Roasting of coffee beans results in the formation of melanoidins (van Dam et al 2020). Effects observed in epidemiological studies are sometimes the reverse of those expected from animal studies or acute clinical trials in which pure caffeine is used (Beaudoin and Graham 2011). Kolb et al (2020) attribute many of the beneficial effects of coffee to phenolic acids and polyphenols, compounds that activate the Nuclear factor erythroid 2-related factor-2 (Nrf2) system, which induces the expression of cell defence genes.

Caffeine prolongs sleep latency, shortens sleep time, increases light sleep, and decreases deep sleep. REM sleep is the phase least affected, but latency to the first REM phase is shortened. Habitual caffeine consumers acquire some tolerance to the effects of caffeine on sleep. Caffeine has beneficial effects on performance and mood in sleep-deprived people such as shift workers (Porkka-Heiskanen 2011). Few studies have investigated the effects of < 100 mg caffeine on sleep. A dose of 1.1mg/kg bw caffeine had negligible effect on sleep patterns in healthy young men who were habitual consumers of 1 to 4 cups of coffee per day. Clear, dose-related effects are evident at doses of 300 to 400 mg caffeine (Turnbull et al 2016).

In caffeine-naïve subjects, caffeine consumption results in acute increases in epinephrine levels and blood pressure. Results of trials of repeated doses of caffeine, but not coffee, tend to indicate that increases in blood pressure persist, whereas in habitual coffee consumption, tolerance to hypertensive effects develops in about a week. Therefore, tolerance may reflect the action of other components of coffee such as chlorogenic acid (van Dam et al 2020).

Antagonism of adenosine receptors by caffeine and other methylxanthines promotes relaxation of the smooth muscles of airways, leading to bronchodilation (Tilley 2011).

Acute caffeine intake reduces insulin sensitivity in humans in a dose dependent manner, from a threshold dose that may be less than 1 mg/kg bw (Beaudoin et al 2013). This effect is thought to be mediated through caffeine's effects on skeletal muscle, which is the dominant tissue for glucose disposal, being insulin-sensitive and representing 35 to 40% of body mass. It appears that the effect is mediated through epinephrine release from the adrenal medulla, because it is not observed when caffeine is administered together with propranolol, a β-adrenergic receptor blocker (Beaudoin and Graham 2011).

Caffeine can act as a diuretic, although habitual moderate (≤ 400 mg/day) intake does not adversely affect hydration (van Dam 2020). The dose of caffeine required to induce acute diuresis is in the order of 300 mg (Osswald and Schnerman 2011).

There is considerable variation between individuals in responses to the various effects of caffeine. As examples, some individuals are particularly susceptible to its anxiogenic effects, and some are particularly susceptible to sleep disturbance. Also highly variable between individuals are the extent to which tolerance develops with habitual use, and the severity of caffeine withdrawal symptoms. Inherited differences have been identified in the pharmacokinetics and in the pharmacodynamics of caffeine. Studies in twins indicate that the heritability of most caffeine-related traits including caffeine-related insomnia, caffeine toxicity, caffeine tolerance, caffeine withdrawal and perception of caffeine's bitterness ranges between 0.36 and 0.58, on a scale from 0 (not heritable) to 1 (completely inherited), while heritability of heavy caffeine consumption is higher, at around 0.77. Studies investigating the effect of stage of life on caffeine consumption indicate that family environment has the greatest influence on caffeine consumption between the ages of 9 and 14, but genotype becomes increasingly influential through adolescence and caffeine use in adulthood is usually stable over time (Yang et al 2010).

Results of a small study in trained male cyclists (n = 35) suggest that people who are fast metabolizers of caffeine (AA homozygotes at position 163 of *CYP1A2*) derive more ergogenic effect from caffeine consumed before exercise than carriers of the C allele do (Womack et al 2012). Polymorphisms in the adenosine receptors have also been shown to influence the effects of caffeine in humans. Single nucleotide polymorphisms have been identified in ADORA2A, the gene that encodes the A2A receptor, that markedly influence the anxiogenic effects of caffeine, its effects on the sleep cycle, and its effects on vigilance (Childs et al 2008; Yang et al 2010; Bodenmann et al 2011). Dopamine mediates the locomotor effects of caffeine. Dopamine D2 and adenosine A2A receptors form heteromeric complexes in dorsal a2011nd ventral striatal neurons. Although caffeine does not bind to dopamine receptors directly, chronic treatment of animal models with caffeine has been shown to alter dopamine-mediated responses. A single nucleotide polymorphism in the DRD2 gene, that encodes the dopamine D2 receptor, has been associated with anxiogenic effects of caffeine in humans (Yang et al 2010). Other genes associated with variations in human response to caffeine include AHR, NAT2, NRCAM, ULK3, PDSS2, CAB39L, XDH, and the 23-kb long 5' flanking region commonly shared between CYP1A1 and CYP1A2 genes (Sulem et al 2011; Amin et al 2012; Pirastu et al 2016; Nehlig 2018).

Summary

At normal levels of dietary consumption of caffeine, the only significant mechanism of action is the antagonism of adenosine receptors. Studies in which coffee, rather than caffeine, is assessed should be interpreted with caution because the effects of coffee consumption are not necessarily mediated by caffeine.

2.3. Beneficial effects of caffeine and coffee

Caffeine in doses of 32 to 300 mg (approximately 0.5 to 4 mg/kg in a 75 kg person) is reported to enhance aspects of cognitive performance including attention, vigilance, and reaction time (McLellan et al 2016).

Caffeine can contribute to pain relief when added to analgesic agents (van Dam et al 2020). In a small (n = 62) study in adults, habitual caffeine consumption was inversely related to pain sensitivity in healthy adults (Overstreet et al 2018). The effects of caffeine on pain are attributed to blocking of central adenosine receptors, which affects pain signalling, and blocking of peripheral adenosine receptors on sensory afferents. Caffeine is therapeutic in hypnic headache, and is also therapeutic in post-dural puncture headache, possibly through increasing production of cerebrospinal fluid (Nowaczewska et al 2020).

Caffeine is associated with improvements in several physical performance metrics (McLellan et al 2016) discussed further in Section 2.6.6. and in the Nutrition assessment.

Caffeine may improve energy balance by reducing appetite and increasing basal metabolic rate and food-induced thermogenesis. These effects may be mediated by stimulation of the sympathetic nervous system and the uncoupling of protein-1 expression in brown adipose tissue (van Dam et al 2020). The thermogenic effects of caffeine do not adversely affect athletic performance in hot conditions (McLellan et al 2016). Acute caffeine consumption can increase resting thermogenesis by up to 10%, but there is a lack of evidence that chronic caffeine consumption through coffee is associated with significant weight loss (Beaudoin and Graham 2011).

Although acute caffeine intake reduces insulin sensitivity (Beaudoin et al 2013) several recent studies and meta-analyses have shown an inverse relationship between coffee consumption and risk of developing Type 2 diabetes mellitus, although there is generally no difference between normal coffee and decaffeinated coffee (Chrysant 2017). Consumption of caffeinated coffee, but not decaffeinated coffee, shows significant inverse association with serum ALT and liver fat score, and non-alcoholic fatty liver disease is a significant predictor of Type 2 diabetes, so the inverse relationship between coffee and Type 2 diabetes may be mediated by protective effects of caffeine on the liver (Dickson et al 2015). Wedick et al (2011) found in a randomized controlled trial of effects of coffee in 45 healthy, overweight volunteers, that caffeinated coffee is associated with a mean increase in circulating adiponectin, a hormone that is protective against insulin resistance, while decaffeinated coffee was associated with decreased circulating fetuin-A. Fetuin-A promotes insulin resistance.

Prospective epidemiological studies reviewed by van Dam et al (2020) have shown that coffee consumption is inversely associated with incidence of endometrial cancer and hepatocellular carcinoma. For endometrial cancer, the strength of the association is similar between regular coffee and decaffeinated coffee, suggesting that the effect may not be mediated by caffeine, but for hepatocellular carcinoma, the inverse association is stronger for regular coffee than decaffeinated coffee. This is consistent with animal studies that show that caffeine inhibits hepatocellular carcinoma. Coffee may also be associated with slightly reduced risk of melanoma and other skin cancers (van Dam et al 2020). Nkondjock (2009) concluded from a review that coffee consumption is associated with a reduced risk of liver, kidney, and to a lesser extent, premenopausal breast and colorectal cancers, while it is unrelated to prostate, pancreas and ovary cancers. However, Pauwels and Volterrani (2020) concluded that although coffee consumption may reduce risk of breast cancer in postmenopausal women, evidence is conflicting regarding its effects on risk of cancers originating in oesophagus, pancreas, colorectum, kidneys, bladder, ovaries or prostate.

Coffee has consistently been associated with lower circulating levels of hepatic enzymes, lower risk of hepatic fibrosis, and lower risk of hepatic cirrhosis, and *in vitro* evidence suggests that these beneficial effects are at least partly mediated by caffeine. Coffee has also been associated with decreased risk of gallstones and of gallbladder cancer, and the associations are stronger for regular coffee than for decaffeinated coffee. (van Dam et al 2020). Caffeine has been shown to prevent the formation of cholesterol gallstones in a canine model (Lillemoe et al 1989). In human volunteers, caffeinated coffee was shown to promote gallbladder contractions, although the mean effect was only slightly lower in response to decaffeinated coffee (Douglas et al 1990).

In three large ongoing cohort studies, consumption of coffee was associated with reduced risk of kidney stones, with caffeinated coffee having a significantly greater effect than decaffeinated coffee (Ferraro et al 2013).

Caffeine has beneficial effects in patients undergoing general anaesthesia and surgery. In animal models, caffeine is associated with enhanced ventilator response to hypoxia and hypercapnia, and in both animals and human volunteers, caffeine improves recovery from general anaesthesia, with decreased time to recovery of gag reflex and decreased residual sedation. Habitual caffeine consumption also increases pain threshold (Pleticha et al 2021).

Caffeine levels in cerebrospinal fluid are positively associated with prognosis in traumatic brain injury (Chen and Chern 2011), and caffeine also appears to be beneficial in neurodegenerative disorders. Caffeine prevents Parkinson's disease in animal models, possibly by inhibiting dopaminergic neurotoxic effects, and prospective cohort studies in the USA, Europe and Asia have shown a strong inverse association between caffeine intake and risk of Parkinson's disease (van Dam et al 2020). A number of epidemiological studies have shown that regular coffee consumption is associated with reduced risk of Alzheimer's disease and reduction in age-related cognitive decline (Chen and Chern 2011; Chen 2014).

2.4. Acute toxicity of caffeine

Acute effects of caffeine summarized by FSANZ in 2019 (P1054) are reproduced in Table 2.

Table 2: Acute effects of caffeine in adults

Acute dose (mg)	Effects/Comments
>20 mg	Self-reported positive effects on mood[a]
60	Measurable decrease in reaction time[a]
80–95	Single cup of coffee[a,b]
100	May delay sleep and reduce sleep duration[a, c]
140	Minor increase in diastolic pressure[a]
200	Up to this level not associated with safety concerns[c]
200–250	Effects including an increase in blood pressure and plasma catecholamines. Reduction in myocardial blood flow when exercising[c]
280	Reduction in perceived exertion during exercise[c]
400-500	Increase in anxiety in psychologically normal subjects[c]
>500	Rate of clearance of caffeine is decreased[b]
1200	Tachycardia, ventricular arrhythmia, seizures[a,b]
3000	Lowest lethal dose identified by FSANZ[a]
5000–10,000	Life-threatening dose[a]

[a]FSANZ (2000); [b]US FDA (2018) https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-highly-concentrated-caffeine-dietary-supplements; [c]EFSA (2015)

As shown in Table 2, intake of caffeine of up to 210 mg (approximately 3 mg/kg bw) is not associated with safety concerns. Above that dose, caffeine intake is generally associated with increases in blood pressure, plasma catecholamines and anxiety. At or above 1200 mg more serious effects such as tachycardia, ventricular arrhythmia or seizures may develop, and urgent medical attention may be required. Death has been reported at a dose of 3000 mg, however it is more commonly associated with doses of around 5000 to 10,000 mg (5 to 10 g) caffeine.

At toxic doses, caffeine has a number of effects in addition to adenosine receptor antagonism, including blocking of GABA receptors (Ådén 2011), inhibition of phosphodiesterase, stimulation of calcium release from sarcoplasmic reticulum and inhibition of calcium reuptake (Cappelletti et al 2018). At serum concentrations over 25 µg/mL, caffeine can block monoamine oxidase (MAO), resulting in increased epinephrine, dopamine and glutamate. Direct and indirect consequences of these neurotransmitters are generalized vasoconstriction, increased heart rate, hypokalaemia, and increased excretion of water and sodium. The combination of increased calcium levels and decreased potassium levels in serum may lead to cardiac dysrhythmia (Carreon and Parsh 2019).

The direct cause of death in caffeine poisoning is usually ventricular fibrillation. From a systematic review and meta-analysis of 92 case reports, Cappelletti et al (2018) concluded that the subpopulations most at risk of fatal caffeine poisoning are athletes, psychiatric patients, and infants.

Clinical signs of moderate caffeine toxicosis include restlessness, anxiety, tremors and gastrointestinal discomfort, which may include vomiting. Caffeine ingestion exceeding 6 mg/kg bw can result in decrease of both physical and cognitive performance, as well as severe gastrointestinal distress. Signs of severe, life-threatening caffeine toxicosis include hypokalaemia, ventricular dysrhythmias, hypotension, and rhabdomyolysis (Carreon and Parsh 2019) and are usually associated with a blood caffeine concentration greater than 80 mg/L (Cappelletti et al 2018; Laitselart et al 2018). Patients with caffeine toxicosis may also present with signs such as recurrent seizures, hypertonicity, tachycardia, psychosis, hyperglycaemia with acidosis, or renal failure secondary to rhabdomyolysis. Fatality is usually associated with an acute dose of ≥ 150 mg/kg bw (Carreon and Parsh 2019). Terminal signs of caffeine toxicosis are convulsions, coma, and apnoea (Jones 2017).

There is no antidote for caffeine toxicosis, and the mainstays of treatment are “the three Bs”: Bolus crystalloid for significant gastrointestinal losses, diuresis, and any hypotension; benzodiazepines for seizure activity and to decrease catecholamine release; and a beta-blocker to reduce the beta agonism of catecholamine release (Carreon and Parsh 2019).

In a review of caffeine levels in post-mortem blood of 51 fatal cases of caffeine toxicosis, Jones (2017) reported a median concentration of 187 ± 96 mg/L and a range of 33–567 mg/L. There was no significant difference between men and women. Jones (2017) cited other reviews of caffeine blood levels that concluded that a caffeine concentration in blood below 10 mg/L may be considered harmless, a concentration between 15 and 20 mg/L is elevated but not a danger to health, but levels between 80 and 180 mg/L may be fatal. A concentration of > 100 mg /L caffeine in post-mortem blood should be interpreted as a poisoning. Post-mortem redistribution from blood to tissues is not a significant phenomenon (Jones 2017) and therefore post-mortem levels are likely to reflect those in life.

2.4.1 Available information from Poisons Centres in Australia and New Zealand

Data from the New Zealand Poisons Centre show that caffeine was the subject of 91 calls

between 2017 and 2021. The age of the subject of the call was recorded in 86 of those calls, and 45 calls concerned caffeine consumption by subjects less than 12 years of age. There were four calls concerning infants less than 12 months old, 17 calls concerning children aged 1 year, nine calls about children aged 2, four calls about children aged 3, three calls about children aged 4, four calls about children aged 5, two calls about children aged 6, two calls about children aged 7, one call about a child aged 11 and two calls about children aged 12. Data on age are incomplete in the records obtained by FSANZ from Australian Poisons Centres but show that pre-schoolers are frequent subjects of calls concerning caffeine exposure.

Gunja and Brown (2012) conducted a retrospective review of calls concerning energy drink exposure to the NSW Poisons Information Centre, the largest centre of its type in Australia, for the period January 2004 to December 2010. Sixty-two children were reported to have accidentally consumed energy drinks The mean age of these paediatric exposures was 38 months ± 24 months; range, 7–120 months). Of these, 14 children had symptoms probably related to energy drink consumption, most commonly hyperactivity, and nine required assessments in hospital. Similarly, an analysis of reports made to the US National Poison Data System concerning energy drink consumption (Seifert et al 2013) found that 50.7% of reports were about unintentional consumption by children under 6 years old.

Summary

Acute caffeine toxicosis is generally associated with a blood concentration greater than 80 mg/L, equivalent to consumption of 10 to 20 g of caffeine in an average adult. Subpopulations most at risk of caffeine toxicosis are athletes, psychiatric patients, and infants. Cause of death is usually ventricular fibrillation. Poisons Centre data indicate that children are at particular risk of caffeine toxicity.

2.5. Chronic toxicity of caffeine

Most caffeine is consumed as coffee (Beaudoin and Graham 2011) and there is a lack of information on the consequences of chronic caffeine consumption, independent of other chemicals in coffee or tea, in adults. Commonly used sources of caffeine other than tea and coffee are sports supplements, energy drinks and therapeutic doses of pure caffeine given to treat apnoea of prematurity, but these are sources largely or wholly specific to certain subpopulations and are therefore reviewed in section 2.6, Vulnerable Subpopulations.

There is a lack of evidence that chronic, moderate consumption of coffee or tea (up to 400 mg/day caffeine) is associated with significant adverse effects in the general adult population. On the contrary, a systematic review by van Dam et al (2020) showed that consumption of two to five standard cups of coffee/day has been associated with reduced mortality in numerous cohort studies worldwide, in persons of European, African-American, and Asian ethnicity. For people consuming more than five cups of coffee per day, the risk of death is either lower than, or similar to, the risk with no coffee consumption, after adjustment for confounding by smoking status. Genetically based variations in the rate of caffeine metabolism between individuals make no difference to the inverse association between coffee consumption and all-cause mortality in cohort studies (van Dam et al 2020). In particular, chronic consumption of caffeine is not associated with increased risks of major causes of degeneration and mortality including cardiovascular disease, cancer or neurodegenerative diseases (Beaudoin and Graham 2011).

Chronic consumption of unfiltered coffee (such as French press, Turkish, or Scandinavian boiled coffee) may increase serum cholesterol, but this effect is due to the presence of the diterpene cafestol, rather than caffeine (van Dam et al 2020) and is therefore not relevant to this review.

Caffeine consumption is typically self-limiting and is considered to have little potential for abuse (Addicott 2014). That is, consumers generally learn to regulate their intake to gain the beneficial effects while avoiding the adverse effects.

Summary

Chronic moderate consumption of caffeine at up to 400 mg/day is not associated with significant adverse effects in the general adult population, with the exception of pregnant women (see Section 2.6.3).

2.6. Vulnerable subpopulations

2.6.1. Infants and children

2.6.1.1. Infants

2.6.1.1.1. Therapeutic use

Caffeine is a highly valuable therapeutic for management of premature infants and has greatly reduced mortality and morbidity in these patients. It is universally used as a respiratory stimulant for treatment of apnoea of prematurity. It is also an effective treatment for postoperative apnoea which affects up to 47% of infants who undergo surgery. Caffeine acts as a broncho-relaxant, improves diaphragmatic function, increases respiratory system compliance (Aranda et al 2010), and improves chemoreceptor sensitivity to CO_2 (Ådén 2011). Caffeine reduces the need for other pharmacological interventions, or surgical intervention, to correct patent ductus arteriosus. Use of caffeine in premature infants has substantially reduced the incidence of bronchopulmonary dysplasia and of retinopathy of prematurity (Aranda et al 2010) and may improve microstructural development of white matter in the brain (Torres-Ugalde et al 2020). When caffeine is used to treat apnoea of prematurity, serum levels in infants are sufficiently high that in addition to adenosine receptor blockade, there may be some blockade of phosphodiesterases and GABA A receptors. (Cappelletti et al 2018).

A large, international randomised controlled trial “Caffeine for Apnea of Prematurity trial” followed a cohort for up to 11 years (Schmidt et al 2012; Schmidt et al 2017; Mürner-Lavanchy et al 2018; Schmidt et al 2019; Synnes and Grunau 2020). A total of 2006 infants were originally enrolled and randomly assigned to receive either caffeine citrate or a saline control. At five years of age, 833 children in the caffeine group and 807 in the control group were assessed for motor impairment, cognitive impairment, behaviour problems, general health, deafness and blindness (Schmidt et al 2012). Variable numbers of children from both the treated and placebo cohorts were also assessed at 11 years of age for academic performance, motor impairment, behaviour problems (Schmidt et al 2017), general intelligence, attention, executive function, visuomotor integration and perception (Mürner-Lavanchy et al 2018) and their own opinion of their quality of life (Schmidt et al 2019). In all parameters, there was either no significant difference between the caffeine cohort and the control cohort, or the caffeine cohort performed better than the control cohort. Collectively, the results of the trial indicate that even high doses of caffeine in premature infants have no long-term adverse effects.

2.6.1.1.2. Breast feeding

A proportion of circulating caffeine enters the milk of lactating women. Milk: serum concentration ratios of 0.52 to 0.81 have been measured. (Arnaud 2011).

EFSA (2015) concluded that caffeine consumed by lactating women at up to 200 mg per day does not give rise to safety concerns for the breastfed infant, based on a calculation that caffeine intake by the infant would not exceed 0.3 mg/kg bw. McCreedy et al (2018) undertook a systematic review of the effects of maternal caffeine consumption on the breastfed child. However, they found a lack of studies that met their inclusion criteria after excluding cross-sectional studies, case reports, qualitative research, editorial commentaries, conference abstracts and reviews. Only five studies met the inclusion criteria, comprising two prospective cohort studies, two crossover studies and one N-of-1 trial. Endpoints investigated in association with maternal caffeine consumption included sleep behaviour, heart rate, crying, colic, and atopic dermatitis. One study investigated whether caffeine consumers had a shorter duration of full breastfeeding than those who abstained. McCreedy et al (2018) concluded that their most prominent findings were the extreme paucity of data concerning caffeine consumption in lactating women, and the limited quality of the studies that do exist, making it difficult to draw any conclusions about the effects of caffeine exposure during breastfeeding.

Newborn infants may show signs of caffeine withdrawal if the mother has habitually consumed high levels of caffeine during pregnancy, and breastfeeding is not promptly established. Signs of caffeine withdrawal in neonates include ‘jitteriness’, high-pitched cry, hypertonia in the limbs, brisk tendon reflexes and vomiting. Episodes of apnoea have been observed in some infants in caffeine withdrawal. Signs of caffeine withdrawal usually resolve in one to two days (Ådén 2011) although Martín et al (2007) reported a case of neonatal caffeine withdrawal in which the infant was still exhibiting episodes of irritability when discharged from hospital at 24 days of age. The mother had been habitually consuming homemade yerba mate.

2.6.1.2. Children

Several regulatory agencies, including FSANZ, EFSA and BfR, recommend a maximum caffeine intake of 3 mg/kg bw/day for children, although Health Canada (Nawrot et al 2003) and the IOM recommend a lower intake of 2.5 mg/kg bw/day, and the VKM cited two toxicological reference points set by EFSA; 3 mg caffeine/kg bw/day for general adverse health effects, and 1.4 mg caffeine/kg bw/day for sleep disturbance.

Cappelletti et al (2018) identified infants as one of the three subpopulations most at risk of fatal caffeine poisoning, but it is evident from the context that Cappelletti et al were referring to toddlers rather than neonates. Causes of fatal caffeine toxicosis included accidental consumption of caffeinated products by toddlers, and child abuse.

Wikoff et al (2017) considered evidence relating to healthy adults, pregnant women, adolescents, and children. They concluded that the recommendations made by Nawrot et al (2003) remained valid although they considered that there was a lack of information concerning the effects of caffeine on behaviour in children.

A systematic review by Torres-Ugalde et al (2020) found negative effects of caffeine in children at moderate (~3 mg/kg bw/day) and high (~5 mg/kg bw/day) intake including alteration of the sleep cycle and alterations in affective states including anxiety and depression. The authors noted deficiencies in the available evidence including a paucity of longitudinal studies, poor specification and differentiation of ages, and a lack of consideration of dose-response relationships.

Zhang et al (2020a) extracted data from the Adolescent Brain Cognitive Development (ABCD) study to identify any associations between caffeine intake and cognitive function in

children. The ABCD study is a longitudinal cohort study that started in 2017 in the USA. Data were from 11,718 children aged between 9 and 10 inclusive, with a similar proportion of boys and girls. Children undertook a cognitive battery to provide data on seven core cognitive functions; vocabulary comprehension, reading decoding, inhibitory control, working memory, cognitive flexibility, processing speed, and episodic memory. After adjustment for age, gender, sleep and socioeconomic status, caffeine was found to be negatively associated with vocabulary comprehension, working memory, cognitive flexibility, processing speed, and episodic memory. This adverse effect remained when data from children who had consumed caffeine within 24 h prior to the cognitive assessment, and from children who had been diagnosed with Attention Deficit/Hyperactivity Disorder (ADHD) were excluded. Acknowledged limitations of the study were that intake was self- or parent-reported; that the data were skewed in that there were few high consumers of caffeine; and that the sugar content of caffeinated beverages was not considered. The authors concluded that caffeine may have adverse effects on cognitive development in children.

Caffeine-associated sleep impairment may have negative effects on academic performance, and for this reason, paediatricians may recommend that caffeine consumption should be limited in school-aged children and adolescents, and avoided altogether within a few hours of bedtime (Temple 2019).

Caffeine added to novel flavoured sugar-sweetened beverages increases the liking of these beverages, and motivation to consume them, in children and adolescents (Temple 2019) which may have a negative effect on overall quality of nutrition.

Summary

The therapeutic use of high doses of caffeine in premature infants does not appear to have any long-term adverse consequences. Heavy consumption of caffeine during pregnancy may result in caffeine withdrawal in neonates. There is a lack of evidence concerning the effects of caffeine in breastmilk. Infants and pre-schoolers are at considerable risk of accidental or malicious caffeine poisoning, due to their low bodyweight. Caffeine has negative effects on sleep in children, and this may lead to impaired academic performance. It has been suggested that caffeine may have direct negative effects on cognitive development in children and may promote consumption of beverages with high sugar content.

2.6.2. Adolescents

Temple (2019) reviewed studies showing an association between caffeine consumption and behavioural problems in adolescents. These included a study of 7400 adolescents aged 14 and 15 years in which there was an association between caffeine and anger; a study of 15- and 16-year-olds in which caffeine was associated with violent behaviour, and a study in adolescents and young adults in which there was a strong correlation between energy drink consumption and risk-taking behaviour including illicit substance use, risky sexual behaviour, participation in extreme sports, and physical violence (Temple 2019). Kaminer (2010) also listed tobacco smoking and failure to wear a seat belt among risk taking behaviours associated with energy drink use by adolescents.

The significance of co-consumption of energy drinks and alcohol in adolescents is the subject of considerable commentary in the literature. Temple (2019) states that energy drink consumption appears to promote excessive alcohol consumption. In a study of American college students, energy drink users consumed alcohol more frequently than nonusers, got drunk twice as often as those who consumed alcohol only and were significantly more likely to be injured, require medical treatment, or ride with an intoxicated driver. Students who combined energy drinks and alcohol were more likely to be victims or perpetrators of aggressive sexual behaviour. The effects remained after controlling for the amount of alcohol

consumed (O'Brien et al 2008). In contrast, Verster et al (2017) concluded, on the basis of a systematic review and meta-analysis, that energy drink consumption is unlikely to increase alcohol consumption or associated risk-taking behaviour.

Caffeine increases the reinforcing effects of nicotine and, because of increased caffeine metabolism among smokers, they consume more caffeine than non-smokers (Kaminer 2010). Caffeine may, therefore, contribute to adolescents becoming smokers.

Caffeine is one of a number of contributors to insufficient sleep in adolescents, which is associated with increased risks of depression, suicidal ideation, substance abuse, obesity, risk-taking behaviours, drowsy driving, and poor academic performance (Owens and Weiss 2017).

Arria et al (2011) collected data from 1097 students at a large public university in the USA and found that energy drink consumption was strongly associated with alcohol dependence, as defined by DSM-IV criteria. High frequency users of energy drinks were at significantly greater risk for alcohol dependence relative to both nonusers (AOR[5] = 2.40, 95% CI[6] = 1.27 to 4.56, p = 0.007) and low-frequency users (AOR = 1.86, 95% CI = 1.10, 3.14, p = 0.020). In a cross-sectional study of this type, causality cannot be inferred. Interactions of caffeine and alcohol are discussed further in Subsection 2.6.8.2.

Summary

Caffeine contributes to poor sleep quality in adolescents and is associated with aggression, risk-taking behaviour and alcohol consumption. Caffeine consumption may increase the risk of adolescents becoming smokers. FSANZ notes that it is difficult to distinguish direct effects of caffeine in adolescents from the effects of inadequate sleep, the effects of alcohol, and the potential effects of other components of energy drinks, which are a common source of caffeine in adolescents. There is a lack of new information on which to base a quantitative estimate of safe levels of caffeine in adolescents. However, caffeine clearance in adolescents is likely to be at least that of adults, so the recommended level for adults (i.e., 5.7 mg/kg bw/day) is also applicable to adolescents.

2.6.3. Pregnant women

2.6.3.1. Effects on fertility and conception

Hatch et al (2012) evaluated the relationship between caffeinated beverage consumption and time to pregnancy in a prospective cohort study of 3628 women planning a pregnancy in Denmark (2007–2010). Women reported beverage intake at baseline and every eight weeks during follow-up until they became pregnant, or for up to 12 cycles. Caffeinated beverages were divided into coffee, tea and caffeinated soda. They did not find a dose-response relationship between coffee intake and time to pregnancy. They found weak associations between soda consumption and longer time to pregnancy, and between tea consumption and shorter time to pregnancy, and considered that the results may have been confounded by unmeasured factors. Overall, there was a lack of evidence that caffeine consumption had any effect on time to pregnancy.

Several members of the Hatch et al (2012) research team contributed to a similar prospective cohort study of women planning pregnancy in the USA and Canada, published by Wesselink et al (2016). The study design was similar to that of Hatch et al (2012) but male partners were included in the study. A total of 2135 women and 662 male partners were

[5] Adjusted overall risk
[6] Confidence interval

included in the study. No significant association between caffeine intake and time to pregnancy was found in women.

Chavarro et al (2009) extracted data on 18,555 women from the Nurses Study, a large prospective study, on caffeine consumption and ovulatory disorder infertility. No association was found between total caffeine exposure and ovulatory disorder infertility, but intake of caffeinated soft drinks was positively associated with ovulatory disorder infertility (RR 1.47 (1.09 –1.98; p = 0.01). However, similar associations were observed for noncaffeinated, sugared, diet, and total soft drinks. The association was therefore unrelated to the caffeine content or the sugar content of soft drinks.

Recent studies of the influence of caffeine intake on success of conception assisted by *in vitro* fertilization (IVF) (Abadia et al 2017; Lyngsø et al 2019) do not show any significant adverse effect of caffeine.

2.6.3.2. Effects on the embryo and fetus

There is some evidence of teratogenic effects of high doses of caffeine in animal studies, including increased prevalence of cleft palate and cardiovascular abnormalities, but epidemiological studies have failed to demonstrate similar effects in human beings (Ådén 2011).

Brent et al (2011) reviewed developmental and reproductive studies in animal models, at the request of the Caffeine Committee of the International Life Science Institute (ILSI) and concluded that there is a lack of evidence that caffeine is abortifacient in animals at doses equivalent to range of human consumption. Furthermore, teratogenic effects are only seen in animals when the plasma level is ≥ 60 ng/mL, which far exceeds the level attained in humans by consumption of caffeine in food or beverages, and fetal growth retardation is also seen in animals only at doses that are not realistic in humans.

In a large (1411 infants) retrospective study in the Netherlands, it was found that the increase in risk of major congenital abnormalities from maternal use of phenobarbital as an antiepileptic drug was not significant in women who did not consume caffeine but was significant in women who did consume caffeine (Samŕen et al. 1999).

Chen et al (2012) undertook a case-control study to assess associations between maternal caffeine intake and congenital limb deformities, analysing data from 844 cases of limb deformity and 8069 controls over a ten-year period. They found a weak association but there was no dose-response relationship. They noted that women who forgo caffeine altogether during pregnancy may lead a healthier lifestyle overall that those who do not, which may be a confounding factor.

Some studies reviewed by Ådén (2011) show associations between caffeine and miscarriage, intrauterine growth restriction and stillbirth, but others show no association. Ådén (2011) remarked that nausea in the first trimester is a marker of fetal viability, but suggested that it may reduce caffeine consumption, confounding statistical analysis of data. In contrast, Gianelli et al (2003) found a strong negative association between first trimester nausea and miscarriage in a case-control study of 160 women who miscarried and 314 women who did not, but no association between first trimester nausea and coffee consumption. A prospective cohort study of 1063 women by Weng et al (2008) demonstrated an elevated risk of miscarriage associated with caffeine consumption of ≥ 200 mg/day which was independent of nausea and vomiting. Bech et al (2007) note that women with high caffeine intake during pregnancy are more likely to smoke than those with low caffeine intake, and also have a higher alcohol consumption, and are generally less well educated.

Bech et al (2007) comment that there are limits to how well correction can be made for these factors.

A systematic review with dose-response meta-analysis for associations between caffeine consumption and miscarriage, stillbirth, preterm delivery, low birthweight and small for gestational age (SGA) infants by Greenwood et al (2014) included 60 unique publications from 53 studies. Metaanalysis of the associations between caffeine intake included data from nearly 15,000 cases of miscarriage from 180,000 women, 700 still births from 120,000 women, 8000 preterm deliveries from nearly 110,000 women, 5000 low birth weight infants from nearly 78,000 women, and nearly 12,000 SGA infants from 160,000 women. The studies were from a variety of countries with different levels of caffeine intake, ranging from non-consumers to caffeine consumption exceeding over 1000 mg/day. An increment of 100 mg/day caffeine was associated with a 14% (95% CI 10–19 %) increase in risk of miscarriage, 19% (5–35%) stillbirth, 2% (-2 to 6 %) preterm delivery, 7% (1–12%) low birth weight, and 10% (6–14%) SGA. There was substantial heterogeneity in all models, but this was partly explained by adjustment for smoking and previous obstetric history. It was concluded that caffeine intake is positively associated with increases in miscarriage, stillbirth, low birth weight, and SGA, but not preterm delivery. It was not possible to identify a threshold for these adverse effects, but the authors noted that the associations are generally modest within the range of usual dietary intake. It is not possible to conclude that the associations are causal, but they are consistent with animal studies. Greenwood et al (2014) concluded that there was insufficient evidence to support further reductions in the current maximum recommended intake of 200 mg caffeine/day.

The risks associated with high caffeine consumption (> 3 cups coffee/day) during pregnancy are increased if the woman is also a smoker (Morales-Suárez-Varela et al 2018).

Coffee consumption had no effect on second-trimester fetal growth in a small study conducted by Conde et al (2011) but, in conjunction with maternal anxiety was associated with a decrease in limb movements, which the authors considered could be a marker of effects on neurobehavioural development. Conde et al (2011) found that maternal anxiety and tobacco use were significant predictors of maternal coffee consumption, highlighting the confounding potential of these factors.

Analysis of data from a cohort of 936 healthy pregnancies showed a positive association between maternal consumption of >300 mg caffeine/day and a slight increase (2 days 95%CI = 0.12 ± 4.21, p = 0.03)) in gestational age at birth. The authors considered this to be a possible effect of caffeine (van der Hoeven 2017).

Analysis of data from 47,491 mother-child pairs in the Danish National Birth Cohort led Mikkelsen et al (2017) to conclude that maternal consumption of more than 8 cups/day of coffee or tea at 15 weeks' gestation was associated with increased risk of behavioural disorders in the offspring at 11 years of age. Specifically, maternal coffee consumption ≥ 8 cups/d at 15 weeks of gestation (n = 1285; 2.7% of the total number of women) was associated with increased risk of hyperactivity-inattention disorder (RR 1.47; 95% CI 1.18-1.83), conduct-oppositional disorders (RR 1.22; 95% CI 1.01-1.48), and any psychiatric disorder (RR 1.23; 95% CI 1.08-1.40). Maternal tea consumption ≥ 8 cups/d at 15 weeks of gestation (n = 2050; 4.3% of the total number of women) was associated with increased risk of anxiety-depressive disorders (RR 1.28; 95% CI 1.09-1.52) and any psychiatric disorder (RR 1.24; 95% CI 1.11-1.40). Caffeine consumption from sources other than coffee and tea was not available. The authors acknowledged that the associations may be due to genetic or socioeconomic confounders.

In contrast to the findings of Mikkelsen et al (2017), Miyake et al (2019) found, as part of the prospective Kyushu Okinawa Maternal and Child Health Study, that maternal caffeine intake

was inversely associated with peer problems in children, measured at the age of 5 years. Subjects were 1199 mother-child pairs. Maternal caffeine intake was recorded during pregnancy by questionnaire. At 5 years of age, children were assessed using scales for emotional problems, conduct problems, hyperactivity, peer problems and prosocial behaviour. Compared with maternal caffeine consumption during pregnancy in the lowest quartile, consumption in the third and fourth quartiles was significantly associated with a reduced risk of peer problems in the children, showing an inverse linear trend in crude analysis and after adjustment for confounding variables. The adjusted ORs (95% CIs) for childhood peer problems in the first, second, third, and fourth quartiles of maternal caffeine consumption during pregnancy were 1 (reference), 0.61 (0.35–1.06), 0.52 (0.29–0.91), and 0.51 (0.28–0.91), respectively (P for trend = 0.01). No association was found between maternal caffeine intake during pregnancy and emotional problems, conduct problems, or hyperactivity problems in the children. Miyake et al (2019) commented that the association may have occurred by chance.

Tanaka et al (2021) used data from 1522 mother-child pairs in the Kyushu Okinawa Maternal and Child Health Study to investigate whether maternal caffeine consumption during pregnancy is associated with risk of food allergy in children. Compared with the lowest tertile of maternal caffeine intake, the second tertile, but not the highest tertile, was significantly associated (hazard ratio 1.46 (95% CI 1.10–1.96)) with an increased risk of food allergy. The authors interpreted this as suggesting that maternal caffeine intake increases risk of food allergy in children, despite the lack of a dose-response relationship. The authors acknowledged that the association could be due to chance. They noted that the study relied on mothers reporting food allergy, rather than requiring medical diagnosis.

Data from the Generation R study, a prospective population-based cohort study in Rotterdam, the Netherlands, were used to investigate the association between maternal caffeine intake and fat deposition in children at the age of 10. Data from 4770 mother-child pairs were available. Adjustment was made for maternal ethnicity, education, smoking during pregnancy, alcohol consumption during pregnancy, folic acid supplementation use, and childhood television watching time. When compared to maternal consumption of < 180 mg caffeine/day during pregnancy, maternal consumption of ≥ 360 mg caffeine/day was associated with higher body mass index, total body fat mass index, android/gynoid fat mass ratio, and abdominal, subcutaneous, and visceral fat mass indices in children (Voerman et al 2019). Differences between the strata were generally modest, although dose-response relationships were evident.

2.6.3.3. Effects on the pregnant woman

Adeney et al (2007) conducted a prospective study of 1744 pregnant women who were recruited during the first trimester. The association between coffee consumption before and during pregnancy and the risk of developing gestational diabetes mellitus (GDM) was analysed. Women who reported moderate intake of caffeinated coffee prior to pregnancy were at significantly lower risk of GDM (adjusted RR 0.50; 95% CI 0.29 to 0.85) compared with women who did not consume coffee. No risk reduction was associated with decaffeinated coffee intake, supporting the conclusion that moderate consumption of caffeine prior to pregnancy may be protective against GDM (Adeney et al 2007).

In a double-blind randomized crossover trial of 19 women without GDM and eight women with GDM, consumption of caffeine (3 mg/kg pre-pregnancy bodyweight) after overnight fasting impaired insulin sensitivity in the women with GDM but not in those without GDM. Specifically, glucose AUC was greater ($p < 0.01$), C-peptide AUC was greater ($p < 0.05$), and insulin sensitivity index was lower (18%, $p < 0.05$) after caffeine than after placebo in the women with GDM (Robinson et al 2009).

The associations of caffeine intake in different trimesters of pregnancy with repeated measurements of blood pressure were examined in a large cohort of 7890 pregnant women (Bakker et al 2011). Data on caffeine consumption were obtained by questionnaires completed in each trimester, and blood pressure was measured during each trimester. Data on a range of covariates was also collected. Caffeine intake was positively associated with higher systolic blood pressure measurement in the first and third, but not the second, trimester. There was no consistent association between caffeine and diastolic blood pressure, or the risk of pregnancy-induced hypertension. Moderate caffeine intake (180 to 350 mg/day) was significantly associated with a decreased risk of pre-eclampsia, when compared to low (< 180 mg/day) intake, suggesting a protective effect of caffeine (Bakker et al (2011).

Consumption of a cup of coffee had no effect on blood flow in the maternal uterine artery, fetal umbilical artery or fetal middle cerebral artery, in 10 pregnant women. All the women were in the third trimester (33.5 ± 2.8 weeks) of an uncomplicated pregnancy. Blood flow was measured by Doppler ultrasound before, and 30 min after, coffee consumption. Coffee intake had no effect on salivary cortisol levels in 25 nonpregnant women, but decreased salivary cortisol ($p < 0.05$) in the 10 pregnant women (Tsubouchi et al 2006).

Kuczkowski (2009, 2010) reported cases of women who suffered severe headache after childbirth which was initially thought to be post-dural puncture headache, but which was found to be due to caffeine withdrawal.

Summary

There is a lack of evidence that caffeine consumption has any adverse effect on fertility in women. Maternal clearance of caffeine decreases significantly in the second and third trimesters of pregnancy due to downregulation of metabolizing enzymes, while both the placenta and the fetus lack enzymes that metabolize caffeine. Available information on potential effects of caffeine generally supports the recommendation that pregnant women should limit their caffeine intake to ≤ 200 mg caffeine/day. Potential adverse effects on the fetus of high caffeine consumption during pregnancy include miscarriage, stillbirth, and fetal growth restriction. There is also some evidence of adverse behavioural and fat deposition effects on the child. Moderate caffeine consumption reduces the risk of GDM and pre-eclampsia but may exacerbate existing GDM. There is conflicting evidence concerning the effect of caffeine on length of gestation. Women who habitually consume caffeine should continue doing so in the perinatal period, in order to avoid caffeine withdrawal.

2.6.4. Consumers of energy drinks and other sports supplements

Musgrave et al (2016) identify energy drinks as high-risk sources of caffeine. They note that although energy drinks are generally labelled with a maximum intake of 500 mL energy drink/day, consumption levels can far exceed those recommendations. They cite the 2012 report by Gunja and Brown in which the authors record that callers to the New South Wales Poisons Information Centre had a median intake of five energy drinks, with the highest consumption being 80 energy drinks.

Habitual consumers of caffeinated beverages such as coffee and tea may experience adverse effects due to inadvertent ‘stacking’ of caffeine if they also consume caffeine that is surreptitiously added, or accidentally or deliberately hidden in the label, or overlooked in supplements. Musgrave et al (2016) suggest that herbal supplements marketed as body-building products or weight loss products may be of particular concern. In a review paper they cited two studies in which undeclared caffeine was found in herbal supplements. They

also commented that even if the presence of a caffeine-containing plant material or extract is declared on the label of a supplement, it may not be recognized by the consumer if the Linnaean name is used. As examples, *Camellia sinensis, Coffea canephora* and *Paullinia cupana* might not recognized by consumers as sources of caffeine (Musgrave et al 2016; IOM 2014).

A review of caffeine-based sports supplements available in Portugal, including powders, shots, concentrated liquids for dilution, energy drinks, energy bars, gels and pills found that approximately 22% of products provided 200 mg caffeine or more per serve, and 11% provided more than 400 mg caffeine/day if used as directed. The products were very often inadequately labelled (Bessada et al 2018).

Sports supplements may declare the caffeine content on the label while simultaneously recommending daily consumption of the supplement that results in high daily intake of caffeine. A case report by Carol (2013) of rhabdomyolysis in three US Army soldiers in association with a sports supplement highlights this fact. The label of the sports supplement indicated that the caffeine content was 500 mg/serving but recommended daily use of two servings/day. Rhabdomyolysis was attributed in all three cases to 'stacked caffeine consumption'.

Users of sports supplements may fail to appreciate the risks associated with excessive caffeine consumption. Jagim et al (2019) conducted an electronic survey of 872 regular users of pre-workout supplements, which typically contain 250 to 400 mg caffeine/serving. Most users were men who participated in resistance training and exercised 4 to 6 times per week. Although most users followed the package instructions regarding serving size, 14% reported that they consume two or more serving sizes at a time, and 18% reported using pre-workout supplements more than once a day. More than one-third of respondents to the electronic survey (34.9%) also reported using other sources of caffeine at the same time. More than half (54%) of respondents reported adverse effects that they attributed to the use of pre-workout supplements. The main adverse effects were skin reactions, effects on the heart, and nausea, but light-headedness and dizziness were also reported. Nevertheless, most respondents (85%) considered their use of pre-workout supplements to be safe.

In a systematic review of case reports of toxicosis following energy drink consumption, Ali et al (2015) located 43 case reports. Of those, 53% (n = 23) of presentations were for cardiac symptoms (n = 23) and 35% of the presentations for cardiac symptoms (n = 8) were related to arrhythmias. The doses at which these effects occurred were not reported. Ali et al (2015) noted that positron emission tomography (PET) scans conducted after caffeine consumption have demonstrated that caffeine causes a significant drop in myocardial blood flow during exercise. Consequently, myocardial perfusion reserve decreases by 14% to 22% in healthy subjects, and the effect is even greater in individuals with pre-existing coronary heart disease.

The second most common class of adverse effect in the series reviewed by Ali et al (2015) was neuropsychiatric and included six cases of first-onset seizures and several cases of exacerbation of psychiatric conditions. Causation could not be proved in any of the cases; however, the observed cardiac and neuropsychiatric outcomes are consistent with known toxic effects of caffeine. Other case reports included reports of thrombocytopaenia in association with energy drinks containing taurine, two cases of anaphylaxis (due to taurine in one case and vitamin B2 in the other), one case of profound hypokalaemia and one case of hepatic injury.

Data from Poisons Centres provide further information on high-risk sources of caffeine. Haller et al (2009) collaborated with the US FDA to conduct a one-year (2006) surveillance project of data from the San Francisco Division of the California Poison Control System on

adverse effects associated with dietary supplements. Calls concerning beverages and energy bars were excluded. There was a total of 275 calls included in the project. Causality assessment was based on the World Health Organization (WHO) Classification for Adverse Drug Reactions. Supplements containing caffeine, either alone or with substances with additive, potentiating, or synergistic effects, were consumed in 47% of cases in which there were adverse events, and complaints were those of sympathetic nervous system stimulation and/or gastrointestinal disturbances consistent with the known toxicology of caffeine. Eight cases required hospital admission, and there was a single fatality, that of a 39-year-old bodybuilder whose death was possibly due to use of a sports supplement containing yohimbine and caffeine. Death was due to infarction of the left middle cerebral artery.

Of 91 calls concerning caffeine made to the NZ Poison Centre between 2017 and 2021 inclusive, 78 concerned consumption of energy drinks, six concerned over the counter (OTC) health supplements containing caffeine, and seven concerned Coca-cola. Combined data from Australian state Poison Centres from January 2017 to the 31st of July 2021 yielded 245 calls made concerning caffeine. Of these, 86 were in relation to coffee, tea, chocolate, or other caffeine-containing foods, 71 were in relation to energy drinks, 58 were in relation to No-Doz tablets, 17 were in relation to sports supplements or fat burners, and 11 were unspecified. The balance were various OTC products for energy, sports supplementation, or fat burning.

Gunja and Brown (2012) reviewed calls made to the NSW Poisons Information Centre from January 2004 to December 2010 concerning energy drink consumption. There was a total of 279 calls. The most common symptoms were palpitations, agitation, tremor, and gastrointestinal upset. Twenty-one subjects had signs of serious cardiac or neurological toxicity, including hallucinations, seizures, arrhythmias, or cardiac ischaemia. At least 128 subjects (of whom 57 had consumed only energy drinks and no other substances) required hospitalisation. Nearly 60% of calls reporting recreational use of energy drinks came from Emergency Departments at hospitals.

Energy drinks have been shown to reduce cerebral blood flow velocity in young, healthy subjects (n = 45; 22 women and 23 men), and the effect is greater in women than in men (-12.3 ± 0.8 versus $-9.7 \pm 0.8\%$, $P<0.05$). The effect is likely to be due to caffeine, although the additional presence of sugar may contribute. Reduced cerebral blood flow can lead to syncope (fainting), which is reported twice as often in women as in men (Monnard et al 2016).

Nadeem et al (2020) conducted a systematic review and meta-analysis of clinical studies reporting adverse events after energy drink consumption, up to November 2019. A total of 32 studies and 96,549 individuals were included. Frequently reported adverse events in the subjects younger than 19 years of age were insomnia (35.4%), stress (35.4%), and depressive mood (23.1%). In adults, the most frequently reported adverse events were insomnia (24.7%), jitteriness/restlessness/shaking hands (29.8%), and gastrointestinal upset (21.6%). Mixtures of alcohol and energy drinks significantly reduced the likelihood of sedative effects of alcohol. Nadeem et al (2020) noted that many of the reported adverse effects of energy drinks were consistent with the known effects of caffeine intoxication. Rates of suicidal ideation and suicide attempts were significantly higher in subjects who consumed energy drinks more than once a day, followed by those who consumed 3 to 6 drinks a week and 1 to 2 drinks a week. Consumers who mixed alcohol with energy drinks drank significantly more alcohol than consumers who drank alcohol alone.

Energy drinks often contain other ingredients such as guarana, B vitamins, ginseng, taurine, gluconolactone, inositol, pantenol, bitter orange (which contains synephrine), green tea and “proprietary herbal blends” (Kaminer 2010; Temple 2019). Fletcher et al (2017) conducted a randomised, double-blind, controlled, crossover study of effects of energy drinks in 18 young,

healthy volunteers. The participants consumed either an energy drink or a caffeinated control drink, both of which contained 320 mg of caffeine, separated by a 6-day washout period. Electrocardiograph (ECG), peripheral blood pressure and central blood pressure measurements were obtained prior to consumption and at 1, 2, 4, 6, and 24 hours after drink consumption. Results were compared to time-matched results for the other intervention, and to baseline values. A group mean prolongation of QTc, relative to baseline, was observed two hours after consumption of the energy drink, but not after consumption of the caffeine control drink. Group mean systolic blood pressure was significantly higher at 6 hours following energy drink consumption than following caffeine consumption (4.72 ± 4.67 mm Hg versus 0.83 ± 6.09 mm Hg, respectively; p=0.01). Other group mean values were similar between the two interventions. These results suggest that other ingredients of energy drinks may have physiological effects of their own or may interact with caffeine.

In response to anecdotal reports of an association between energy drinks and myocardial infarction, Worthley et al (2010) conducted a study of the effects of energy drinks on platelet aggregation and endothelial function. Participants were 50 healthy volunteers (34 male, 16 female) in their early twenties (22 ± 2) who had abstained from caffeine and alcohol for seven days prior to the study. Platelet aggregation and endothelial function were tested before, and one hour after, the consumption of 250 mL of either a sugar-free, caffeinated energy drink (n = 30) or 250 mL carbonated water (n = 20). Energy drink consumption was associated with significant increases in arterial blood pressure and platelet aggregation, and decreased reactive hyperaemia index, a measure of endothelial function. Carbonated water did not have any effects. The authors note that there is no evidence in the literature that caffeine increases platelet aggregation, and there is some evidence that caffeine improves endothelial function. In addition, chronic caffeine consumption at normal dietary levels is not associated with adverse cardiovascular events. It was therefore concluded that the observed effects are unlikely to be due to caffeine.

In a study of the cardiovascular effects of energy drinks containing 80 mg caffeine in 44 healthy young adults, Hajsadeghi et al (2016) found a significant increase (p = 0.004) in the incidence of ST-T changes (ST depression or elevation, flattening of the T-wave, biphasic T-wave, and T-wave inversion). ST-T changes can be signs of subendocardial damage (Hajsadeghi et al 2016). It is not clear whether the observed effects were due to caffeine.

Summary

The use of sports supplements that are not accurately labelled regarding the caffeine content, in a way that can be clearly understood, creates a risk of caffeine overdose. In addition, there may be a general lack of awareness among users of these products of the danger of excessive caffeine intake. Energy drinks and other sports supplements figure significantly in calls to poisons centres. These calls include calls from hospitals. Many reports of adverse effects, including cardiovascular, neuropsychiatric, and gastrointestinal effects, are consistent with toxicosis due to caffeine. Some other adverse effects may be mediated by other components of energy drinks and other sports supplements. There appears to be a general lack of information about how the various ingredients of these products may interact with each other.

2.6.5. Men planning fatherhood

Chronic administration of high levels of caffeine to laboratory rats causes severe testicular atrophy, with aspermatogenesis or oligospermatogenesis, as well as degenerative changes in epididymides, prostate and seminal vesicles. However, there is a lack of evidence that moderate caffeine consumption (up to 400 – 450 mg/day) has any negative effects on fertility in men (Minelli and Bezzella 2011).

No evidence of a linear association between caffeine intake and testosterone level was found in 2581 men who participated in the US National Health and Nutrition Examination Survey (NHANES) 1999-2004 and 2011-2012 cycles. The NHANES studies are cross-sectional and have different participants in each cycle. It was not possible to exclude a nonlinear association (Lopez et al 2019).

Wesselink et al (2016) reported that caffeinated soda and energy drink intake by men was associated with greater time to pregnancy of their female partners. In contrast, Monteiro et al (2016) suggest that caffeine and other methylxanthines may have beneficial effects on male fertility, based on *in vitro* findings that include a positive effect of caffeine on nutritional support of spermatogenesis, by Sertoli cells, and beneficial effects on sperm calcium transport and in the regulation of cAMP levels, which may correlate with increased sperm motility. They further note that caffeine has been reported to be a useful additive in sperm storage and *in vitro* fertilization.

Minelli and Bezzella (2011) reviewed data from large retrospective studies in humans and concluded that caffeine does not have adverse effects on male fertility. The authors acknowledged that the observed results may have been due to chance or confounding by unmeasured variables. The results of the studies by Hatch et al (2012) and Wesselink et al (2016) are consistent with this conclusion, but have the strength that they were prospective, rather than retrospective, studies.

Summary

There is a lack of evidence that caffeine *per se* has any effect on male fertility.

2.6.6. Athletes

In a systematic review of caffeine-related deaths, Cappelletti et al (2018) identified athletes as one of the three groups most at risk from fatal caffeine toxicosis. In the five case reports they found, death was due to ventricular fibrillation.

Borron et al (2018) noted that sports supplements such as powders may be conflated with ‘energy drinks’ in databases recording case reports of toxicity. They queried Texas Poison Center Network data for single substance exposures to ‘energy drinks’ from 2010 to 2014, then analysed adverse events by product type. They found that concentrated sports supplements were associated with a greater number of adverse events than caffeinated beverages.

Most studies show minimal effect of physical exercise on the pharmacokinetics of caffeine (Arnaud 2011). Wu et al (2015) cited evidence that caffeine reduces muscle pain intensity during and after exercise. Caffeine is also reported to reduce the perception of effort and fatigue during physical exertion (Bramstedt 2007). While athletes would probably view these effects as positive, they introduce risks of excessive exertion and exacerbation of muscle damage.

As noted in section 2.6.4, sports supplements may also declare the caffeine content on the label while simultaneously recommending daily consumption of the supplement that results in high daily intake of caffeine (Carol 2013). In addition, sports supplements may contain more caffeine than the label states, users often consume caffeine from other sources at the same time, and significant minorities of users use more doses of sports supplement/day than the product label recommends (Jagim et al 2019).

In some individuals with a physiological predisposition, a combination of excessive ingestion

of caffeine and strenuous physical activity can induce coronary vasospasm, leading to potentially fatal myocardial ischaemia (Cappelletti et al 2018).

Cappelletti et al (2018) noted evidence that bodybuilders often have muscle dysmorphia, leading them to resort to unhealthy eating, heavy exercise, and even drug-taking, and they speculate that caffeine may contribute to muscle dysmorphia through inducing neurological changes in the neural reward circuit or affecting mechanisms of resilience to stress.

It is commonly claimed that caffeine is a potent diuretic and as such, increases the risk of dehydration, particularly when combined with physical exertion (Hackett 2010; Zhang et al 2015). Zhang et al (2015) conducted a meta-analysis to evaluate the diuretic effect of caffeine in adults, both at rest and in association with exercise. Sixteen studies met the inclusion criteria, providing data from 246 men and 133 women. The median caffeine dosage was 300 mg, with a range of 114 to 741 mg. The diuretic effect of caffeine was found to be small, although slightly greater in women than in men, and was abolished by exercise. No dose-response relationship was detected. Zhang et al (2015) suggest that exercise may exert an anti-diuretic effect via sympathoadrenal activation, cancelling out the small diuretic effect of caffeine.

A review of the effects of plant-based supplements on immune function of athletes by Senchina et al (2014) concluded that subjects who consume caffeine prior to exercise generally exhibit unchanged or increased circulating leukocytes and lymphocytes (or specific subpopulations) post-exercise, when compared to exercised but placebo-treated controls, apart from T-cells. Post-exercise natural killer (NK) cell activation, neutrophil activity, plasma interleukins IL-6 and IL-10, adrenalin, cortisol, and β-endorphin are normally increased in subjects treated with caffeine, relative to subjects treated with placebo. The average dose of caffeine in the studies was 5.3 mg/kg bw. There is a lack of evidence that any of these immunomodulatory effects in athletes are of any significance to health or safety of athletes.

The websites of high-altitude resorts often warn against the consumption of caffeine at high altitude. Hackett (2010) reviewed the literature concerning the use of caffeine at high altitudes. Data from male volunteers indicate that at 4300 m above sea level, there is a mean decrease in caffeine half-life of approximately 30%, with mean decrease in AUC of 32% and mean increase in clearance of 36%. These effects may be mediated by an increase in hepatic blood flow. Hackett (2010) noted that laypeople often overestimate the diuretic effects of caffeine and suppose it to be a major risk factor for acute mountain sickness (AMS), although there is no compelling evidence that dehydration affects the risk of AMS. In athletes who consume caffeine, studies conducted both at sea level and at high altitude fail to support the notion that caffeine contributes significantly to dehydration in either situation. Hackett (2010) suggests that because of its respiratory stimulant property, caffeine may improve acclimatization to high altitudes, and should be investigated for preventative and/or therapeutic potential against AMS. Hackett further notes that theoretically, caffeine, which reduces resting cerebral blood flow at sea level, and decreases the ratio of cerebral blood flow to cerebral metabolic rate for oxygen, could be beneficial against altitude-related hypoxia, since vasodilation and overperfusion would be minimized without sacrificing oxygenation and metabolism. Similarly, the vasoconstrictive properties of caffeine could reduce high-altitude headache. Caffeine consumed in the evening is likely to exacerbate the sleep disturbance often reported by newcomers to high altitude, but caffeine is likely to be therapeutic against high altitude lassitude, another common complaint. Hackett (2010) concluded that the available evidence is insufficient to draw firm conclusions on the effects of caffeine on exercise performance, pulmonary function, or coronary blood flow at high altitude. Finally, Hackett noted the great similarity in symptoms and clinical duration between caffeine withdrawal and AMS and speculated that many cases of caffeine withdrawal at high altitude may be misdiagnosed as AMS.

Summary

Caffeine has positive effects on physical exertion, and the purported risks of dehydration or acute mountain sickness from the diuretic effect of caffeine appear to be unfounded. In fact, caffeine may be more beneficial than harmful at high altitude. However, athletes are at elevated risk of caffeine toxicosis. Reasons for this include misleading labelling of sports supplements, failure to follow the recommended daily dose, deliberate or inadvertent 'stacking' by consuming caffeine from multiple sources, and a general lack of appreciation of the risks of high caffeine consumption. Caffeine may exacerbate body dysmorphia in bodybuilders.

2.6.7. Aged people

The effects of caffeine in neurodegenerative conditions, which most often affect the aged, were reviewed by Kolahdouzan and Hamadeh (2017). A number of large studies have shown that caffeine has a significant negative effect on age-related cognitive decline. Prospective studies suggest that caffeine consumption reduces the risk of Alzheimer's disease, and caffeine shows therapeutic effects in mouse models of Alzheimer's disease, although at serum concentrations which are close to a toxic level in humans. Caffeine is also associated with reduction of risk of developing Parkinson's disease, with a stronger effect in men than in women. The sex difference may reflect the fact that both caffeine and oestrogen are metabolised by CYP1A2. Large prospective studies have not shown any association between caffeine and risk of developing Amyotrophic Lateral Sclerosis (ALS). Blockade of the A2 adenosine receptor is beneficial in mouse models of ALS. Riluzole, which is used to treat ALS, is metabolised by CYP1A2 so it is possible that caffeine may delay clearance of riluzole. One study showed that in 80 patients with Huntington's disease (HD), which is an inherited neurodegenerative disorder which typically manifests in late middle age, caffeine consumption at > 190 mg/d in the previous 10 years was associated with a 1.6 year earlier age of onset of HD. In rat models of HD, 40 mg/kg/day caffeine had beneficial effects on motor function, but high doses exacerbated the disease, possibly due to blockade of the ryanodine receptors, which occurs at around 1520 mg/day in humans. There is some evidence that caffeine may delay the progression of another inherited neurodegenerative disease, Machado-Joseph disease (Kolahdouzan and Hamadeh 2017).

In a cross-sectional study using data from NHANES 2013-2014, Iranpour et al (2020) evaluated the association between caffeine consumption and cognitive function in 1440 adults who were ≥ 60 years old. They concluded that after correction for several covariates, there is a weak positive association between caffeine intake and cognitive function, that is stronger in men than in women.

With age, people become more sensitive to the effects of caffeine on sleep (Robillard et al 2015; Clark and Landolt 2017), which may be perceived as positive or adverse depending on the desired outcome. Often consumed to improve alertness and ward off sleepiness, caffeine typically prolongs sleep latency, reduces total sleep time and sleep efficiency, and leads to poorer perceived sleep quality. Caffeine typically reduces slow-wave sleep and electroencephalographic (EEG) slow-wave activity, and increases stage-1 sleep, wakefulness, and arousal (Clark and Landolt 2017).

The effects of caffeine on bone mineral density are of concern regarding osteoporosis, which is primarily a disease of aged people. Caffeine increases urinary excretion of calcium and may also inhibit calcium absorption (Nawrot et al 2003), and *in vitro* studies have found that caffeine inhibits the proliferation and activity of osteoblasts (Zhou et al 2009). Caffeine has also been shown to inhibit the function of vitamin D receptors of osteoblasts (Belayneh and Molla 2020). However, results of epidemiological studies investigating associations between

caffeine intake and osteoporosis have been inconsistent (Chau et al 2020) with some large studies, such as that of Choi et al (2016) showing a beneficial effect of caffeine on the bone density of postmenopausal women. Similarly, Chau et al (2020) found that habitual coffee intake was positively and significantly associated with bone mineral density in the Hong Kong Osteoporosis Study. Furthermore, caffeine metabolites 5-acetylamino-6-formylamino-3-methyluracil, 3-hydroxyhippurate, and trigonelline were positively and significantly associated with bone mineral density.

Wetmore et al (2008) conducted a prospective study in 625 women aged between 14 and 40, and found that there was no association between heavy habitual consumption of caffeinated beverages and bone mineral density. There was a modest inverse association between caffeine consumption and bone mineral content, but not bone mineral density, in women using depot medroxyprogesterone acetate.

Summary

Caffeine has neurological benefits in the aged, and is associated with reductions in the rate of age-related cognitive decline as well as the risks of developing Alzheimer's disease and Parkinson's disease. However, people at risk of developing Huntington's disease may prefer to limit their caffeine intake. The effects of caffeine on sleep become more pronounced with age. Caffeine consumption does not appear to be a significant risk factor for osteoporosis.

2.6.8. Consumers using substances that interact with caffeine

2.6.8.1. Substances for which antagonism may occur

Oral caffeine reduces the absorption of dietary or supplemental iron by up to 90% and should not be consumed within an hour of consuming iron. Caffeine also significantly inhibits the absorption of a number of pharmaceuticals including escitalopram, thyroxine, midazolam, alendronate, butyrophenone, and several phenothiazines. Caffeine inhibits the penetration of the blood-brain barrier by memantine and donepezil, used to treat Alzheimer's disease. Caffeine can lower the plasma concentration and AUC of paracetamol by upregulation of cytochrome P-448 (Belayneh and Molla 2020), but conversely, caffeine potentiates the analgesic effect of several OTC pain relievers including paracetamol (see subsection 2.6.8.2). Caffeine greatly increases the excretion rate of anabolic steroids oxandrolone and epioxandrolone (Belayneh and Molla 2020). Caffeine significantly decreases the AUC of fluvoxamine, an antidepressant (Fukasawa et al 2006), partially antagonises the pharmacodynamic effects of zolpidem, a widely prescribed hypnotic (Cysneiros et al 2007), and promotes the excretion of lithium, used to treat bipolar disorder and major depression (Carillo and Benitez 2000). There is some evidence that caffeine counteracts the anti-inflammatory action of methotrexate, used to treat rheumatoid arthritis (Haskó and Cronstein 2011).

In laboratory rodents, caffeine lowers the seizure threshold, and reduces the efficacy of several antiepileptic drugs including carbamazepine, phenobarbital, phenytoin, valproate, and topiramate, although it does not impair the efficacy of anti-epileptic drugs lamotrigine, tiagabine, and oxcarbazepine in rodents. There is clinical evidence of increased seizure frequency in epileptic patients who consume high levels of caffeine (Chrościńska-Krawczyk et al 2011).

The metabolism and excretion of caffeine is increased by cigarette smoking (Arnaud 2011), consumption of cruciferous vegetables (*Brassica* spp) large doses of ascorbic acid (Vitamin C) (Nehlig 2018), and use of omeprazole, a pharmaceutical used to treat peptic ulcer and gastro-oesophageal reflux (Arnaud 2011).

Regular consumption of three or more cups of coffee per day reduces the adverse side effects of combined use of peginterferon and ribavirin in patients with Hepatitis C (Saab et al 2014).

2.6.8.2. Substances with additive, potentiating, or synergistic effects

Methylxanthine alkaloids have been found in around 100 species within 13 orders in the plant kingdom. The naturally occurring methylxanthine alkaloids are theobromine, theophylline, and paraxanthine (Monteiro et al 2016). Some paraxanthine is present in coffee beans (Daly 2007) but its potency appears to be very low (Stavric 1988). Theophylline is a significant methylxanthine in tea and shares biological activities with caffeine. Theobromine is present in cacao beans and their products, such as cocoa and chocolate (Daly 2007).

Of the natural methylxanthine alkaloids, caffeine has the most potent effects on the central nervous system and the respiratory system, whereas theophylline is the most potent regarding cardiac stimulation, coronary dilatation, and smooth muscle relaxation. Theobromine has cardiostimulatory properties and has been used to dilate coronary arteries, although it is less potent than theophylline (Monteiro et al 2016).

In addition to the naturally occurring methylxanthine alkaloids, several xanthines and related compounds have been synthesized as research tools and potential therapeutic agents (Daly 2007). Examples include pentoxifylline and doxofylline (Singh et al 2018). Online information[7] recommends limiting caffeine intake when taking pentoxifylline, and the Medsafe data sheet notes that it may interact with other xanthines, causing excessive CNS stimulation[8]. The severity of side effects to doxofylline may also be exacerbated by caffeine[9].

Aminophylline, a bronchodilator used for the treatment of asthma, chronic obstructive pulmonary disease, and some cardiovascular diseases, is a combination of theophylline and ethylenediamine in 2:1 ratio (Singh et al 2018) and users are recommended to limit caffeine intake[10]. Furafylline is a methylxanthine derivative that has been introduced as an alternative to theophylline for treatment of asthma because it appears to be devoid of effects on the central nervous system. However, it is a potent and selective inhibitor of CYP1A2, and has caused signs of mild caffeine toxicity in volunteers who had moderate dietary caffeine intake (Carillo and Benitez 2000).

Use of oral contraceptives significantly increases the half-life of caffeine. Arnaud (2011) cites results from different studies of this effect. In one study, women taking oral contraceptives showed an increase in caffeine half-life from 6.2 ± 1.6 h to 10.7 ± 3.0 h ($p < 0.001$). In another study, the mean caffeine half-life in women taking oral contraceptives was 7.88 h whereas that of women not taking oral contraceptives was 5.37 h.

Caffeine has been reported to increase the pain-relieving properties of OTC analgesics such as paracetamol, aspirin, and ibuprofen (Monteiro et al 2016). Lipton et al (2017) concluded as the result of a review of the literature that 130 mg caffeine enhances the efficacy of OTC analgesics, including aspirin, paracetamol and ibuprofen, tension-type headaches. Caffeine in doses of ≥ 100 mg enhances benefits of analgesics in migraine.

A number of other pharmaceuticals interact with caffeine. Pharmaceuticals that inhibit

[7] https://go.drugbank.com/drugs/DB00806
[8] https://www.medsafe.govt.nz/profs/Datasheet/t/Trentaltabinj.pdf
[9] https://go.drugbank.com/drugs/DB09273
[10] https://go.drugbank.com/drugs/DB01223

clearance of caffeine include antimycotic drugs including fluconazole, ketoconazole and terfinafine; mexiletine, used to treat some ventricular arrhythmias; fluvoxamine, a selective serotonin reuptake inhibitor; idrocilamide, a myorelaxant; psoralens methoxsalen and 5-methxypsoralen, used for treating psoriasis and several other dermal conditions; and quinolone antibacterials (e.g., enoxacin, ciprofloxacin, norfloxacin, pipemidic acid). It has been suggested that some adverse effects ascribed to either mexiletine or fluvoxamine or psoralens are effects of elevated plasma caffeine, and mild caffeine toxicity has been reported in association with idrocilamide. Caffeine competitively inhibits the metabolism of clozapine, an antipsychotic and this competition has led to adverse effects in habitual users of high levels of caffeine. Calcium channel blockers verapamil and diltiazem inhibit metabolism of theophylline, so it is likely they would also inhibit caffeine metabolism (Carillo and Benitez 2000). *In vitro*, caffeine antagonizes the antibiotic efficacy of ciprofloxacin against Gram positive organisms (Woziwozska et al 2021). Caffeine is a weak hERG channel blocker, a property it shares with several pharmaceuticals including tricyclic antidepressants and some antibiotics, such as erythromycin. Zheng et al (2017) suggest that consumption of caffeine in association with use of other hERG channel blockers may be the mechanism for some caffeine-related fatalities.

As previously mentioned in subsection 2.6.3.2, there is some evidence that the combination of caffeine and phenobarbital during pregnancy is teratogenic, although neither xenobiotic is a significant human teratogen alone (Samŕen et al. 1999).

Ephedrine is often included in sports supplements due to properties that include enhancement of aerobic capacity, reduction of fatigue, and improvement of alertness and reaction time, although it is prohibited by the World Anti-Doping Agency (WADA) (Sellami et al 2018). It is commonly mixed with caffeine because the two chemicals are thought to work synergistically, with caffeine increasing the effect of ephedrine by interfering with a negative feedback system involving cyclic AMP (Rhidian 2011). The US Food and Drug Administration banned the sale of ephedrine in 2004 because of a considerable number of reports of adverse cardiovascular complications. In a large case-crossover analysis of data from Statistics Denmark, Hallas et al (2008) found that there was no increased risk of adverse cardiovascular outcomes from the use of prescribed combinations of caffeine and ephedrine. However self-administration of sports supplements containing ephedrine and caffeine may lead to severe adverse effects. Rhidian (2011) described the case of a 36-year-old man who collapsed while running a half-marathon after taking a sports supplement before the race that contained ephedrine (30 mg), caffeine (120 mg) aspirin (30 mg), and narnegin (80 mg). The patient suffered hypoxia, tachycardia, and seizures, and developed rhabdomyolysis which led to acute renal failure. Rhidian (2011) noted that there are several case reports in the literature of significant adverse effects related to ephedrine containing supplements, including arrhythmias, myocardial infarction, stroke, and seizures. Although caffeine promotes vasodilation, ephedrine stimulates vasoconstriction and vasospasm, which can lead to thrombotic events such as myocardial infarction and ischaemic stroke.

Carillo and Benitez (2000), writing in Spain, expressed particular concern about the OTC availability of phenylpropanolamine. This pharmaceutical is a potent inhibitor of caffeine metabolism, increasing the plasma concentration up to 280%, and adverse effects have been reported following concurrent use of phenylpropanolamine and caffeine. However, this interaction is not highly relevant to Australia or New Zealand, because phenylpropanolamine is not available in Australia, and not available as an OTC medication in New Zealand.

Caffeine interacts with several drugs of abuse. It potentiates the psychostimulant effects of amphetamines and exacerbates the toxic effects of both MDMA (Ecstasy) and methamphetamine. Caffeine also potentiates the psychostimulant effects of cocaine. Results of animal studies suggest that caffeine may potentiate effects of phencyclidine and ketamine. Caffeine appears to amplify the effects of methylphenidate (Morelli and Simola 2011) (Ritalin

®) which is available by prescription to treat ADHD in Australia and New Zealand but may be obtained illicitly to as a study aid by students.

Some traditional herbal remedies affect caffeine metabolism by inhibiting CYP1A2 (Nehlig 2018), but it is not clear if these effects are clinically significant. Grapefruit juice consumption decreases caffeine clearance by 23% and prolongs caffeine half-life by 31%. Turmeric, curcumin, and apiaceous vegetables (e.g., carrots, celery, and parsley) decrease the activity of CYP1A2 (Nehlig 2018), but it is not clear if this has any significant effect on caffeine kinetics.

Cigarette smoking almost doubles the rate of caffeine metabolism (Nehlig 2018), but caffeine potentiates the stimulant and reinforcing properties of nicotine. A positive association between coffee consumption and tobacco smoking has been found in epidemiological studies. Caffeine counteracts some symptoms of nicotine withdrawal (Morelli and Simola 2011) while the rate of metabolism of caffeine rapidly decreases after smoking cessation (Nehlig 2018). It has been suggested that the association between coffee consumption and tobacco smoking might be due to personality characteristics of the user, rather than pharmacological interactions (Morelli and Simola 2011).

Consuming caffeinated energy drinks with alcohol is common, particularly among adolescents (de Sanctis et al 2017). Caffeine has both antagonizing and potentiating effects with alcohol. Caffeine is a stimulant while alcohol is sedating, and caffeine reduces the subjective feeling of drunkenness (Arria et al 2011). Caffeine antagonizes the adverse effects of alcohol on balance (Marczinski et al 2018). However, rat studies have shown that adenosine receptor antagonists, including caffeine, can increase alcohol self-administration, and caffeinated energy drinks typically contain a lot of sugar, which could make alcoholic drinks more palatable. By making the drinker feel less inebriated, caffeine could cause the drinker to consume more alcohol than they otherwise would have, and by counteracting sleepiness, caffeine could prolong drinking sessions (Arria et al 2011). Intake of substantial amounts of alcohol prolongs the half-life of caffeine and decreases its clearance (de Sanctis et al 2017; Musgrave et al 2017). Combining energy drinks and alcohol is associated with increased risk-taking in adolescents and combining energy drinks with alcohol may also favour the development of alcohol dependence (Higgins et al 2010).

Ehlers et al (2019) cited a case of a 17-year-old boy who suffered acute renal failure after consuming three litres of energy drinks in combination with one litre of vodka, and noted a study in rats in which the combination of energy drink (10 mL/kg bw) and alcohol (2 g/kg bw) (20% v/w) induced a transitory nephrotoxicity which did not occur in rats administered either energy drink or alcohol alone. Given the long history of use of both alcohol and caffeine, it seems unlikely that the nephrotoxicity observed in this case was due to caffeine.

In chronic alcoholism, the metabolism of caffeine is decreased, leading to a longer half-life. (Mangi et al 2017).

Summary

Xenobiotics that interact with caffeine may do so by antagonism, additive effects, potentiation, or synergy. It may be expected that interactions with prescription pharmaceuticals will be managed by the medical profession or by information provided by the pharmacy that fills the prescription. Similarly, the potentiating effect of caffeine on illicit drugs is likely to be familiar to emergency physicians. For many other identified interactions, there is a lack of evidence of any adverse effects on a population basis. Some interactions are beneficial, such as the potentiation of OTC analgesics, and the moderation of adverse effects of the combination of peginterferon and ribavirin in patients with Hepatitis C. Changes in the clearance of caffeine by such factors as going on the contraceptive pill, or quitting

smoking, are likely to be self-managed in most cases.

The interaction between caffeine and nicotine is complicated, with nicotine increasing the rate of clearance of caffeine, and caffeine potentiating the effects of nicotine but also counteracting some symptoms of nicotine withdrawal. The interaction between caffeine and alcohol is also complicated, with caffeine having both antagonizing and potentiating effects on the effects of alcohol, while heavy alcohol consumption decreases the clearance of caffeine. There is evidence from animal studies that caffeine can increase alcohol consumption, and it has been claimed that combining energy drinks with alcohol increases the risk of alcohol dependence.

2.6.9. Diseases in which caffeine may be contraindicated

2.6.9.1. Cardiovascular diseases

A meta-analysis of the effects of caffeinated beverages on blood pressure, including 11 articles and 470 subjects, found that short-term (< 4 weeks) consumption of caffeinated beverages led to an overall slight increase in systolic and diastolic blood pressure, of 3.04 and 2.45 mm Hg respectively. However, the effect on systolic blood pressure was more pronounced in adolescents, averaging 5.31 mm Hg. When subjects were stratified by daily dose, increased systolic blood pressure was observed in both the low (< 245 mg/day caffeine) and high (> 245 mg/day caffeine) strata, but increased diastolic blood pressure was only observed in the high dose stratum. Some attenuation with continued consumption was evident, in that the mean increase after less than one week was 5.23/2.14, whereas after more than a week the mean increase was 2.62/2.66 (Xu et al 2021), but the effect on blood pressure remains partial with chronic use of caffeine (Beaudoin and Graham 2011). Caffeine also has a direct chronotropic effect on the heart due to blockade of adenosine receptors (Zheng et al 2017), and acute intake of high levels of caffeine can trigger atrial and ventricular arrhythmias because of increased circulating catecholamine levels and promotion of cytoplasmic calcium overload (Enriquez and Frankel 2017). These well-characterised effects notwithstanding, there is a lack of evidence from large epidemiological studies that chronic moderate coffee consumption is a risk factor for cardiovascular diseases. On the contrary, regular coffee consumption is associated with decreased prevalence of subclinical atherosclerosis, and decreased risk of atrial fibrillation, and has no effect on the occurrence of ventricular premature beats. The available epidemiological evidence indicates that habitual coffee consumption is neutral to beneficial regarding the risks of coronary heart disease, congestive heart failure, arrhythmias, and stroke (Zulli et al 2016). Coffee does not increase the risk of cardiovascular disease in people who have already had a myocardial infarction (Beaudoin and Graham 2011), despite the finding of Namdar et al (2009) that 200 mg caffeine reduces myocardial blood flow during exercise to a significantly greater degree in patients with coronary arterial disease than in age-matched controls (18 to 25% versus 14%). A meta-analysis of prospective cohort studies showed that long term coffee consumption is associated with decreased incidence of new-onset hypertension (Grosso et al 2017). Beneficial effects of coffee may not be due to caffeine, and therefore these effects may not be applicable to products in which pure caffeine is an ingredient, such as energy drinks or sports supplements. Even if the effects are due to caffeine, caffeine consumption may nevertheless pose risks to people with pre-existing cardiovascular disorders.

Lemery et al (2015) conducted a randomised, placebo-controlled study of effects of caffeine in 80 patients with supraventricular tachycardia (SVT). A moderate dose (5 mg/kg bw) of caffeine had a significant effect on systolic and diastolic blood pressure, as expected, but had no significant effects on heart rate, cardiac refractoriness, cardiac conduction, tachycardia inducibility, or rates of electrically induced tachycardia. The authors concluded that moderate caffeine intake does not need to be restricted in patients with SVT. This is

consistent with the conclusion reached based on literature review by Pelchovitz and Goldberger (2011), that there is no reason to advise patients with known arrhythmias to restrict their caffeine intake below moderate levels.

Consumption of energy drinks containing a moderate amount (e.g., 160 mg) of caffeine may cause QT prolongation in individuals with familial long QT syndrome, a congenital disorder found in approximately 1 in 2500 people which can present as syncope, seizures, or sudden death due to cardiac arrest (Dufendach et al 2012; Gray et al 2017).

It is considered that blood caffeine concentration of < 80 mg/L is not associated with fatality in people with healthy hearts, but a blood caffeine concentration of 49 mg/L was fatal to a person with dilated cardiomyopathy (Musgrave et al 2016). Enriquez and Frankel (2017) described a case of a 23 year old woman with a history of peripartum cardiomyopathy who had an episode of syncope after consuming a single can (volume not specified) of Red Bull, and they cited other case reports of serious adverse effects of moderate energy drink consumption in people with long QT syndrome, undiagnosed Brugada syndrome (an inherited disorder that can cause ventricular tachyarrhythmia), repaired tetralogy of Fallot (congenital combination of four cardiac defects), left ventricular hypertrophy, and mitral valve prolapse. Mangi et al (2017) cited the cases of three people, one of whom had a history of aortic aneurysm, who developed aortic dissection following consumption of energy drinks.

As noted in subsection 2.6.4, the study of Fletcher et al (2017) suggests that other ingredients of energy drinks may potentiate the effects of caffeine on QT interval and blood pressure.

Steinke et al (2009) stated that patients with cardiovascular disease often have impairment of baroreflex buffering, manifested as a greater response to vasoactive medications when compared to healthy adults. They suggested that such patients might experience greater increases in heart rate and blood pressure after energy drink consumption than healthy adults.

Summary

Caffeine slightly increases blood pressure, an effect which is attenuated with habitual consumption, and is cardiotoxic in acute overdose. However, the epidemiological evidence indicates that habitual coffee consumption is neutral to beneficial regarding the risks of hypertension, coronary heart disease, congestive heart failure, arrhythmias, and stroke, even in people who have already had a myocardial infarction. The beneficial effects of coffee may not be due to caffeine, and therefore may not be applicable to products in which pure caffeine is an ingredient, such as energy drinks or other sports supplements.

Caffeine may be contraindicated in specific cardiovascular disorders such as familial long QT syndrome, Brugada syndrome, mitral valve prolapse, left ventricular hypertrophy, or a history of cardiomyopathy, Tetralogy of Fallot, or aortic aneurysm. It may be expected that the risk to these specific subpopulations would be managed by the medical profession.

2.6.9.2. Epilepsy

Clinical evidence from patients using theophylline as a bronchodilator has shown that it can cause seizures, even in people with no history of epilepsy. It is thought that caffeinated beverages can lower seizure thresholds in patients with epilepsy, although Boison (2011) notes that there is a lack of well-designed, randomized, and placebo-controlled clinical trials to confirm or disprove this belief. In mice, caffeine was pro-convulsant when administered acutely to naïve animals, but when given repeatedly (two weeks) elevated the seizure thresholds for N-methyl-D-aspartate (NMDA)-, bicuculline-, and pentylenetetrazol- induced

seizures. Similarly, dosing rats with 40 mg caffeine/kg bw for seven days increased the thresholds for theophylline-induced seizures (Boison 2011).

As previously mentioned in subsection 2.6.3.2, authors of a large (1411 infants) retrospective study concluded that concurrent use during pregnancy of phenobarbital as an antiepileptic and caffeine is associated with increased risk of major congenital abnormalities (Samŕen et a. 1999).

Summary

It is thought that caffeine may lower seizure thresholds in epilepsy, although studies in laboratory rodents suggest that this effect is reversed with repeated consumption. There is evidence that caffeine is contraindicated in pregnant women who are being treated with phenobarbital for epilepsy.

2.6.9.3. Diabetes mellitus

Consumption of more than four cups of coffee per day may increase the risk of developing Type 1 diabetes mellitus (Sharif et al 2017).

Dewar and Heuberger (2017) conducted a systematic review of the effects of caffeine on glycaemic control in patients who have diabetes mellitus Type 1 or Type 2. They concluded that there is evidence that caffeine affects blood glucose metabolism, although the results are mixed. In both Type 1 and Type 2 diabetics, caffeine appears to potentiate the increase in blood glucose due to carbohydrate consumption, but may not increase blood glucose when consumed alone. Exercise may induce hypoglycaemia in both types of diabetes, and it has been suggested that consuming caffeine and a carbohydrate could be used to prevent this response. However, results of studies have been mixed. A weakness of the available studies is that the subjects typically had poor glycaemic control. Dewar and Heuberger (2017) concluded that caffeine, when taken with carbohydrates, may prolong elevation of blood glucose in patients with diabetes, but that there is a need for more studies in diabetic patients with good glycaemic control.

In a cross-over study of the acute effects of espresso coffee in people with Type 2 diabetes who were habitual coffee consumers, Krebs et al (2012) found only a marginal effect on blood glucose, when compared to decaffeinated coffee and to placebo. They concluded that it was premature to make recommendations to people with Type 2 diabetes concerning caffeine consumption.

Summary

Results of studies of the effect of caffeine on glycaemic control in diabetes mellitus are mixed, and there is a need for more studies on this subject.

2.6.9.4. Kidney and urinary tract disorders

As noted in subsection 2.6.6, a meta-analysis by Zhang et al (2015) found that the diuretic effect of caffeine is small and is abolished by exercise. The dose of caffeine required to induce significant, acute diuresis is around 300 mg, equivalent to four cups of coffee. The diuretic effect of caffeine is decreased by habituation and by increasing age (Osswald and Schnermann 2011).

Caffeine promotes renal excretion of sodium, by inhibiting resorption in the proximal

convoluted tubules (Osswald and Schnermann 2011; Reuter et al 2021) and could exacerbate hyponatraemia. There is a lack of evidence from the scientific literature that this is a significant problem.

In animal models, caffeine accelerates the development of nephropathies, promoting interstitial fibrosis and glomerulosclerosis (Osswald and Schnermann 2011). However, a systematic review and meta-analysis by Srithongkul and Ungprasert (2020) found that caffeine consumption is significantly associated with a decreased risk of chronic kidney disease (pooled risk ratio of 0.87 (95% CI, 0.81-0.95; I2 of 57%)).

Peerapen and Thongboonkerd (2018) reviewed the role of caffeine in nephrolithiasis (kidney stone disease). Kidney stones are often composed of calcium oxalate. Caffeine promotes calcium excretion and is mildly diuretic, and both coffee and tea contain oxalates, so it is reasonable to speculate that caffeine consumption might lead to nephrolithiasis. However, data from three large cohort studies show a significant inverse relationship (10 to 26% decrease in risk) between consumption of caffeinated coffee intake and nephrolithiasis, with a lesser decrease for decaffeinated coffee (Ferraro et al 2014). The increase in excretion of calcium and oxalate is offset by increased urinary volume, which reduces the risk of calcium and oxalate precipitating as calcium oxalate crystals. In addition, urinary excretion of citrate is increased by caffeinated beverages, and citrate is known to be a potent inhibitor of the formation of calcium oxalate crystals. In addition, there is *in vitro* evidence that caffeine reduces the adhesion of calcium oxalate crystals to renal tubular epithelial cells, by inducing translocation of annexin A1, a protein that binds to calcium oxalate crystals, from apical membranes to cytoplasm (Peerapen and Thongboonkerd 2018). The beneficial effect of caffeine on risk of nephrolithiasis may not be applicable for energy drinks, because they are often sugar-sweetened sodas. Ferraro et al (2013) found, in analysis of three large ongoing prospective studies, that there was a 23% higher risk of developing kidney stones in the highest stratum of consumption of sugar-sweetened cola-flavoured sodas compared with the lowest stratum (P for trend=0.02) The corresponding increased risk for sugar-sweetened noncola sodas was 33% (P for trend=0.003). Artificially sweetened sodas were marginally associated with kidney stones, with an inverse relation for colas and a direct relation for noncolas.

It has been suggested that coffee consumption increases the risk of bladder cancer. Results of epidemiological studies have been inconsistent. Villanueva et al (2009) conducted a case-control study in which they also collected data on cigarette smoking and on genotype regarding CYP1A2, CYP1A1, CYP2E1 and N-acetyltransferase 2 (NAT2). A total of 1136 people with bladder cancer were compared to 1138 controls, matched by sex, age group (5-year strata) and residence area. Overall, bladder cancer risk among coffee drinkers was slightly increased, but there was no significant dose–response relationship (p trend = 0.082). Drinkers of ≥ four cups of coffee per day or more had an OR of 1.27 (95% CI 0.88–1.81). The authors noted that coffee consumption was highly correlated with smoking habits, and the increased risk of bladder cancer among coffee drinkers could partly be explained by residual confounding among smokers. Among people who had never smoked, an increased risk of bladder cancer was only observed in the highest category of coffee drinking (≥ 4 cups/day).

Summary

The diuretic effect of caffeine is small, subject to habituation, and abolished by age. Caffeine accelerates the development of nephropathies in animal models, but habitual coffee consumption is inversely related to risk of chronic kidney disease in humans, suggesting that either caffeine does not exacerbate nephropathies in humans, or other ingredients in coffee have a stronger, protective effect on the kidneys. There is also a significant inverse relationship between consumption of caffeinated coffee intake and nephrolithiasis. However, this protective effect may not apply to energy drinks, because a significantly increased risk of

nephrolithiasis has been associated with the consumption of sugar-sweetened sodas. Available evidence suggests that moderate consumption of coffee does not increase risk of bladder cancer.

2.6.9.5. Migraine

Both caffeine and caffeine withdrawal have been identified as triggers for migraine headache. Nowaczewska et al (2020) note that it is possible that premonitory symptoms of impending migraine, such as diminished energy level and sleepiness, cause migraineurs to drink coffee or other caffeinated beverages, leading to the mistaken conclusion that they triggered a migraine. In a meta-analysis, they found that caffeine was identified as a trigger by only a minority (2.4 to 30%) of migraineurs, and that one study found that caffeine withdrawal was a more frequent trigger than caffeine consumption. Only a minority of migraineurs report a decrease in frequency of migraines in response to abstention, and increased frequency of migraine is only found in consumers of more than 200 mg/day. However, there is evidence that triptans are significantly more effective in migraineurs who do not consume caffeine than in those that do (72.2% reported effectiveness versus 40.3% reported effectiveness). A combination of caffeine, aspirin and paracetamol is more effective for treating migraine than ibuprofen, but a study comparing combination of paracetamol and caffeine with paracetamol alone found no significant difference. Caffeine potentiates the therapeutic effect of diclofenac in migraine. Nowaczewska et al (2020) recommend that migraineurs should not consume more than 200 mg caffeine/day and should endeavour to be consistent in the amount of caffeine they consume and the times of day that they consume it.

Abstinence from caffeine consumption from dawn to dusk during Ramadan was associated with an increase in frequency of migraines, attributed to caffeine withdrawal, in 32 migraineurs who kept migraine diaries. In a control month, the mean number of migraine days was 3.7 ± 2.1 (range 1-10), but during the month of Ramadan, there were 9.4 ± 4.3 migraine days (range 3–20) ($p<0.001$), and migraine attacks increased in duration. Two patients were unable to complete Ramadan fasting because of migraines. Based on prevalence of migraine of 12% in adults, it is calculated that 90 million Muslims are migraineurs. The authors of the study recommended that physicians should discuss the issue of Ramadan with migraineurs who are observant Muslims and regular consumers of caffeine, and prescribe analgesics with a long half-life that will last from dawn to dusk (Abu-Salameh et al 2010).

Summary

Both caffeine and caffeine withdrawal have been identified as triggers for migraine headache. Caffeine reduces the effectiveness of triptans, but potentiates the effectiveness for diclofenac for treatment of migraine. A daily caffeine intake of ≤ 200 mg is recommended for migraineurs. Migraineurs who fast for religious reasons may require long-acting analgesics to manage migraines associated with abstention from caffeine.

2.6.9.6. Ocular disorders

Heavy caffeine consumption was incriminated in four of five cases of acute onset of central ring scotoma. The four patients who were heavy caffeine consumers included a man who consumed 10 caffeinated beverages per day, a woman who consumed a litre of caffeinated soft drinks per day, a woman who drank six to eight cups of coffee per day, and a man who consumed 20 cups of coffee per day. The final case was a woman who had given birth the day before and experienced a postpartum hypotensive episode during epidural anaesthesia. Kerrison et al (2000) attributed all the cases to transient retinal ischaemia. They noted that adenosine is a potent retinal vasodilator, and that heavy caffeine use could therefore

precipitate retinal vasoconstriction. Gupta et al (2019) reported a case of acute macular neuroretinopathy which they also attributed to caffeine-induced ischaemia. The patient was a healthy young woman who presented with a three-day history of unilateral scotoma. She had consumed multiple caffeinated energy drinks while studying for examinations. The authors cited two other cases in the literature of acute macular neuroretinopathy associated with caffeine consumption. Consistent with the cases reported by Kerrison et al (2000) and Gupta et al (2019), Zhang et al (2020b) demonstrated, in 13 healthy individuals, that caffeine impairs neurovascular coupling in the three retinal vascular plexuses during dark and light adaptation, and they suggest that these delayed vascular responses may present potential risk of capillary ischemia. Similarly, Karti et al (2019), using quantitative optical coherence tomography angiography analysis, found that caffeine caused a significant decrease in macular flow area and vessel density in eyes of healthy participants, of whom 26 consumed caffeine, and 26 consumed a placebo.

In a placebo-controlled double-blind and balanced crossover study, 40 healthy participants were assigned to low-(n = 21) and high (n = 19)-caffeine groups, according to their daily caffeine consumption. All participants consumed caffeine (4 mg/kg) or placebo in each arm of the crossover study. Intra-ocular pressure (IOP) was measured 30, 60, and 90 minutes later. Acute caffeine consumption led to an increase in IOP, but the increase was significantly lower in the high-caffeine group than in the low caffeine group, indicating partial habituation to this effect of caffeine. The authors noted that it is advisable for patients, especially those with ocular hypertension or glaucoma, to avoid caffeine consumption before IOP evaluation, to obtain an accurate IOP measurement (Vera et al 2019). In a second placebo-controlled, double-blind, balanced crossover study of 18 physically active young adults, the same research team found that caffeine (4 mg/kg) consumed 30 minutes beforehand counteracted the IOP-lowering effect of low-intensity exercise (30 minutes of cycling at 10% of maximal power production). The authors of the study concluded that caffeine consumption before exercise should be discouraged in individuals who would benefit from decreased IOP, such as those with glaucoma or at risk of glaucoma (Vera et al 2020).

Kim et al (2021) did not find evidence of a causal effect of caffeine on IOP on analysis of data from 121,374 individuals. In fact, higher caffeine consumption was weakly associated with lower IOP. However, this finding was modified when they included a polygenic risk score (PRS) that combined the effects of 111 genetic variants associated with IOP. Among those in the highest PRS quartile, consuming > 480 mg/day versus < 80 mg/day was associated with a 0.35-mmHg higher IOP ($P_{interaction}$ = 0.01). Using logistic regression, the relationship between caffeine and glaucoma was null, but this finding was also modified when the PRS score was considered. At a caffeine intake of 321 mg/day, those in the highest PRS quartile, at a caffeine intake of 321 mg/day, had a 3.90-fold higher glaucoma prevalence ($P_{interaction}$ = 0.0003). It was concluded that overall, caffeine consumption was not associated with increased IOP or glaucoma, but among individuals with a high genetic susceptibility to elevated IOP, high caffeine intake was associated with elevated IOP and glaucoma.

The conclusions of Vera et al (2020) and Kim et al (2021) are consistent with the conclusions reached earlier as the result of a systematic review and meta-analysis conducted by Li et al (2011). Meta-analysis of six studies available at that time led to the conclusion that caffeine is not associated with significant changes in IOP in people with no history of glaucoma or ocular hypertension but is associated with a significant increase in IOP for patients with glaucoma or ocular hypertension.

Summary

Heavy caffeine use may impair the blood supply to the retina, increasing risk of neuroretinopathy and associated scotoma. Caffeine does not appear to increase the risk of ocular hypertension or glaucoma but exacerbates both if they exist. Such patients should

avoid the consumption of caffeine before exercise.

2.6.9.7. Liver disorders

Caffeine exacerbates acute liver injury in laboratory rodents by blocking the anti-inflammatory effect of endogenous adenosine (Ohta and Sitkovsky 2011; Haskó and Cronstein 2011). However, epidemiological studies have consistently shown an inverse relationship between coffee consumption and chronic liver diseases. Coffee consumption is inversely correlated with the occurrence and severity of both alcoholic and non-alcoholic cirrhosis, with a dose-response relationship evident. There is an inverse relationship between coffee consumption and serum levels of markers of liver damage including gamma glutamyltransferase (GGT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (Ohta and Sitkovsky 2011). The inverse association between these markers of liver damage and coffee intake shows a dose-response relationship. Review of the effects of caffeine in viral hepatitis found only one study regarding Hepatitis B, which showed no beneficial effects of caffeine. In contrast, caffeine consumption is associated with reduced inflammation and necrosis in Hepatitis C (Saab et al 2014)

Machado et al (2014) evaluated the effects of caffeine in 136 patients with chronic Hepatitis C and found that caffeine intake ≥ 123 mg/day (the 75th percentile of caffeine intake by dietary assessment) was associated with lower levels of serum AST and reduced hepatic fibrosis, when compared to caffeine intake < 123 mg/day. The authors noted that the daily caffeine consumption of 123 mg/day is lower than the typical intake in the USA or Europe.

Liver disease may impair clearance of caffeine. Caffeine half-lives of up to 160 h have been reported in individuals with severe liver disease (Turnbull et al 2016). The step of caffeine metabolism most sensitive to liver disease appears to be impaired synthesis of paraxanthine (Nehlig 2018).

Summary

Caffeine exacerbates acute liver injury in laboratory rodents, but habitual coffee consumption is inversely related to the severity of chronic liver diseases in humans. Caffeine metabolism may be impaired in severe liver disease.

2.6.9.8. Other physical diseases

Uwaifo (2019) described a toxic triad syndrome of gastritis, hepatitis, and pancreatitis in a man with well-controlled type 2 diabetes and non-alcoholic fatty liver disease. The toxic triad was attributed to the consumption of two to three Monster Energy drinks every day for several months. The patient recovered quickly after stopping his intake of energy drinks. Each can of energy drink he consumed contained 320 mg caffeine, but the patient showed no clinical signs of caffeine toxicity. Uwaifo (2019) cited three other cases of acute hepatitis which had been attributed to energy drinks but acknowledged that a causal relationship could not be verified in this case. As the result of a systematic review and meta-analysis, Wijarnpreecha et al (2018) concluded that there is a significantly decreased risk of pancreatitis among heavy coffee-drinkers.

Sharif et al (2017) conducted a review of the literature concerning the role of coffee consumption in autoimmune diseases. They concluded that coffee consumption appears to increase the risk of developing rheumatoid arthritis and type 1 diabetes mellitus, but to be inversely related to risk of multiple sclerosis, primary sclerosing cholangitis, and ulcerative colitis. No association was found between coffee consumption and risk of systemic lupus erythematosus, psoriasis, primary biliary cholangitis, or Crohn's disease. There is a lack of information concerning any association between caffeine and risk to humans of autoimmune

thyroid disease, celiac disease, or other autoimmune disorders.

There is some *in vitro* evidence that caffeine at concentrations of 100 μM or higher may downregulate monocyte/macrophage function, but plasma concentrations of caffeine rarely exceed 60 μM under normal patterns of consumption (Haskó and Cronstein 2011).

Summary

There is a lack of clear evidence of adverse effects of caffeine on the pancreas. Caffeine appears to increase the risk of rheumatoid arthritis and type 1 diabetes mellitus, but appears to have some protective role against some other autoimmune disorders. There is a lack of evidence that caffeine has an adverse effect on immune response at normal levels of consumption.

2.6.9.9. Psychiatric conditions

In their review of caffeine-related deaths, Cappelletti et al (2018) identified psychiatric patients as one of the three subpopulations most at risk, the others being infants and athletes. Of the 37 case reports they reviewed of caffeine-related fatalities in psychiatric patients, 20 were in patients with depression, and six were alcoholics.

Of relevance to caffeine's neurological effects are that antagonism of A1 receptors has flow-on effects on dopamine D1 receptors and affects release of neurotransmitters including dopamine, glutamate, and acetylcholine, while antagonism of A2A receptors increases neurotransmission through dopamine D2 receptors (Lara 2010). Caffeine also increases cortisol secretion by increasing the production of ACTH by the pituitary gland. Daily consumption of caffeine at typical dietary levels attenuates, but does not abolish, this effect (Lovallo et al 2005)

At high doses, caffeine can induce psychiatric symptoms that mimic a clinical picture known as mixed mood disorder (Lara 2010). Symptoms of caffeine intoxication include psychiatric symptoms such as rambling thought and speech, nervousness, excitement, insomnia, and psychomotor agitation. A dose of 750 mg caffeine can induce panic attacks in psychologically normal individuals (Broderick and Benjamin 2004).

In a study conducted in psychologically healthy people who did not usually consume caffeine, Giles et al (2017) found that caffeine increased negative emotion (e.g., tension, depression, anger, confusion), arousal and anxiety, but appeared to mitigate subjective emotional response to specific negative stimuli such as photographs of disease or injury. Caffeine did not influence subjects' choice on how they regulated their emotions, or their ability to do so.

Analysis of data concerning 3706 individuals in a database of Caucasian twins found that heavy caffeine use, caffeine toxicity and caffeine dependence were significantly and positively associated with major depression, generalized anxiety disorder, panic disorder, alcohol dependence, adult antisocial behaviour and cannabis and cocaine abuse/dependence. However, when data from monozygotic twin pairs were analysed while controlling for genetic and family environmental factors, the positive statistical associations became non-significant. The authors of the study concluded that the associations are unlikely to be causal, and more likely to be due to shared familial characteristics (Kendler et al 2006).

Caffeine-induced anxiety is clinically indistinguishable from general anxiety disorder at presentation. Patients with diagnosed anxiety disorders are more sensitive to caffeine than the general population and report greater symptoms of anxiety at lower doses (Broderick and Benjamin 2004). Patients with panic disorder are also more sensitive to anxiogenic effects of

caffeine than the general population. However, although obsessive-compulsive disorder is classed as an anxiety disorder, caffeine can be therapeutic in this condition (Lara 2010)

Botella and Parra (2003) conducted a study on the effect of caffeine on anxiety in male and female university students with no history of psychiatric disorder. Participants completed a test of anxiety 25-30 minutes after consuming coffee containing 2, 75, 150 or 300 mg caffeine. Participants were not informed of the amount of caffeine given. Men showed a dose-related increase in state anxiety, but women did not, despite having similar levels of salivary caffeine. Daily habitual caffeine intake was included as a covariate in the statistical analysis. The authors attributed the difference between the sexes to the higher dopamine activity in women, and the protective function of oestrogen on dopaminergic function. These findings may have relevance to anxiety disorders in men.

Psychiatric patients typically consume seven times as much caffeine as the general population. Symptoms of depression in psychiatric patients show a correlation with caffeine intake, but the mechanism is unclear. One hypothesis is that patients with depression consume caffeine as a stimulant, to self-medicate. A second hypothesis is that caffeine causes depressive symptoms by modifying neurotransmitter activity (Broderick and Benjamin 2004). However, in the general population, habitual caffeine consumption has beneficial effects on mood, and is associated with lower risk of depression. A significant inverse association between moderate caffeine intake and risk of suicide has been reported. The association between caffeine and suicide may be J-shaped, with lower suicide risk at low or moderate caffeine intake but a significant increase in suicide risk in those who consume 8 or more cups of coffee per day (Lara 2010). Doses of 50–100 mg of caffeine are usually sufficient to induce effects on mood, and in some individuals, clear effects on mood can be observed after only 20 to 30 mg caffeine (Lara 2010).

High intake of caffeine may hamper the recovery of patients with bipolar disorder or manic-type mood episodes. This is consistent with the psychostimulant and antidepressant effects of caffeine, and consistent with the findings that in healthy volunteers, 250 mg caffeine can increase elation and 500 mg caffeine can increase irritability (Lara 2010).

Lara (2010) concluded that for mood and anxiety disorders, caffeine may have beneficial effects for depressive but may be detrimental for some hypersensitive patients with panic and/or performance anxiety disorder, as well as for patients with bipolar disorder. However, he considered that total abstinence is unlikely to lead to significant improvement in patients with low to moderate caffeine intake.

No association was found between tea consumption and postpartum depression, and a nonlinear association between coffee and postpartum depression was found in only one of two adjusted models, in a study by Iranpour et al (2017).

At toxic doses, caffeine can induce psychosis in individuals with no history of mental illness. It has also been shown to exacerbate psychotic symptoms in patients with schizophrenia, while improving mood, energy, and social interactions (Broderick and Benjamin 2004). Reducing caffeine intake in patients with psychosis has produced inconsistent results. Patients with schizophrenia often choose to consume high levels of caffeine. It has been suggested that caffeine attenuates some side effects of antipsychotics prescribed to people with schizophrenia (Lara 2010).

Caffeine may be therapeutic in attention deficit-hyperactivity disorder (ADHD) (Lara 2010).

Genetic associations exist between caffeine intake and alcohol intake. People with alcoholism (alcohol use disorder or AUD) typically consume 30% more caffeine per day than the general population and tend to increase their caffeine intake when they stop drinking

alcohol (Cappelletti et al 2018).

Increased intake of caffeine has frequently been reported in people with eating disorders such as anorexia nervosa and bulimia nervosa (Bramstedt 2007). It is likely that high amounts of caffeine help to counter the fatigue associated with caloric restriction, and suppress appetite. However, patients with eating disorders are at risk of cardiac morbidity and electrolyte disorders and therefore may be at greater risk of caffeine triggering arrhythmia and conduction abnormalities than the general population (Bedi et al 2014).

Summary

Psychiatric patients are likely to be heavy users of caffeine but are a subpopulation at particular risk of fatality from caffeine toxicosis. Patients with anxiety disorders and panic disorders are often more sensitive to caffeine than the general population. Caffeine in moderate doses reduces the risk of depression and suicide in the general population, but heavy caffeine use (≥ eight cups of coffee/day) may be associated with increased risk of suicide. Heavy caffeine use may also be contraindicated in patients with bipolar disorder or manic-type mood episodes, patients with panic and/or performance anxiety disorder, and patients with eating disorders. The effects of caffeine on schizophrenia are mixed.

2.6.10. Caffeine dependence and caffeine use disorder

The IOM (2014) considers that the development of withdrawal symptoms if caffeine is not continued comprises caffeine dependence. In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published in 2013, the American Psychiatric Association combined substance dependence and substance abuse into a single disorder, substance use disorder. They specifically excluded caffeine as a substance for which a substance use disorder can be diagnosed[11]. However, they proposed criteria for caffeine use disorder, to stimulate further research. The proposed criteria include: (i) A persistent desire or unsuccessful effort to control use; (ii) substance use continued despite knowledge of having a persistent or recurrent physical or psychological problem likely to be caused or exacerbated by the substance; and (iii) withdrawal (Addicott 2013).

Summary

There is currently insufficient information to create diagnostic criteria for caffeine use disorder.

2.6.11. Hypersensitivity to caffeine

Despite the very widespread use of caffeine, there are very few reports of allergy or other hypersensitivity reactions to caffeine in the published literature.

Sugiyama et al (2015) reported a case of a 27-year-old woman who suffered an anaphylactic reaction after consuming a piece of candy containing 42 mg caffeine, intended as an aid to prevent drowsiness while driving. Five days after the incident, she noticed a pruritic throat after consuming green tea and again after consuming coffee jelly. She concluded that she had a caffeine allergy and stopped consuming foods containing caffeine. Caffeine allergy was subsequently confirmed by skin prick test. The authors noted that the woman had consumed caffeine in green tea since childhood.

[11] https://www.psychiatry.org/File%20Library/Psychiatrists/Practice/DSM/APA_DSM-5-Substance-Use-Disorder.pdf

A case of allergic response to caffeine was described by Infante et al (2003). The patient was 21 at the time, but the allergic response had first been detected when he was 9 years old. The patient developed urticaria, cough, wheezing and dyspnoea if he consumed coffee or more than two drinks of cola (~23 mg caffeine each). He was able to tolerate tea and chocolate. Caffeine allergy was confirmed by skin prick test.

Coffee and chocolate are among known triggers of adrenergic urticaria, a rare dermal disorder due to a mast cell response. The urticaria is characterised by presence of pale haloes of vasoconstricted skin surrounding small red or pink wheals, and is accompanied by wheezing, cardiac palpitations, tachypnoea, paraesthesias and malaise. Mast cells have a variety of receptors including adrenergic, histaminergic and high-affinity IgE receptors. In most urticarias, mast cells are activated by IgE and the response is mediated by histamine, but in adrenergic urticaria, it appears that the mast cells respond to elevated serum catecholamines. The hypothesis that adrenergic urticaria is triggered by increased catecholamine levels rather than IgE is supported by the response to treatment with propranolol, which is a nonselective beta-adrenergic antagonist. Patients are characteristically suffering from stress or anxiety at the time of episodes (Hogan et al 2014).

Cases of caffeine-associated urticaria have been reported by Hinrichs et al (2002) and Tognetti et al (2014). In the latter case, the patient had recurrent episodes of urticaria but was diagnosed after she also developed glottal oedema and loss of consciousness and was hospitalized.

Summary

Hypersensitivity reactions to caffeine appear to be rare.

2.6.12. Caffeine withdrawal

DSM-5 includes diagnostic criteria for Caffeine Withdrawal, which consists of prolonged daily use of caffeine and three or more withdrawal symptoms occurring within 24 hours of abrupt cessation or reduction of caffeine use. These symptoms include headache, marked fatigue or drowsiness, dysphoric mood/depressed mood/irritability, difficulty concentrating, and flu-like symptoms (Addicott 2013). Symptoms of caffeine withdrawal typically peak one to two days after cessation of caffeine intake, and last from two to nine days (van Dam et al 2020). Avoidance of withdrawal symptoms plays a role in reinforcement among regular consumers. Around 9 to 13% of habitual caffeine consumers experience significant functional impairment during withdrawal (i.e., are unable to do what they usually do) (IOM 2014).

The incidence of caffeine withdrawal symptoms in adolescents is reported to be increasing (Morelli and Simola 2011).

Habitual consumption of caffeine causes upregulation of adenosine receptors in the brain. In acute caffeine withdrawal, there are increased effects of adenosine including cerebral vasodilation, which causes increased cerebral blood flow, which in turn causes headache and nausea. The duration of caffeine withdrawal symptoms reflects the time required for the number of adenosine receptors in the brain to revert to normal levels (Hackett 2010).

Caffeine withdrawal can be prevented or minimised by gradually reducing caffeine consumption (van Dam et al 2020). The most effective treatment of caffeine withdrawal is a combination of both an analgesic and a small amount of caffeine (Hackett 2010).

Abstention from caffeine in association with general anaesthesia and surgery is frequently associated with perioperative headache, but habitual users of caffeine who consume caffeine preoperatively or shortly after surgery are less likely to suffer postoperative headache than

people who abstain from caffeine. Caffeine may also be administered intravenously to reduce postoperative headache (Pleticha et al 2021).

Summary

Caffeine withdrawal may cause significant physical symptoms and functional impairment. Habitual caffeine consumers should avoid abstention for episodes such as general anaesthesia and surgery.

2.7. Discussion

There is consensus among national and international regulatory agencies that 400 mg caffeine/day is not associated with adverse effects in most adults. Some susceptible subpopulations, including pregnant women, lactating women, children, adolescents, and people with cardiovascular disorders, have been identified by overseas regulatory agencies. Levels of safe caffeine intake for pregnant women of up to 200 mg/day (EFSA 2015, US FDA) or 300 mg/day (Health Canada (Nawrot et al 2003) have been proposed. Safe levels for children and adolescents in the range 2.5 to 3.0 mg/kg bw/day have been extrapolated based on bodyweight from the recommended level for healthy adults, although VKM (V019) note that EFSA identified a lower level of 1.4 mg caffeine/kg bw/day is associated with sleep disturbance in children.

Caffeine is rapidly and completely absorbed, and widely distributed in the body. It can be found in all body fluids. The half-life is in the range 3 to 7 hours. CYP1A2 is responsible for more than 90% of the first step in caffeine metabolism, other enzymes in the cytochrome P450 family have minor roles in later steps. Up to a dose of 10 mg/kg bw, caffeine elimination is a first-order process described by a one-compartment open model. Caffeine and its metabolites are primarily excreted in the urine.

Assessment of the available literature on caffeine is complicated by the fact that animal studies and many acute studies in human volunteers are conducted using pure caffeine, whereas epidemiological studies examine the effects of caffeinated beverages, usually coffee. Coffee and tea contain numerous pharmacologically active compounds besides caffeine, and some of the effects of habitual coffee consumption are the reverse of those expected for caffeine. At normal levels of dietary consumption of coffee, the only significant mechanism of action of caffeine is the antagonism of adenosine receptors.

Acute caffeine toxicosis is associated with a blood concentration greater than 80 mg/L, equivalent to consumption of 10 to 20 g of caffeine in an average adult. Subpopulations most at risk of caffeine toxicosis are athletes, psychiatric patients, and infants. Cause of death is usually ventricular fibrillation. Chronic moderate consumption of caffeine at up to 400 mg/day is not associated with significant adverse effects in the general adult population and has several health benefits.

The use of supplements that are not accurately labelled regarding the caffeine content, in a way that can be clearly understood, creates a risk of inadvertent caffeine overdose. In addition, there may be a general lack of awareness among users of these products of the danger of excessive caffeine intake. Energy drinks and other sports supplements figure significantly in calls to poisons centres about caffeine overdoses. Many reports of adverse effects of these products, including cardiovascular, neuropsychiatric, and gastrointestinal effects, are consistent with toxicosis due to caffeine. Some other adverse effects may be mediated by other components of energy drinks and other sports supplements. There appears to be a general lack of information about how the various ingredients of these products may interact with each other.

The therapeutic use of high doses of caffeine in premature infants does not appear to have any long-term adverse consequences. Heavy maternal consumption of caffeine during pregnancy may result in caffeine withdrawal in neonates. FSANZ notes that caffeine clearance in infants reaches or exceeds adult levels by 5 to 6 months of age and therefore an extrapolation from safe adult levels based on bodyweight has a rational basis. Infants and pre-schoolers are at elevated risk of accidental or malicious acute caffeine poisoning, due to their low bodyweight. Caffeine has negative effects on sleep in children, and this may lead to impaired academic performance. Caffeine may also have direct negative effects on cognitive development in children and may promote consumption of beverages with high sugar content. FSANZ notes that the American Academy of Paediatrics discourages the consumption of caffeine by children and adolescents.

Caffeine contributes to poor sleep quality in adolescents and is associated with aggression, risk-taking behaviour, and alcohol consumption. Caffeine consumption may increase the risk of adolescents becoming smokers. FSANZ notes that it is difficult to distinguish direct effects of caffeine in adolescents from the effects of inadequate sleep, the effects of alcohol, and the potential effects of other components of energy drinks, which are a common source of caffeine in adolescents. There is a lack of new information on which to base a quantitative estimate of safe levels of caffeine in adolescents. However, caffeine clearance in adolescents is likely to be at least that of adults, so the recommended level for adults (i.e., 5.7 mg/kg bw/day) is also applicable to adolescents.

There is a lack of evidence that caffeine consumption has any adverse effect on fertility in women. Maternal clearance of caffeine decreases significantly in the second and third trimesters of pregnancy due to downregulation of metabolizing enzymes, while both the placenta and the fetus lack enzymes that metabolize caffeine. Available information on potential effects of caffeine supports the recommendation that pregnant women should limit their caffeine intake to ≤ 200 mg caffeine/day. Potential adverse effects on the fetus of high caffeine consumption during pregnancy include miscarriage, stillbirth, and fetal growth restriction. There is also some evidence of adverse behavioural and fat deposition effects on the child. Moderate caffeine consumption reduces the risk of gestational diabetes mellitus and pre-eclampsia but may exacerbate existing gestational diabetes mellitus. There is conflicting evidence concerning the effect of caffeine on length of gestation. Women who habitually consume caffeine should continue doing so in the perinatal period, to avoid caffeine withdrawal. There is a lack of information on the effects of caffeine in breastmilk.

There is a lack of evidence that caffeine *per se* has any effect on male fertility, although there is limited evidence that caffeine consumed as soda or energy drink could decrease male fertility.

Caffeine has positive effects on physical exertion, and the perceived risks of dehydration or acute mountain sickness from the diuretic effect of caffeine appear to be unfounded. In fact, caffeine may be more beneficial than harmful at high altitude. However, athletes are at elevated risk of caffeine toxicosis. Reasons for this include misleading labelling of sports supplements, failure to follow the recommended daily dose, deliberate or inadvertent ‘stacking’ by consuming caffeine from multiple sources, and a general lack of appreciation of the risks of high caffeine consumption. Caffeine may exacerbate body dysmorphia in bodybuilders.

Caffeine appears to have neurological benefits in the aged, being associated with reductions in the rate of age-related cognitive decline as well as in the risks of developing Alzheimer’s disease and Parkinson’s disease. However, people at risk of developing Huntington’s disease should not consume more than 190 mg caffeine/day. The effects of caffeine on sleep become more pronounced with age. The effects of caffeine on calcium excretion

notwithstanding, there is a lack of evidence that caffeine consumption is a significant risk factor for osteoporosis.

Xenobiotics that interact with caffeine may do so by antagonism, additive effects, potentiation, or synergy. It may be expected that interactions with prescription pharmaceuticals will be managed by the medical profession or by information provided by the pharmacy that fills the prescription. Similarly, the potentiating effect of caffeine on illicit drugs is likely to be familiar to emergency physicians. For many other identified interactions, there is a lack of evidence of any adverse effects on a population basis. Some interactions are beneficial, such as the potentiation of OTC analgesics, and the moderation of adverse effects of the combination of peginterferon and ribavirin in patients with Hepatitis C. Changes in the clearance of caffeine by such factors as going on the contraceptive pill, or quitting smoking, are likely to be self-managed in most cases.

The interaction between caffeine and nicotine is complicated, with nicotine increasing the rate of clearance of caffeine, and caffeine potentiating the effects of nicotine but also counteracting some symptoms of nicotine withdrawal. The interaction between caffeine and alcohol is also complicated, with caffeine having both antagonizing and potentiating effects on the effects of alcohol, while heavy alcohol consumption decreases the clearance of caffeine. There is evidence from animal studies that caffeine can increase alcohol consumption, and it has been claimed that combining energy drinks with alcohol increases the risk of alcohol dependence.

Caffeine slightly increases blood pressure, an effect which is attenuated with habitual consumption. However, the epidemiological evidence indicates that habitual coffee consumption is neutral to beneficial regarding the risks of hypertension, coronary heart disease, congestive heart failure, arrhythmias, and stroke, even in people who have already had a myocardial infarction. The beneficial effects of coffee may not be due to caffeine, and therefore may not be applicable to products in which pure caffeine is an ingredient, such as energy drinks or other sports supplements.

Contraindications of caffeine in specific physical disorders may be expected to be managed by the medical profession or through advice provided by pharmacists. Such contraindications for consumption of caffeine include, or may include, familial long QT syndrome, Brugada syndrome, mitral valve prolapse, left ventricular hypertrophy, cardiomyopathy (or history of cardiomyopathy), Tetralogy of Fallot, aortic aneurysm, epilepsy being treated with phenobarbital during pregnancy, migraine being medicated with triptans, history of ocular hypertension or glaucoma, some psychiatric disorders (such as anxiety disorders and panic disorder), and adrenergic urticaria. In addition, it is reasonable to conclude that it is the sphere of the medical profession to advise patients with a history of migraine to consume less than 200 mg caffeine per day and to be consistent in the time/s of consumption; to prescribe long-acting pain relievers to migraineurs who consume coffee and undertake fasts; to advise patients with a history of nephrolithiasis to avoid sugar-sweetened sodas, including those containing caffeine; and to discourage heavy use of caffeine in patients with depression, bipolar disorder, manic-type mood disorders, or eating disorders.

Caffeine consumption is generally self-limiting in adults, due to consumers' familiarity with adverse effects. This self-limiting mechanism is likely to be applied to several susceptible subpopulations identified in this review, including patients with anxiety disorders or panic disorder, migraineurs in whom caffeine is a trigger, people with genetic polymorphisms that make them unusually susceptible to the adverse effects of caffeine, and people allergic to caffeine.

There is evidence of a lack of knowledge of the hazards of caffeine in athletes and adolescents, and caffeine consumption poses a risk of acute poisoning to infants and small

children.

2.8. Conclusions

Chronic moderate consumption of caffeine at up to 400 mg/day is not associated with significant adverse effects in the general adult population. The caffeine intake of pregnant women should be limited to ≤ 200 mg caffeine/day. There is a lack of information on which to base recommendations for breastfeeding women. Safe levels of caffeine for children and adolescents in the range 2.5 to 3.0 mg/kg bw/day have previously been extrapolated from adults based on bodyweight. However, 3.0 mg/kg bw/day has been associated with adverse effects on affective states in children, and > 1.4 mg/kg bw/day has been associated with sleep disturbance in children. The rate of clearance of caffeine in adolescents is comparable to that of adults, so caffeine intake up to 5.7 mg/kg bw/day is safe for this age group.

Most of the contraindications of caffeine identified in this review may be expected to be managed by consumers, by the medical profession, or through advice provided by pharmacists. Subpopulations at potential risk that are not managed through these avenues include users of supplements that are not accurately labelled, infants and pre-schoolers, and athletes. There is evidence of a lack of knowledge of the hazards of caffeine, particularly in athletes and adolescents, and caffeine consumption poses a risk of acute poisoning to infants and small children.
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