

## **Caffeine and Epilepsy: A systematic review and quantitative analysis**

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### **Abstract**

**Purpose:** Caffeine is the most commonly used CNS stimulant. The relationship between caffeine, seizures, epilepsy and anti-epileptic drugs is complex and not fully understood. Case reports suggest that caffeine triggers seizures in susceptible people. Our systematic review reports on the relationship between caffeine, seizures and drugs in animal and human studies. Quantitative analyses were also done on animal studies regarding the effects of caffeine on anti-epileptic drugs.

**Methods:** PubMed was searched for studies assessing the effects of caffeine on epilepsy, seizure susceptibility and drug interactions in people and in animal models. To quantify the interaction between anti-epileptic drugs and caffeine the data of six animal studies were pooled and analyzed using a general linear model univariate analysis or One-way Analysis of Variance.

**Results:** In total, 442 items were identified from which we included 105 studies. Caffeine can increase seizure susceptibility and protect from seizures, depending on the dose, administration type (chronic or acute) and the developmental stage at which caffeine exposure started. In animal studies, caffeine decreased the anti-epileptic potency of some drugs; this effect was strongest in topiramate

**Conclusion:** Pre-clinical studies suggest that caffeine increases seizure susceptibility. In some cases, chronic use of caffeine may protect against seizures. Caffeine lowers the efficacy of several drugs, especially topiramate. It is unclear how these findings in models can be translated to the clinical condition. Until clinical studies suggest otherwise, caffeine intake should be considered as a factor in achieving and maintaining seizure control in epilepsy.

## 1 Introduction

Caffeine (1,3,7-trimethylxanthine) is the most widely consumed CNS stimulant.[1] Globally, the average intake is around 300 mg/day, mostly as coffee, tea, soft drinks and energy drinks.[2,3] An average cup of coffee (200 ml) contains ca. 74 mg caffeine.[2] Chocolate, certain plants and a wide variety of drugs also contain caffeine.[4]

Caffeine counters fatigue and enhances vigilance, reaction speed, information processing, arousal and motor activity.[1] These effects are probably mediated by neuronal adenosine-receptors.[5] When firing, neurons produce the inhibitory neuromodulator adenosine as a by-product.[6] Adenosine promotes sleep through adenosine receptors and reduces cortical excitability.[7] The molecular structure of caffeine is similar to adenosine and it is a mixed competitive adenosine A1 and A2A receptor antagonist. Caffeine affects the responsiveness to gamma-aminobutyric acid (GABA), an important inhibitory neurotransmitter, by modulating GABA-A receptors.[8–10] Moreover, adenosine A1-receptor activation is involved in the inhibition of dopamine, a neurotransmitter involved in focus and motivation, and release of glutamate, an important excitatory neurotransmitter. Caffeine increases dopamine and glutamate release and inhibits GABA, resulting in a "pepping" effect.[11,12]

Epilepsy is a paroxysmal neurological condition characterized by recurrent seizures, with a prevalence of up to 0.7% in the general population.[13–15] There are several case studies in which caffeine seemed to trigger seizures in people with and without epilepsy (summarized in table 1). Seizures occurred after toxic doses of caffeine intake[16–23] or prolonged periods of caffeine intake.[3,24–27] In one case, a man had at least six focal seizures each week.[25] Treatment with several anti-epileptic drugs (AEDs) failed. Six months after he stopped drinking coffee (>2 L/day), he became seizure-free. Another report described a man with generalized epilepsy who had been seizure-free on AEDs.[3] His seizures suddenly recurred when he started drinking large quantities of caffeinated iced tea. After he switched to decaffeinated iced tea, the seizure frequency decreased. A woman who drank around half a liter of coffee on weekdays, and almost 2 liters on Fridays, Saturdays and Sundays had several episodes of status epilepticus (SEs) at the weekends. When she stopped drinking coffee on these days, she had fewer seizures and no SEs.[27] In electroconvulsive therapy, a treatment for severe depression, caffeine has been used to prolong seizures.[28]

The question thus arises as to how caffeine affects seizure susceptibility. We conducted a systematic review aiming to answer three questions: Firstly, what information do pre-clinical studies provide about the effects of caffeine on seizures? Secondly, do pre-clinical and/or clinical studies point to interactions between caffeine and AEDs? Given the large body of data on this topic, we performed a quantitative analysis of available data.[29–42] Lastly, we reviewed the literature on pathophysiological mechanisms that may link seizures to caffeine exposure.

**Table 1 :** Case reports: Overview of case studies describing potential seizure-inducing effects of caffeine. Cases are discussed in the introduction.

Reference	Gender (M/F)	Age (in years)	Epilepsy (+/-)	Type of seizure (Focal, Tonic-clonic, Absence)	Caffeine dose (mg)	Caffeine intake through:	AED (other relevant drugs)	Comments
3	M	49	+	Focal, Tonic-clonic and Absence	168 (in 3 h)	Snapple Iced Tea (4 pints)	Phenytoin & primidone (unchanged)	Consumed in 3 hours on an empty stomach. After switching to decaffeinated Snapple Iced Tea, no more seizures.
16	F	neonate	-	Equivalent of tonic-clonic seizures in neonate	250.04 (94 mg/kg)	<i>im</i> injection of CSB	Phenobarbital + (dexamethasone)	Hypoxia causes CNS irritability
16	M	neonate	-	Equivalent of tonic-clonic seizures in neonate	511.36 (two times 68 mg/kg)	<i>im</i> injection of CSB	(Dexamethasone + atropine)	Two injections of 255.68 mg caffeine. Hypoxia causes CNS irritability
16	M	neonate	-	Equivalent of tonic-clonic seizures in neonate	248.64 (84 mg/kg)	<i>im</i> injection of CSB	(Naloxone hydrochloride)	Hypoxia causes CNS irritability
16	F	neonate	-	Equivalent of tonic-clonic seizures in neonate	62.280 (36 mg/kg)	<i>im</i> injection of CSB	-	Hypoxia causes CNS irritability
17	F	17	-	Tonic-clonic	Unknown	“Pick-me-up-pill” (Caffeine+ phenylpropanolamine + pseudoephedrine)	-	Seizures after taking “pick-me-up-pill”.
18	F	24	-	Tonic-clonic	1000 (in 3 h)	<i>iv</i> injection of CSB	(Analgesia + anesthesia for C-section)	CSB + epidural blood patch to treat persisting postpartum headache.

19	F	27	- (migraine)	Tonic-clonic	500	<i>iv</i> injection of CSB	-	-
20	F	45	- (migraine)	Tonic-clonic	250 per day	Coffee	(Aspirin, 5 g/day)	Withdrawal of caffeine and aspirin caused seizures and headaches.
21	F	21	-	Tonic-clonic	1000 (in 23h)	Pills (250 mg each)	-	After complicated delivery of a healthy child, caffeine pills to treat headaches.
22	M	40	+	Focal, Tonic-clonic	~800	Coffee	Carbamazepine (unchanged)	Stopped drinking coffee, no more seizures.
23	F	18	-	Presumed seizure	Unknown (1 Energydrink)	Energydrink (unknown label)	(Aspirin 1000 mg)	Collapsed in a nightclub setting, flashing lights.
24	M	25	-	Tonic-clonic	480	Energydrink (Rockstar)	-	Twice seizures 30-60 minutes after drinking large amounts of energydrink.
24	F	28	- (migraine)	Tonic-clonic	Unknown	Energydrink (Monster) + Diet pills with caffeine	-	Only seizures (twice) when energydrink + Diet pills containing caffeine
24	M	19	- (migraine)	Tonic-clonic	>480	Energydrink (unknown label)	-	Subject could not remember the amount or label: "couple of 24-oz cans".
24	M	26	-	Tonic-clonic	>480	Energydrink (Monster)	-	Two or more 24-oz cans Monster energydrink caused seizures
25	M	15	-	Tonic-clonic	~480	Coffee + Energydrink (5-hour ENERGY)	-	-
26	unknown	25	-	"Convulsive crisis"	unknown	Coffee	(Tramadol, 2400 mg)	Tramadol abuse
26	unknown	21	-	"Convulsive crisis"	unknown	Coffee	(Tramadol, 720 mg)	Tramadol abuse
26	unknown	17	-	"Convulsive crisis"	unknown	Coffee	(Tramadol, 1200 mg)	Tramadol abuse

26	unknown	20	-	“Convulsive crisis”	unknown	Coffee	(Tramadol, 1200 mg)	Tramadol abuse
26	unknown	15	-	“Convulsive crisis”	unknown	Coffee	(Tramadol, 840 mg)	Tramadol abuse
26	unknown	17	-	“Convulsive crisis”	unknown	Coffee	(Tramadol, 1200 mg)	Tramadol abuse
27	F	33	+	Seizures and Status Epilepticus	Unknown (24 ounces coffee on weekdays; 60 on Fr, Sa, Su)	Coffee	Levetiracetam, carbamazepine and zonisamide	Underwent left temporal lobectomy and responsive neurostimulation therapy for medically refractory epilepsy.

(AED = Anti-epileptic Drug; CSB = Caffeine Sodium Benzoate; CNS = Central Nervous System)

## 2 Material and Methods

### 2.1 Systematic review

A systematic PubMed search with no language or time restrictions was conducted (last updated September 2017). Search terms included synonyms for caffeine, coffee, epilepsy and seizures and all AEDs on the WHO List of Essential Medicines 2013 and the Medication for Epilepsy list provided by the Epilepsy Society, including synonyms and brand names.[43,44] (See Appendix). Items were screened independently by two reviewers (RRK and PRB or IS). Duplicate articles were removed.

Primary studies assessing the relationship between caffeine and epileptic phenomena or AEDs in vitro, in animal studies or in humans were included. Studies describing the effects of caffeine derivatives (e.g. theophylline and pentoxifylline), were excluded, as were studies reporting on animal studies using the toxic-dose caffeine seizure model. This model uses doses of caffeine much higher than the human average daily intake to induce seizures and does not describe the relationship between *normal* caffeine consumption and epilepsy. The eligibility of items was first based on the title. When a decision could not be reached based on the title, the abstract was obtained. When the abstract was relevant, the full-text was obtained. When a full-text article was not available, the corresponding author was contacted. Both reviewers compared the included studies. Disagreements on relevance were discussed and settled by consensus.

### 2.2 Quantitative analysis

Full-text articles on the interaction between caffeine and AEDs in animal models were screened by two reviewers (RRK and IS). A study was included in the analysis if it presented Effective Dose (ED50) values (i.e, the dose of caffeine producing seizures in 50% of animals) for one or more AEDs. ED50 value, type of AED, number of animals, control (AED only) or treatment (AED + caffeine) group, amount of caffeine, and seizure-inducing method were extracted from the studies, from which a standardized sensitivity was calculated as follows:

$$\text{Sensitivity} = \frac{\text{ED50}_{\text{treatment}} - \text{ED50}_{\text{control}}}{\text{ED50}_{\text{control}} \cdot (\text{Caffeine dose})} \cdot 100\%$$

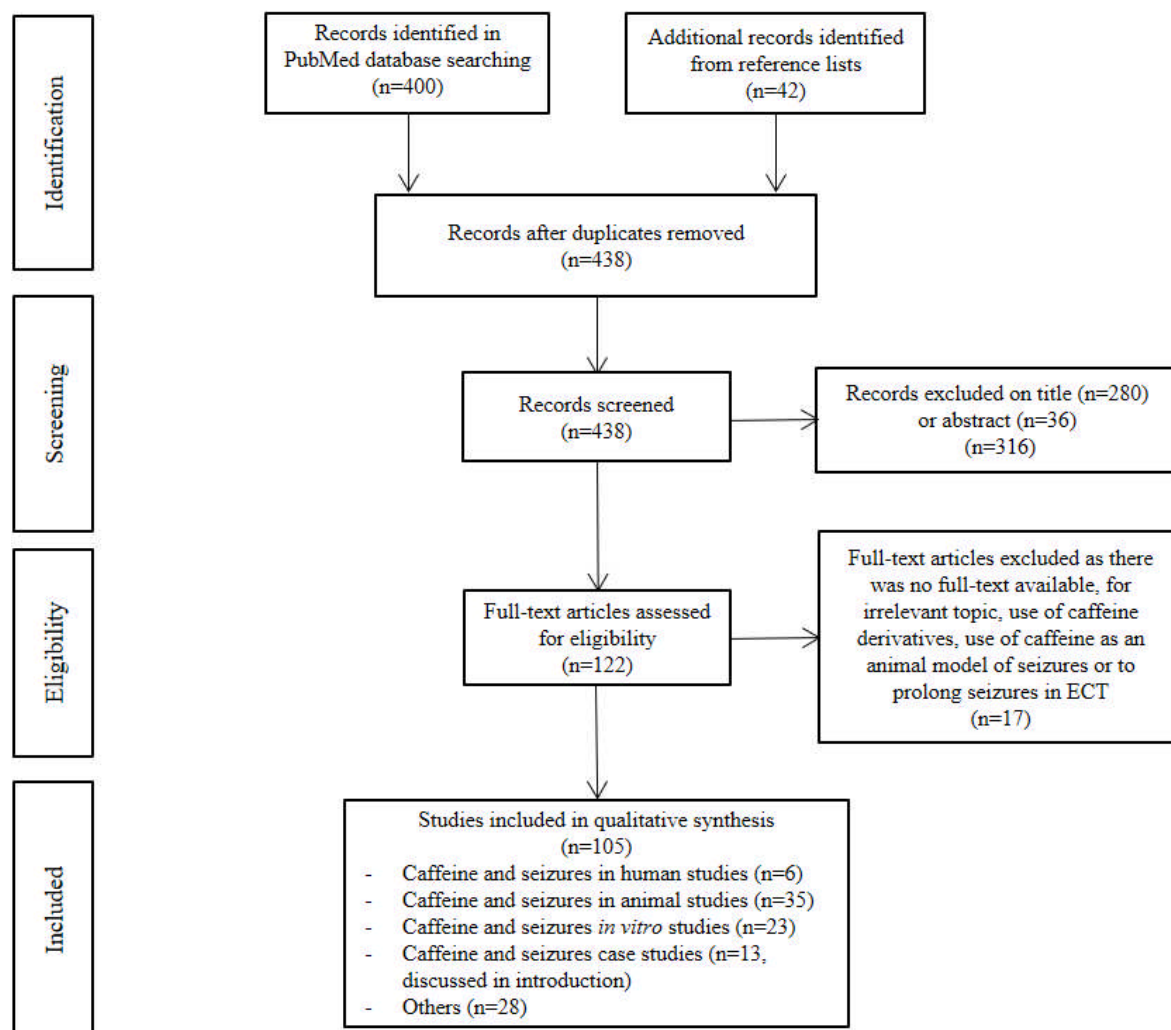
Sensitivity is the percentage change of ED50<sub>control</sub> value per mg/kg caffeine administered. Positive values indicate reduced efficacy of the AED when combined with caffeine, negative values indicate enhanced efficacy. If data were not provided, the corresponding authors were contacted.

Statistical analyses were performed using SPSS (version 20.0 and 21.0 for Windows). A general linear model univariate analysis was used to assess the sensitivity of AEDs (carbamazepine, phenobarbital, phenytoin, valproic acid, ethosuximide, clonazepam, topiramate, oxcarbazepine, lamotrigine) and to analyze the effects of different doses of caffeine on the percentage difference between the ED50 value of the control and treatment condition (% $\Delta$ ED50<sub>treatment-control</sub> value). Sample size, seizure-inducing method (maximal electroshock (MES) 25mA, MES 50mA or pentylenetetrazole (PTZ)) and administration frequency (acute or chronic) were incorporated as covariates in the analysis. One-way Analysis of Variance (ANOVA) with Welch's correction was used to assess the difference in sensitivity among AEDs and to analyze whether administration frequency (acute or chronic) of caffeine leads to differences in sensitivity. Post-hoc Games-Howell pairwise comparisons tests were done to assess which AED was the most sensitive to caffeine. Levene's Test for equality of variances was used to investigate the assumption of homogeneity of variance. The rejection level for all assumptions was set at  $p=0.05$ ; values of  $p<0.05$  were considered statistically significant.

### 3 Results

#### 3.1 Systematic review

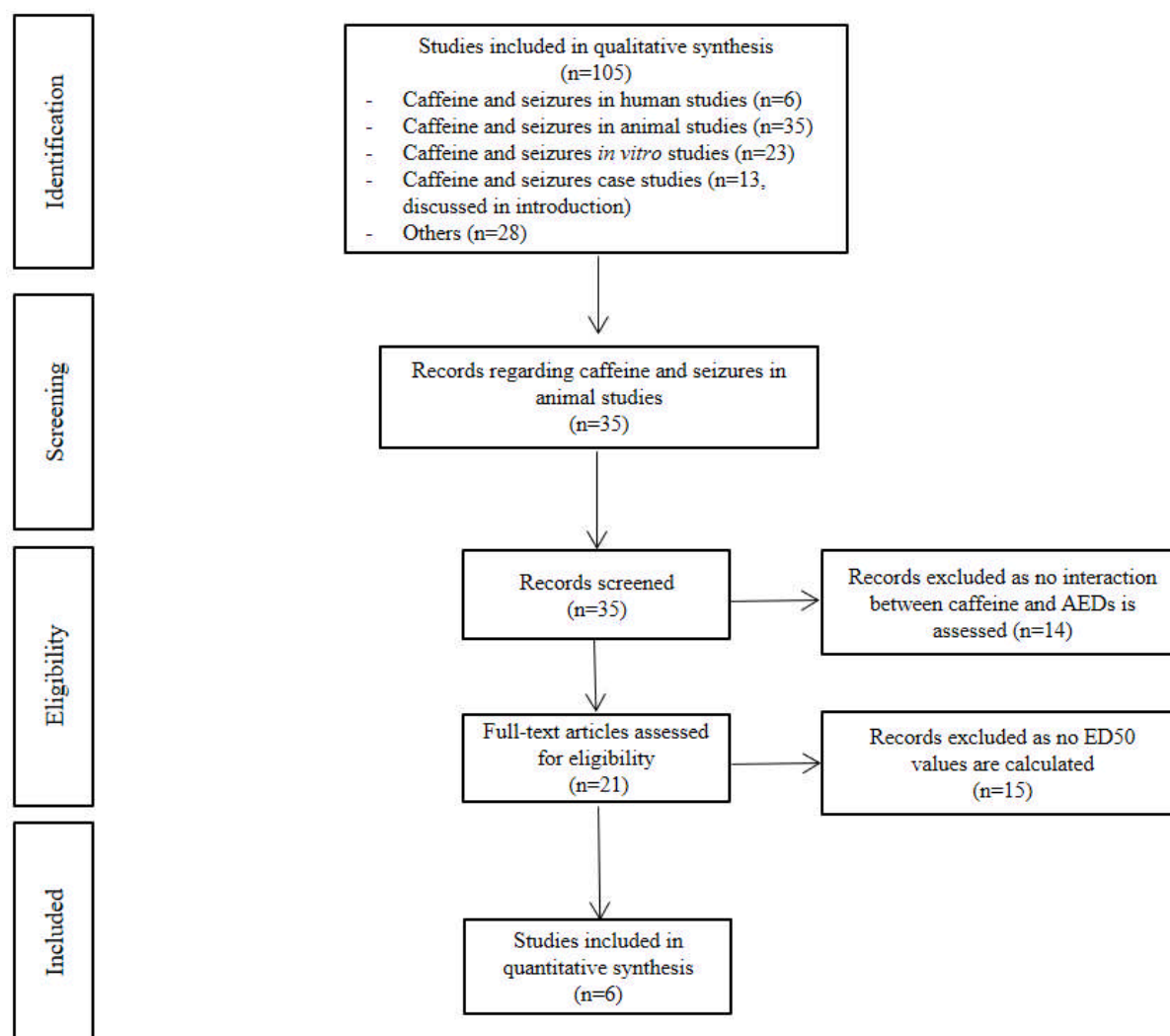
In total, 442 items were identified, including 42 additional records mainly providing background information identified from reference lists, of which 4 duplicates were removed, 280 were excluded on title, 36 on abstract, and 17 as there was no full-text available (see Figure 1.1). One author provided additional information.[45] In total, 105 studies were included.



**Figure 1.1** : Flowchart of the data-filtering process of the qualitative analysis following PRISMA guidelines. (ECT = Electroconvulsive Therapy)

#### 3.2 Quantitative analysis

Of the 105 studies included in the qualitative analysis, 6 were included in the quantitative analysis. These animal studies described the calculation of ED50 values before and after caffeine administration in combination with carbamazepine, phenobarbital, phenytoin, valproic acid, ethosuximide, clonazepam, topiramate, oxcarbazepine and lamotrigine (see Figure 1.2).[30,35,36,38,40,41] The data are summarized in Table 2. Two authors provided additional information.[36,41] In total, 66 ED50 measurements were included in the dataset.



**Figure 1.2 :** Flowchart of the data-filtering process for the quantitative analysis following PRISMA guidelines. (ED50 = Effective Dose 50)



	AED	Group	Sample size	Caffeine dose (mg/kg)	Administration frequency	Seizure-inducing method	ED50	Sensitivity
<i>Gasior et al. 1995(36)</i>	CBZ	Control	32-40	0.0		MES (25 mA)	15.0	
	CBZ	Treatment	32-40	11.55	Acute	MES (25 mA)	14.9	-0,058
	CBZ	Treatment	32-40	23.1	Acute	MES (25 mA)	16.3	0,375
	CBZ	Treatment	32-40	11.55	Chronic	MES (25 mA)	17.8	1,616
	CBZ	Treatment	32-40	23.1	Chronic	MES (25 mA)	21.0	1,732
<i>Czuczwar et al. 1990(35)</i>	CBZ	Control	40	0.0		MES (50 mA)	13.0	
	CBZ	Treatment	40	23.1	Acute	MES (50 mA)	14.0	0,333
	CBZ	Treatment	40	46.2	Acute	MES (50 mA)	17.5	0,749
	CBZ	Treatment	40	92.4	Acute	MES (50 mA)	20.5	0,024
<i>Czuczwar et al. 1990(35)</i>	PBT	Control	40	0.0		MES (50 mA)	19.5	
	PBT	Treatment	40	11.55	Acute	MES (50 mA)	24.5	2,220
	PBT	Treatment	40	23.1	Acute	MES (50 mA)	28.0	1,887
	PBT	Treatment	40	46.2	Acute	MES (50 mA)	32.0	1,388
	PBT	Treatment	40	92.4	Acute	MES (50 mA)	38.0	1,027
<i>Gasior et al. 1996(40)</i>	PBT	Control	32-40	0.0		MES (25 mA)	17.8	
	PBT	Treatment	32-40	11.55	Acute	MES (25 mA)	17.1	-0,340
	PBT	Treatment	32-40	23.1	Acute	MES (25 mA)	24.1	1,532
	PBT	Treatment	32-40	11.55	Chronic	MES (25 mA)	26.1	4,037
	PBT	Treatment	32-40	23.1	Chronic	MES (25 mA)	26.6	2,140
<i>Luszczki et al. 2006(30)</i>	PBT	Control	32	0.0		PTZ	11.4	
	PBT	Treatment	32	92.4	Acute	PTZ	12.0	0,057
<i>Czuczwar et al. 1990(35)</i>	PHT	Control	40	0.0		MES (50 mA)	12.0	
	PHT	Treatment	40	11.55	Acute	MES (50 mA)	12.0	0,000
	PHT	Treatment	40	23.1	Acute	MES (50 mA)	17.0	1,804
	PHT	Treatment	40	46.2	Acute	MES (50 mA)	17.0	0,902
	PHT	Treatment	40	92.4	Acute	MES (50 mA)	24.0	1,082
<i>Gasior et al. 1995(36)</i>	PHT	Control	32-40	0.0		MES (25 mA)	10.2	
	PHT	Treatment	32-40	23.1	Acute	MES (25 mA)	11.4	0,509
	PHT	Treatment	32-40	46.2	Acute	MES (25 mA)	15.9	1,210
	PHT	Treatment	32-40	92.4	Acute	MES (25 mA)	19.3	0,966
	PHT	Treatment	32-40	23.1	Chronic	MES (25 mA)	12.2	0,849
	PHT	Treatment	32-40	46.2	Chronic	MES (25 mA)	15.3	1,082
<i>Czuczwar et al. 1990(35)</i>	VPA	Control	40	0.0		MES (50 mA)	270.0	
	VPA	Treatment	40	23.1	Acute	MES (50 mA)	310.0	0,641
	VPA	Treatment	40	46.2	Acute	MES (50 mA)	365.0	0,702
	VPA	Treatment	40	92.4	Acute	MES (50 mA)	420.0	0,001
<i>Gasior et al. 1996(40)</i>	VPA	Control	32-40	0.0		MES (25 mA)	273.0	
	VPA	Treatment	32-40	11.55	Acute	MES (25 mA)	267.0	-0,190
	VPA	Treatment	32-40	23.1	Acute	MES (25 mA)	288.0	0,238
	VPA	Treatment	32-40	46.2	Acute	MES (25 mA)	324.0	0,404
	VPA	Treatment	32-40	11.55	Chronic	MES (25 mA)	287.0	0,444
	VPA	Treatment	32-40	23.1	Chronic	MES (25 mA)	320.0	0,745
	VPA	Treatment	32-40	46.2	Chronic	MES (25 mA)	324.0	0,404
	VPA	Control	32	0.0		PTZ	130.7	
<i>Luszczki et al. 2006(30)</i>	VPA	Treatment	32	92.4	Acute	PTZ	169.2	0,319
	ETS	Control	32	0.0		PTZ	127.7	
<i>Luszczki et al. 2006(30)</i>	ETS	Treatment	32	46.2	Acute	PTZ	148.1	0,346
	ETS	Treatment	32	92.4	Acute	PTZ	198.3	0,598
	ETS	Treatment	32	69.3	Acute	PTZ	182.3	0,617
<i>Luszczki et al. 2006(30)</i>	CZP	Control	32	0.0		PTZ	0.026	
	CZP	Treatment	32	92.4	Acute	PTZ	0.037	0,458
<i>Chrooecinska-Kruczyk et al. 2016(41)</i>	TPM	Control	8	0.0		MES (25 mA)	44.8	
	TPM	Treatment	8	23.1	Acute	MES (25 mA)	72.1	2,638
	TPM	Treatment	8	46.2	Acute	MES (25 mA)	82.5	1,821
	TPM	Treatment	8	23.1	Chronic	MES (25 mA)	78.4	3,247
	TPM	Treatment	8	46.2	Chronic	MES (25 mA)	95.3	2,440
<i>Chrooecinska-Kruczyk et al. 2009(38)</i>	OXC	Control	8	0.0		MES (25 mA)	13.0	
	OXC	Treatment	8	23.1	Acute	MES (25 mA)	15.6	0,866
	OXC	Treatment	8	46.2	Acute	MES (25 mA)	15.3	0,383
	OXC	Treatment	8	23.1	Chronic	MES (25 mA)	14.2	0,400
	OXC	Treatment	8	46.2	Chronic	MES (25 mA)	14.5	0,250
<i>Chrooecinska-Kruczyk et al. 2009(38)</i>	LTG	Control	8	0.0		MES (25 mA)	7.5	
	LTG	Treatment	8	23.1	Acute	MES (25 mA)	8.2	0,404
	LTG	Treatment	8	46.2	Acute	MES (25 mA)	8.2	0,202
	LTG	Treatment	8	23.1	Chronic	MES (25 mA)	7.6	0,058
	LTG	Treatment	8	46.2	Chronic	MES (25 mA)	7.4	-0,029

**Table 2:** Dataset Quantitative Analysis (AED= Anti-epileptic Drug; MES = Maximal Electroshock; PTZ = Pentylenetetrazole; CBZ = Carbamazepine; PBT= Phenobarbital; PHT = Phenytoin; VPA = Valproic Acid; ETS= Ethosuximide; CZP = Clonazepam; TPM= Topiramate; OXC = Oxcarbazepine; LTG = Lamotrigine)

### 3.3 Pre-clinical studies regarding the effects of caffeine on seizures in animal models

#### 3.3.1. *Seizures after caffeine exposure*

Caffeine influences brain excitability and triggers seizures followed by encephalopathy in rats.[46] Several doses of caffeine were administered during behavioral observations and EEG recordings. Doses of 100 and 200 mg/kg caffeine caused pupillary dilatation, restlessness and intermittent jerks, while the EEG showed bursts of spikes or sharp waves, similar to the EEG pattern seen during epileptic seizures. At doses above 150 mg/kg, generalized seizures occurred. At doses of 300 mg/kg and above, fatal SE occurred in the rats; the same phenomenon is seen in cats, dogs, guinea pigs, mice and rabbits.[47] This shows that extremely high (toxic) doses of caffeine consistently cause seizures; this forms the basis of the caffeine-induced seizure animal model that we will not discuss further.[46] Several studies in rodents, however, have provided evidence for higher seizure susceptibility even after lower doses of caffeine. In one study, rats were pre-treated with caffeine (100 mg/kg) and subsequently with the pro-convulsant PTZ (30 mg/kg), which is an animal model of focal seizures, generalized tonic-clonic seizures (GTCS) and absence seizures.[48,49] Compared to controls (PTZ alone), the caffeine group had more seizures and continuous spiking on the EEG recordings. Severe seizures were seen in 12/15 rats in the caffeine group but not in controls.[49] In two other studies, the amount of PTZ needed to induce seizures in 50% of mice was measured. This significantly decreased in a dose-dependent manner after caffeine administration, suggesting that caffeine either lowers the seizure threshold or enhances the effects of PTZ.[29,30]

#### *Antenatal caffeine exposure*

Long-term caffeine treatment in a dose leading to plasma concentrations similar to those of humans taking three to four cups of coffee a day (0.3 g/L) was given to rat dams during pregnancy and lactation in two different studies.[50,51] This led to a concentration similar to those found in breast-fed infants and umbilical cords of caffeine-consuming mothers (0.5-2 mg/L). This concentration is below 50  $\mu$ M, which in the brain parenchyma of rodents is considered equivalent to brain concentrations in humans after drinking moderate amounts of coffee.[50–53] The control dams were given water without caffeine. Results from one study[51] showed elevated (hyperthermia-induced) seizure susceptibility in newborn pups in the caffeine group, compared to control.[51] In the other study[50] pups were given the pro-convulsant flurothyl six days after birth. With 0.1 flurothyl, none of the pups had seizures, whereas 0.2 ml elicited seizures in all the pups of the treatment group and in 38% of controls. Postmortem examination showed delayed migration of GABAergic neurons into the hippocampus in the treatment group but not in controls. This was associated with a general increase in neuronal network excitability.[50]

In another study in which antenatal effects of caffeine were studied in rats there was no difference in adenosine A<sub>1</sub>, A<sub>2A</sub> and GABA-A receptor mRNA expression between controls and the caffeine group.[52] This study did not assess seizure susceptibility. Antenatal caffeine exposure may thus increase seizure susceptibility through long-lasting changes in neuronal migration and excitability, without affecting receptor density.

#### 3.3.2. *Protective effects of caffeine*

Some animal studies have suggested that caffeine may have beneficial effects on epilepsy and seizures.

*Caffeine exposure in young rodents*

Prolonged, low-dose (10-20 mg/kg) caffeine exposure in young animals was shown to decrease seizure susceptibility. In one experiment, caffeine (15-20 mg/kg) was administered to rats two to six days after birth.[54] They were also infused with one of five pro-convulsants: PTZ, bicuculline, picrotoxin, strychnine or kainic acid at different ages. The infusion of the pro-convulsant was stopped after the first myoclonic jerk. Rats that were exposed to caffeine had a 20-40% higher seizure threshold to PTZ at postnatal day 28 than controls. At 42 days, caffeine-exposed rats had a further increase in seizure threshold (40-50% elevation) to PTZ and picrotoxin. Measurements at adulthood (days 70-90) showed a significant increase of seizure threshold for PTZ and kainic acid in rats that were treated with caffeine compared to controls. In another study, rats were chronically administered physiological levels of caffeine (10-20 mg/kg) 7-11 days after birth.[55] Twelve and 25 days after birth, the seizure susceptibility to one of four pro-convulsants (PTZ, picrotoxin, bicuculline and aminophylline) was measured. Caffeine significantly elevated the seizure threshold for GCTS but not for myoclonic jerks or minimal clonic seizures. At 25 days, the effect of caffeine on PTZ-induced seizures was greater than at 12 days, possibly due to the difference in maturity of neurotransmitter systems. Conversely, in young rats (18 and 25 days old), a single dose of caffeine (10 or 20 mg/kg) decreased the threshold for electrically induced seizures and prolonged afterdischarges (ADs) compared to controls that did not receive caffeine.[56] In rats that received caffeine repeatedly seven to 11 days or 13 to 17 days after birth, the same single dose of caffeine did not significantly alter the seizure threshold or AD duration in response to electrical stimulation.[57] The same results were found when electrical seizures were induced at 67 days.[58]

Low-dose (10-20 mg/kg) exposure to caffeine may protect against absence-type seizures.[59] This was shown in a study where a small dose of PTZ was used in an absence and myoclonic seizure model. The duration of epileptiform episodes was significantly shorter and the frequency decreased in the 10 mg/kg caffeine-group. In the 20 mg/kg caffeine group, there was an almost complete absence of epileptiform episodes.[59]

*Caffeine exposure in adult rodents*

Several studies investigated whether caffeine has the same protective effects when chronic low-dose (<6 mg/kg) exposure is started in adult rodents. In one experiment, adult rats were given caffeinated drinking water for 14 days.[60] They were then injected with a subconvulsant dose of picrotoxin, kainic acid or water (control) and observed for seizure activity. There was no significant effect of caffeine. Conversely, in a study with EEG recordings, adult rats were administered caffeine (6 mg/kg) over 15 days. PTZ (60 mg/kg) was injected to induce seizures on the 16th day.[61] The duration of GTCS significantly decreased and the amplitude of the ictal EEG pattern was reduced in the caffeine group compared to the controls (saline injection).

The conflicting results between these studies may be the result of differences in the dose of pro-convulsant or caffeine[60,61], the use of different pro-convulsants, and differences in plasma caffeine concentration: intraperitoneal injection of caffeine in a dose of 6 mg/kg[61,62] led to a higher plasma caffeine concentration than caffeinated water (0.1% solution) ad libitum.[60] Another study with adult rodents showed that chronic (70 days starting P21) caffeine intake ( $69 \pm 3$  mg/kg/day) in rats, leading to plasma concentrations corresponding to 5-6 cups of coffee in humans, may abrogate consequences of early-life convulsions, especially memory deficits and synaptotoxicity which is linked to increased seizure susceptibility.[62]

A study examined the effects of acute caffeine on the spike-and-wave discharges (SWDs) on intracranial EEG recordings in a rat model of genetic absence epilepsy that was given caffeine.[45] The number and duration of SWDs were dose-dependently reduced after acute physiological-dose (up to 10 mg/kg) caffeine exposure compared to the baseline EEG-recording. No changes were found after

chronic caffeine administration in rats in a dose corresponding to the human intake of around two cups of coffee per day for 14 days.[45] Similarly, an acute dose of caffeine (25 mg/kg intraperitoneally), equivalent to ~8 mg/kg in humans[5] reduced the duration of epileptic bursts in an adult rat model of severe traumatic brain injury.[63] This is consistent with a study in which tottering mutant mice were injected with caffeine (5, 10, 15 mg/kg) or saline (control).[64] Caffeine significantly decreased the occurrence of absence seizures and focal motor seizures for 1-2 hours, compared to the controls. In rats with kindling-induced amygdaloid seizures, however, 50mg/kg caffeine prolonged SWDs and increased seizure severity, showing dose-dependent differences in protective effect in different seizure models. Caffeine may also protect against neurotoxicity and downregulation of A1- and A2A receptors induced by the AED phenobarbital in the frontal cortex, retrosplenial cortex, hypothalamus, thalamus and the dentate gyrus.[65] In mice a physiological dose of caffeine (0.5 mg/kg) significantly reduced the incidence of seizure-induced respiratory arrest which may be involved in sudden death in epilepsy (SUDEP).[34] Overall, in animal models caffeine has beneficial effects on seizure susceptibility, especially in models of absence epilepsy, after early-life convulsions and traumatic brain injury. This effect depends on age, pro-convulsant, seizure model, caffeine dose and administration method.

### ***3.3.3. Interactions between caffeine and anti-epileptic drugs in animal models***

#### *Systematic review*

The interaction between caffeine and AEDs has been widely studied in animal models. In several studies Maximal electroshock (MES) was used to induce seizures to assess the effects of caffeine administration on the anticonvulsant properties of AEDs.[35–41] Rats were injected with caffeine and with one of following AEDs: carbamazepine, phenytoin, phenobarbital, valproic acid, felbamate, oxcarbazepine, lamotrigine, tiagabine, gabapentin and topiramate. Caffeine injections significantly increased the amount of phenobarbital, carbamazepine, phenytoin, topiramate, gabapentin, valproic acid and felbamate necessary to protect 50% of the rats against electroconvulsions (ED50), whereas no changes were seen with oxcarbazepine, lamotrigine and tiagabine.[35,37–41] When caffeine was administered chronically, the amount of phenobarbital, carbamazepine, phenytoin, topiramate, gabapentin and valproic acid needed to protect 50% of the rats against seizures was also increased, but unaltered for oxcarbazepine, lamotrigine and tiagabine.[36,38–41] No data is available on the effects of chronic administration of caffeine on the anti-epileptic potency of felbamate.

A study using PTZ as a pro-convulsant showed that caffeine significantly decreased the amount of PTZ needed to induce the first spike, tonic convulsions, clonic convulsions or death compared to saline.[29] Diazepam increased the threshold to PTZ-induced epileptic phenomena. When diazepam and caffeine were given concomitantly, the anticonvulsant effect of diazepam was smaller. PTZ was also used to induce seizures in mice and rats treated with ethosuximide, carbamazepine, clonazepam, phenobarbital or valproic acid.[30,42] After caffeine injection, the amount of ethosuximide needed to protect 50% of the mice[30] and the amount of carbamazepine needed to protect all the rats[42] against PTZ-induced seizures was significantly elevated. No significant effects were found in mice for clonazepam, phenobarbital and valproic acid.

In another study, seizures were induced in seizure-susceptible mice using rhythmic vestibular stimulation, by tossing them once a week 50 times from a height of ten to fifteen centimeters.[66] The mice were injected with zonisamide and subsequently tossed, after which the seizure scores were determined. The seizures were scored on a scale from 0-4 with 0) no seizures 1), abortive seizures (static, staring mouse) after 50 tosses 2) abortive seizures after 25 tosses; 3), tonic-clonic seizures after 50 tosses; and 4) tonic-clonic seizures after 25 tosses. The seizure score was significantly elevated after 1, 2 and 3 weeks of drinking caffeinated drinking water compared to untreated mice, suggesting that caffeine interferes with the anticonvulsant effects of zonisamide.[31]

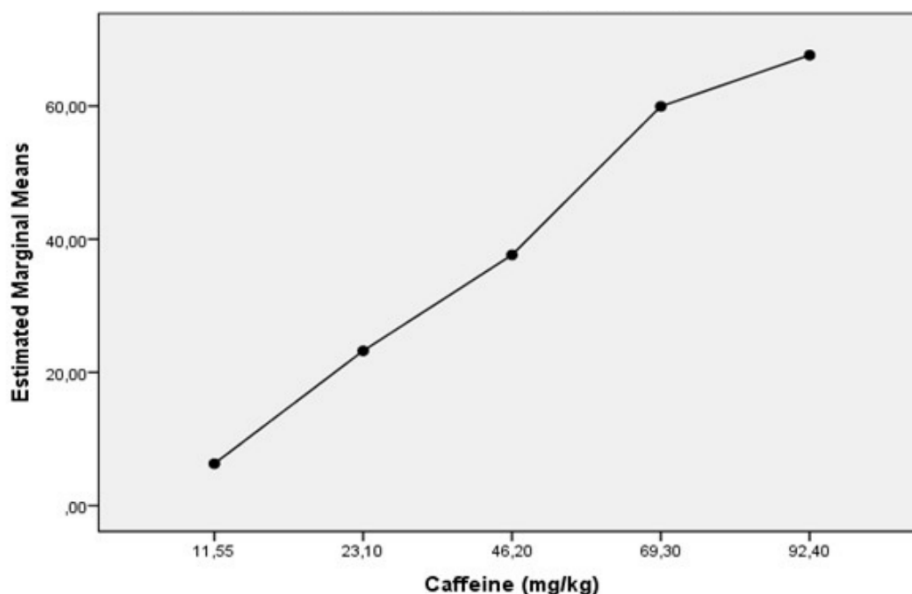
It seems that there are two mechanisms through which interaction effects between caffeine and AEDs can occur. First, as the concentrations of phenobarbital, clonazepam, phenobarbital, valproic acid, carbamazepine, gabapentin, topiramate and ethosuximide remained unaffected in the presence of caffeine, caffeine may act as an antagonist of the anticonvulsant properties of these AEDs.[30,35,40,41] Another, more straight-forward explanation of the pharmacodynamic interaction between caffeine and AEDs is that caffeine increases seizure susceptibility, such that the need for AEDs indirectly increases, making it analogous to the interaction between any seizure precipitants. The concentrations of phenytoin (plasma concentration) and zonisamide (brain concentration) were significantly lowered in caffeine treated mice compared to untreated mice, showing pharmacokinetic effects of caffeine on their anticonvulsant potency.[31]

### Quantitative analysis

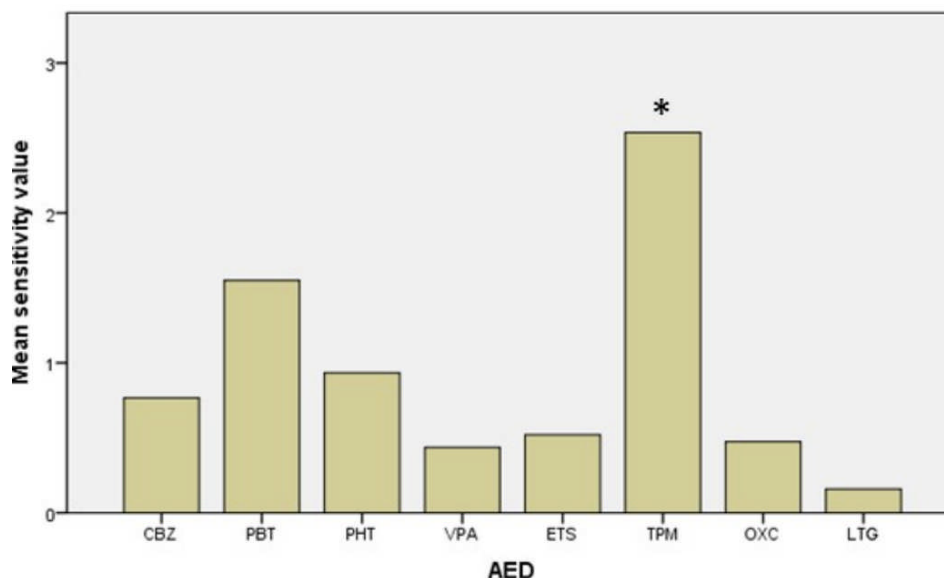
In our quantitative analysis, we assessed the effect of caffeine on the anti-epileptic potency of AEDs, whether this effect depends on the caffeine dose and differs between acute and chronic caffeine exposure. We also assessed the difference in sensitivity to the effects of caffeine, based on the mechanisms of action of the AEDs.[8–12,67–80]

Our analysis shows a medium [ $\eta_p^2 = .086$ ] effect of caffeine on the ED50 of the tested AEDs when compared to their corresponding control groups. The amount of caffeine and the change of ED50 values are positively correlated [ $F(4,43) = 16.122$ ,  $p = .004$ ;  $\eta_p^2 = .294$ ] (figure 2.1). The sensitivity of AEDs to caffeine varies greatly between AEDs [ $\omega^2 = .509$ ]. In post-hoc tests, topiramate is the most sensitive to caffeine ( $p < 0.05$ , for all AEDs except phenobarbital) with a mean sensitivity of 2.54 ( $SD = .59$ ) (figure 2.2). This means that per mg/kg caffeine administered, the ED50 value of topiramate was elevated by an average of 2.54 percent when compared to the control condition.

In general, AEDs were not more sensitive to acute caffeine administration than to chronic administration [Welch's  $F(1, 17.77) = 2.535$ ,  $p = .129$ ; est.  $\omega^2 = .029$ ]. Carbamazepine seems to be more sensitive than the other AEDs to chronic administration of caffeine when compared to acute administration [Welch's  $F(1, 4.914) = 71.034$ ,  $p < .0001$ ; est.  $\omega^2 = .579$ ].



**Figure 2.1:** The effect of different doses of caffeine on the  $\% \Delta ED50_{\text{treatment-control}}$  (estimated marginal means). General linear model univariate analysis was used. Covariates appearing in the model are evaluated at the following values: Seizure-inducing method = 1.51; N = 30.04; Administration frequency = 1.29.



**Figure 2.2:** Sensitivity of different AEDs to caffeine. One-way ANOVA was used. Dependent variable represented the corresponding sensitivity value (treatment condition). Heterogeneity of variances and unequal sample sizes were accounted for by Welch's test. Clonazepam excluded (n=1). Asterisk indicates the statistically significant differences ( $p < 0.05$ ) with every other AED except for PBT. (CBZ= carbamazepine; PBT= phenobarbital; PHT= phenytoin; VPA= valproic acid; ETS= ethosuximide; TPM= topiramate; OXC= oxcarbazepine; LTG= lamotrigine)

Overall, all AEDs seem to be affected by caffeine to some extent. The effect is strongest for topiramate. Only CBZ appears to be more sensitive to caffeine when administered chronically.

### 3.4 Clinical studies

Clinical studies on the relationship between caffeine and epilepsy are sparse. The existing studies are reviewed below.

#### 3.4.1. Clinical studies on the effect of caffeine on seizures

In an observational study, people with epilepsy (n=174), who were hospitalized after a seizure were asked about their caffeine intake prior to their seizure and their normal caffeine intake.[81] There was no significant increase of caffeine intake on a seizure-free day compared to the day prior to the seizure. There may be a role for caffeine withdrawal, as 18 people who habitually drank coffee reported not drinking coffee on the day preceding the seizure.

Two large questionnaire studies examined the effect of prolonged caffeine intake on seizures. The first included 105,941 nurses.[82] Every year, several health and lifestyle parameters were assessed, including epilepsy, seizures and caffeine intake. Between 1989 and 2005, a total of 95 seizures and 151 cases of epilepsy were recorded. Caffeine intake (mean 437 mg/day) was not significantly different between those reporting seizures or epilepsy and the total cohort. The effect of antenatal caffeine exposure on febrile seizures was assessed in a study comprising 35,596 children from women receiving antenatal care in Denmark, using a questionnaire on lifestyle during pregnancy.[83] There was no significant association between maternal caffeine intake and the risk of

febrile seizures in the first three months of life. Other types of seizures were not assessed in this study. A double-blinded randomized controlled trial of early high-dose (80 mg/kg) caffeine citrate therapy in preterm infants (n=174) to improve white matter microstructural development showed a trend towards increased seizure incidence and duration when compared to standard-dose (30 mg/kg) caffeine citrate treatment, but this was not significant.[84] In conclusion, antenatal caffeine exposure was associated with higher seizure susceptibility in animal studies,[50–52] but in humans there is currently no evidence that maternal caffeine-intake and caffeine-exposure in preterm infants increases the risk of epilepsy.[83,84]

#### **3.4.2. Interactions between caffeine and anti-epileptic drugs in humans**

Clinical studies on the interactions between AEDs and caffeine are also scarce. In one study, two groups of hospitalized people with epilepsy were given caffeine concomitantly with AEDs. The groups, either using mephenytoin (n=60) or a combination of mephenytoin, phenytoin and/or barbiturates (n=73) were given caffeine in an AED-to-caffeine ratio of 2:1 after baseline measurements of seizure frequency and EEG-recording. Caffeine reduced the number of seizures and epileptic EEG activity in people with partial seizures, but not in people with generalized seizures. The authors concluded that caffeine can be beneficial in anticonvulsant treatment for some individuals, but not all.[47]

In another study, caffeine and carbamazepine or sodium valproate were given to healthy volunteers.[85] The tissue half-life of carbamazepine doubled in the presence of 300 mg caffeine while its bioavailability was reduced by 32%. Others have shown that phenytoin and phenobarbital alter caffeine metabolism.[32,86] These findings suggest that interactions between caffeine and AEDs also occur in humans.

### **3.5 Pathophysiological mechanisms potentially underlying the effect of caffeine on seizures**

Seizure susceptibility is dynamic and depends on brain excitability (the ratio between inhibition and excitation of neurons) and seizure threshold at a given moment in time. Genetics probably influence (caffeine-related) seizure susceptibility in individuals, as suggested by a study in genetic mutated mice[75]. A recent study suggests that caffeine intake induces long-lasting epigenetic changes linked to neuronal excitability, which may underlie epileptogenesis.[87] Brain excitability is affected differently by caffeine depending on the brain area.[67,72–74,88–90] Several rat studies show that caffeine may act as a pro-convulsant by increasing ADs[91] and seizure duration [92] and behavioral seizure severity in response to electrical stimulation[93]. The seizure threshold, defined as the lowest current intensity to produce an AD, is not significantly lowered by caffeine, however, implying that caffeine interferes with the processes that terminate the electrical seizure activity and suggests that AD occurrence and duration do not necessarily reflect the seizure threshold.[93] Results from *in vitro* studies show that caffeine causes an increase in intracellular Ca<sup>2</sup> release and Ca<sup>2</sup> influx, which is linked to increased seizure activity through elevated neuronal excitability and synchronous firing of neurons.[67,88,89] Similarly, caffeine may facilitate seizures by changing potassium currents leading to a less negative membrane potential[90] and by binding with the inhibitory A1-receptor subtype for endogenous extracellular adenosine.[76,77] Adenosine has a role in seizure termination and postictal depression[94,95] including through control of free radicals[96,97] which are involved in epileptogenesis[68,97]. Long-term exposure to physiological doses (up to ~40 mg/kg/day) of caffeine can lead to neuroprotection by affecting the A1-[98–100] and A2-receptor[62,63,101] density and sensitivity to adenosine and caffeine[98]. These effects are area-[98] and age-dependent[98–100,102] in favor of caffeine-exposure in early life over adulthood, most likely resulting from increased A-receptor density changes due to elevated brain-plasticity at young ages. [98–100,102] Furthermore, as sleep deficiency is an independent seizure trigger [103] and caffeine is shown to counter fatigue[1] as

well as sleep-promoting effects of adenosine[7], caffeine's effect on seizure susceptibility is possibly related to its sleep-disrupting effects.

#### 4. Discussion

We provide a comprehensive overview on the complex interaction between caffeine and epilepsy. Caffeine seems to increase seizure susceptibility and protect from seizures, depending on the dose, administration type (chronic or acute) and the developmental stage at which exposure started. In animal studies, caffeine decreased the anti-epileptic effect of some AEDs particularly topiramate.

Acute caffeine exposure increased seizure susceptibility in several animal studies of good quality (high number of subjects, relevant control conditions and robust design)[29,30,45,46,49,57] and clinical case reports[16–23]. Chronic exposure to caffeine may be related to seizure provocation as was reported in several case studies[3,24–26], but no causal relationship can be established through these studies. A larger study showed that a daily dose of up to 400 mg caffeine (average five cups of coffee) did not make people with or without epilepsy significantly more prone to seizures.[82] Several robust animal studies show that chronic[54,61,98] and single[45,64] low-dose (ca. 5-20 mg/kg) caffeine exposure can protect rodents from chemically and electrically-induced seizures and their resulting damage, and one animal model showed that caffeine may protect against SUDEP[34]. No clinical studies, however, directly demonstrate protective effects of caffeine on seizure susceptibility in humans.[81–84]

The results of the systematic review[29,30,32–42] and quantitative analysis[30,35,36,38,40,41] showed that the sensitivity to the attenuating effects of caffeine differs among AEDs[8–10,67,68,70] and that caffeine, in contrast, can be beneficial in anticonvulsant treatment for some individuals.[47,65]

Chronic administration of caffeine does not affect seizure susceptibility as strongly as acute administration[3,16–26,29,30,45,46,49,57], suggesting the development of tolerance to A1- and A2A-receptor blockade by caffeine.[45,54,56,58,64,100,104] Chronic or acute administration of caffeine did not affect the sensitivity of most AEDs to caffeine[45,54,56,58,64] except for carbamazepine in which chronic administration of caffeine diminished the anti-epileptic potency significantly more than acute administration. This is possibly linked to a decrease of the bioavailability of carbamazepine.[85] Some AEDs discussed in this systematic review (clonazepam, diazepam, mephenytoin, felbamate, diazepam, zonisamide, tiagabine and gabapentin) could not be included in the quantitative analysis due to a lack of (sufficient) data. This impairs the reliability of the pairwise comparison tests and might have led to overestimation of the results of these tests.

Several pre-clinical studies report seemingly conflicting results, which may have been caused by differences in animal models of epilepsy[45,50,52,64,93], seizure-induction method[30,35], administration methods, caffeine doses or pro-convulsant doses.[45,60,61,64,93] Some sample sizes are small and may therefore be less reliable[29,30] Likewise, the number of studies available in which ED50 values can be derived is small, limiting the reliability of the quantitative analysis. The translation of the findings in animal studies to the clinical situation is challenging. Caffeine metabolism is different in animals and humans, and in many studies, including the studies in the quantitative analysis, the caffeine dose in animals is much higher than the equivalent average human caffeine consumption. Most clinical studies[81–83,103] measured caffeine intake in “units per day” but size and caffeine content likely varied. These studies also relied on self-reports, which are sensitive to recall and response biases. Selection bias may have been present in two studies as only women[83]



or Caucasian women[82] were included. If caffeine does not significantly affect seizure susceptibility in humans, lack of reports thereof could be a result of publication bias, as negative results are notoriously more difficult to publish.

#### *Future research*

Our review highlights the scarcity of clinical data on the caffeine – seizure/epilepsy interaction. Most of the current knowledge is derived from pre-clinical animal studies, a handful of clinical studies and several anecdotal case reports. Current data suggest a complex relationship between seizures, caffeine and AEDs, making clear clinical recommendations regarding the consumption of caffeine in people with, or at risk of, epilepsy impossible. The only recommendation that may be made is that when confronted with a sudden change in seizure pattern, or AED-resistant epilepsy, physicians should enquire about (changes in) caffeine consumption. In certain cases, changes in caffeine intake may explain such sudden changes.

Further studies are paramount to understand how the findings in animal models translate to the human situation, especially as the few existing clinical studies do not appear to support pre-clinical evidence of caffeine increasing seizure susceptibility. This may in part be due to sub-optimal design. Large observational population-based studies would form a good base to investigate whether caffeine, in doses consumed by the average person, increase the risk of seizures. They could also assess whether, as in animal models, caffeine can have beneficial effects in some cases, such as absence epilepsy[82] or seizures as a result of traumatic brain injury [63,105] and whether caffeine may have a preventative role in SUDEP[34]. It will also be important to investigate whether caffeine, in doses consumed by the average person, interferes with AEDs. In all cases, it will be vital to quantify caffeine intake accurately and to measure resulting caffeine plasma concentrations.

#### *Conclusion*

Pre-clinical studies suggest that caffeine increases seizure susceptibility. In some cases, chronic use of caffeine may protect against seizures. Caffeine lowers the efficacy of several AEDs, especially topiramate, but it is unclear how these findings in animal models can be translated to humans. Until clinical studies suggest otherwise, caffeine intake should be considered as a factor in achieving and maintaining seizure control in epilepsy.

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#### **Disclosure of Conflicts of Interest**

None of the authors has any conflict of interest to disclose in relation to this work.

#### **Ethical Publication Statement**

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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