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Coffee consumption and seizure frequency in patients with drug-resistant focal epilepsy

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ABSTRACT

Objective: To assess the relation between coffee consumption and seizure frequency in patients with drug-resistant focal epilepsy.

Methods: Cross-sectional analysis of data collected in the SAVE study, which included patients with drug resistant focal epilepsy during long-term EEG monitoring. Patients in whom both coffee consumption and data about seizure frequency, including focal to bilateral tonic-clonic seizures (FBTCS), were available were selected. Coffee consumption was collected using a standardized self-report questionnaire and classified into four groups: none, rare (from less than 1 cup/week to up 3 cups/week), moderate (from 4 cups/week to 3 cups/day) and high (more than 4 cups/day).

Results: 619 patients were included. There was no relation between coffee consumption and total seizure frequency ($p=0.902$). In contrast, the number of FBTCS reported over the past year was significantly associated with usual coffee consumption ($p=0.029$). Specifically, number of FBTCS in patients who reported moderate coffee consumption was lower than in others. In comparison with patients with moderate coffee consumption, the odds ratio (95%CI) for reporting at least 1 FBTCS per year was 1.6 (1.03-2.49) in patients who never take coffee, 1.62 (1.02-2.57) in those with rare consumption and 2.05 (1.24-3.4) in those with high consumption. Multiple ordinal logistic regression showed a trend toward an association between coffee consumption and number of FBTCS ($p = 0.08$).

Conclusions and relevance: Our data suggest that effect of coffee consumption on seizures might depend on dose with potential benefits on FBTCS frequency at moderate doses. These results will have to be confirmed by prospective studies.

INTRODUCTION

Although coffee includes number of bioactive compounds [1], its stimulant effect on the central nervous system is primarily related to caffeine. Caffeine increases arousal, vigilance, motor activity, information processing and reaction speed [2; 3]. These effects are mainly related to blockage of adenosine A1 and A2a receptors [3; 4]. When acting through A1 receptors, adenosine is an inhibitory modulator of neuronal activity, Extracellular adenosine concentrations are increased in the immediate aftermath of a seizure, suggesting that its release might play a role in seizure termination through neuronal activity suppression[5; 6].

However, the results of preclinical studies, which investigated the relation between caffeine administration and seizure threshold are conflicting, Acute administration of high dose of caffeine can thus trigger seizures [7; 8]. However, those very high doses (> 100 mg/kg) do not reflect usual caffeine consumption which is estimated to 37-417 mg/day in European adults [9]. Other data suggested that chronic exposure to lower dose (6-20 mg/kg) of caffeine can protect young and adult rodents from seizures and their complications, including risk of Sudden and Unexpected Death in Epilepsy (SUDEP) [10–12]. In patients with epilepsy, the relation between caffeine intake and seizure frequency remains unclear. Some case reports suggested that coffee, tea or energetic drink might trigger seizures [2; 3]. However, large-scale studies are lacking.

Using a cross-sectional analysis of the data collected in a multicenter trial, the aim of the present study was to assess relation between coffee consumption and seizure frequency, including the frequency of focal to bilateral tonic-clonic seizures, in a large population of patients suffering from drug-resistant focal epilepsy.

METHODS

The study was performed according to the STROBE guidelines for cross-sectional studies (supplementary table 1)

1. Study design and patients

The SAVE study is a multicenter stratified cluster-randomized controlled, parallel group, open-label trial, focusing on the management of antiseizure medications (ASMs) withdrawal during long-term video-EEG monitoring in patients with drug resistant seizures (NCT02679846). The primary objective of the SAVE study is to assess the impact of a standardized protocol of ASMs withdrawal during long-term video-EEG on the frequency of seizure-related serious adverse events occurring during these monitorings. A total of 22 French epilepsy monitoring units are participating to the study. The setting of the study includes a prospective evaluation phase, prior to randomization, during which the organizational characteristics, baseline activity of participating epilepsy monitoring units (EMUs), current management of ASMs withdrawal, and rate of serious adverse events of each participating center are evaluated. Then, half of the EMUs are randomized to the group where the standardized protocol of ASMs withdrawal is used systematically, while the other EMUs continue their current non-standardized practice of ASMs withdrawal, and serve as a control group. This cluster randomization is stratified on the age groups evaluated in each center, ie adults centers versus pediatric centers.

The inclusion criteria of the SAVE study are (i) patients (age ≥ 6 years) with drug-resistant focal epilepsy according to ILAE classification [13] (ii) who underwent long term monitoring using either video scalp EEG or intracranial EEG recordings. In the present study, we selected adult patients (age ≥ 18 years) with drug resistant focal epilepsy included in the SAVE study between 15/02/2016 and 31/10/2018 in whom both coffee consumption and data about seizure frequency were available.

Over this period, a total of 1029 patients were included in the SAVE study, including 176 children (age <18 years) and 853 adults. Among the 853 adults, data about coffee consumption (n=53), seizure frequency (all seizure types, FBTCS or both, n=93) or both (n=82) were missing and the epilepsy diagnosis after the long-term video-EEG monitoring was changed from focal epilepsy to psychogenic non-epileptic seizures in six patients. The 619 remaining patients were included in the present study. Characteristics of excluded patients, which are provided in Table 1, were similar to those of the patients included in the present study. The only exception was the proportion of patients who reported no FBTCS, which was higher in the excluded patients (86% vs 65%).

2. Standard Protocol Approvals, Registrations, and Patient Consents

The SAVE study was approved by ethics committee (CPP Sud Est II 2014–852). All patients gave written informed consent.

3. Data collection

For all included patients, we collected:

- (i) Age, gender, age at epilepsy onset, epilepsy duration. MRI data and detailed medical history, including mental status, psychiatric comorbidities and results of Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)
- (ii) Ongoing ASMs at study inclusion and total score of the Adverse Event Profile.
- (iii) Localization of the epileptogenic zone according to the combined results of all presurgical investigations.
- (iv) Monthly frequency of focal seizures during the three months preceding study inclusion and the total number of focal to bilateral tonic-clonic seizures (FBTCS) over the last 12 months. Considering both the proportion of patients

who did not report any FBTCS and the relation between number of FBTCS per year and risk of SUDEP that was previously reported [14], the number of FBTCS over the past 12 months were further classified into three groups: none, 1-3 FBTCS and > 3 FBTCS.

- (v) Habits regarding coffee consumption were collected at study inclusion [15]. The exact number of cups of coffee during the video-EEG monitoring in the epilepsy monitoring unit was not collected. Accordingly, the level of coffee consumption available in the present study corresponded to the patients' self-reported usual consumption over the last few months. We used a standardized self-report questionnaire where each included patient indicated her/his usual consumption as the following: no consumption, less than 1 cup/week, between 1 and 3 cups/week, between 4 and 6 cups/week, between 1 and 3 cups/day, between 4 and 6 cups/day and more than 6 cups/day. Usual coffee consumption was further classified into four groups: none, rare (from less than 1 cup/week to up 3 cups/week), moderate (from 4 cups/week to 3 cups/day) and high (more than 4 cups/day). Habits regarding coffee consumption in the evening were also collected as the following: never, in a minority of days with coffee intake, in a majority of days with coffee intake and every evening.
- (vi) Regular consumption of tobacco was collected. However, the precise number of cigarettes consumed each day was not included in the database.

4. Statistical analyses

First, the association between coffee consumption and others interest variables were studied using Kruskal Wallis test for numeric variables and Chi2 test (or Fisher if needed) for categorical variables.

Second, the relation between seizures of all type and of FBTCSSs with coffee consumption were studied. The average monthly frequency distributions of all seizures and of FBTCSSs were characterized by the presence of too many small values and large extreme values; especially, that of FBTCSSs was characterized by an inflation of zeros (Figure 1). Common models are not able to fit correctly such distributions, even models that allow for overdispersion (Poisson overdispersed model or negative binomial model). Moreover, rank regression did not seem suitable because of the large number of recurrent values.

Thus, in assessing the effects of various variables on the occurrence of seizures, it seemed relevant to consider the occurrences of all seizures and of FBTCSSs as categorical variables. According to the literature, FBTCSS values were considered in three categories: 0, 1 to 3, and >3 seizures per year. Regarding all seizures, the literature suggests no clear categories; thus, four categories were defined by the quartiles of the distribution. Then, univariate ordinal logistic regressions were used. Variable ‘Coffee consumption’ and all variables significant at $p < 0.1$ in univariate analyses (as per the likelihood ratio test for comparison of nested models) were included in a multivariate ordinal logistic regression. All statistical tests (2-tailed) with p-values less than 5% were considered significant, regardless of the number of tests performed. All analyses were carried out with R version 3.6.1.

5. Data Availability Statement

Anonymized data will be shared on request from any qualified investigator.

RESULTS

1. Patients’ characteristics

The 619 patients included 334 women (54%), had a mean age of 36.1 years [range 18-77] and a mean duration of epilepsy of 18.1 years. Localization of the epileptogenic zone could be

determined in 465 patients (75%) and was temporal in 346/465 (74.4%), frontal in 73/465 (15.7%), parietal in 16/465 (3.4%), occipital in 6/465 (1.3%) and peri-sylvian in 24/465 (5.2%). Patients received a median number of 2.0 ASMs at study inclusion (Interquartile range 1.0). Twelve patients were off treatment at study inclusion. As shown in table 2, ASMs combinations were highly variable across patients. The most frequently used ASMs were lamotrigine (n=226 patients), levetiracetam (n=213) and lacosamide (n=197), The total score of the adverse event profile of ASMs was available for 537 patients and the mean score was +/- SD was 42.7 +/- 11. NDDI-E score was available in 563 patients. The mean +/- SD score was 12.2 +/- 4.3, with 163 patients having a score ≥ 15 . A total of 121 patients (19.5%) reported tobacco consumption.

2. Habits regarding coffee consumption in included patients

Overall, 193 patients (31.2%) reported no coffee consumption, 40 (6.5%) less than 1 cup/week, 109 (17.6%) between 1 and 3 cups/week, 56 (9 %) between 4 and 6 cups/week, 121 (19.5%) between 1 and 3 cups/day, 71 (11.5%) between 4 and 6 cups/day and 29 (4.7%) more than 6 cups/day. Accordingly, usual coffee consumption was rare in 149 patients (24.1%), moderate in 177 (28.6%) and high in 100 (16.2%). The relations between usual coffee consumption and patients' characteristics are presented in table 3, showing that moderate and high consumption was greater in male and in patients who also reported tobacco consumption. Information about coffee intake in the evening was available for 573 patients, 384 (67%) of them indicated that they never consumed coffee in the evening whereas 130 (23%) reported evening intake in a minority of days, 22 (4%) in a majority of days and 37 (6%) every evening.

3. Relation between usual coffee consumption and monthly frequency of all seizure types

The median monthly frequency of all types of seizures during the three months preceding study inclusion was 4.33 (range 0-1551; interquartile range 2-13). According to the distribution of the

seizure monthly frequencies within the whole cohort, the patients were separated into four groups: 170 (27.5%) patients reported ≤ 2 seizures per month, 172 (27.8%) > 2 and ≤ 5 , 137 (22.1%) > 5 and ≤ 13 and 140 (22.6%) > 13 .

As shown in table 4, no relation was observed between coffee consumption and monthly frequency of all seizure types. The only factors associated with the monthly frequency of all seizure types in univariate analyses were the number of ongoing ASMs and the localization of the seizure focus, with greater seizure frequency in patients with extra-temporal epileptogenic zones in comparisons with temporal lobe epilepsy.

4. Relation between usual coffee consumption and number of FBTCS

217 patients (35%) reported at least one FBTCS in the past year, including 60 with 1 to 3 FBTCS per year (10%) and 157 with >3 FBTCS per year (25%). In patients with at least one FBTCS in the past year, the median FBTCS frequency was 1.0 per month (Interquartile range (IR) 1.75).

In univariate analyses, the number of FBTCS reported over the past year was significantly associated with usual coffee consumption ($p=0.029$), epilepsy duration ($p=0.03$) and current use of carbamazepine ($p=0.001$) (table 5). The number of FBTCS decreased with epilepsy duration and was lower in patients whose ongoing ASM included carbamazepine. As shown in figure 2, we observed a U-shape association with lower FBTCS frequency in patients who reported moderate coffee consumption than in others. In comparison with patients with moderate coffee consumption, the odds ratio (95%CI) for reporting at least 1 FBTCS per year was 1.6 (1.03-2.49) in patients who never take coffee, 1.62 (1.02-2.57) in those with rare consumption and 2.05 (1.24-3.4) in those with high consumption.

The analysis was reprocessed after separating moderate coffee consumption into two sub-groups, between 4 and 6 cups/week on one hand (n=56) and between 1 and 3 cups/day (n=121) on the other hand. The results were similar (p=0.04), with lower number of FBTCS in patients who reported between 1 and 3 cups/day than in the other.

When coffee consumption, epilepsy duration, and current use of carbamazepine were included in a multiple ordinal logistic regression. We observed a trend toward an association between coffee consumption and number of FBTCS which did not reach significance (p = 0.08). In comparison with patients with moderate coffee consumption, the odds ratio (95%CI) for reporting at least 1 FBTCS per year was 1.38 (0.89-2.18) in patients who never take coffee, 1.43 (0.90-2.3) in those with rare consumption and 1.94 (1.17-3.24) in those with high consumption. The number of FBTCS reported over the past year remained significantly associated with the current use of carbamazepine (0.57 (0.36-0.86). p=0.01) whereas association observed with epilepsy duration was not significant (0.89 (0.76-1.03). p=0.11).

5. Relation between usual coffee intake in the evening and seizure frequency

Habits regarding coffee intake in the evening were associated neither with the monthly frequency of all seizure types nor with the number of FBTCS (p = 0.54 and 0.93 respectively).

DISCUSSION

Using cross-sectional analysis of data collected in patients with drug resistant focal epilepsy undergoing long-term video-EEG monitoring, we found an association between coffee consumption and FBTCS frequency. This association varies according to the amount of coffee intake. Patients with moderate coffee consumption reported lower rate of FBTCS than those

with no coffee intake or with rare or high coffee consumption. In contrast, there was no relation between coffee consumption and monthly frequency of all seizure types.

Our study suffered from several limitations. Firstly, the statistical distribution of seizures, characterized by extreme values and high number of zeros, raised important issues. Statistical models that allow for overdispersion, such as Poisson overdispersed model or negative binomial model, could not fit correctly the distribution of seizures. In this context, we had to transform seizure frequency into categorical variable. Although the specific characteristics of our dataset did not allow alternative approach, we could not exclude misestimation of the relationship between coffee consumption and seizure frequency. While the associations between coffee consumption and FBTCS frequency were close in univariate and multivariate analysis with quite similar U-shapes, the estimated confident intervals were large, including 1 for the lowest levels of exposure in multivariate analysis. Dedicate studies are needed to confirm and estimate more precisely the strength and the shape of the associations between coffee consumption and FBTCS frequency. Secondly, the cross-sectional nature of this study did not allow for causal relations to be established. 228 patients who had participated to the SAVE study were excluded from the current study because of missing data. Although the results the baseline characteristics of excluded patients were similar, we could not exclude that missing data exerted an influence on the results. Specifically, we could not assess if the patients without data about coffee consumption did not complete the self-reported questionnaire for personal reason or because they never consumed coffee. Considering that FBTCS frequency was lower in patients without available data on coffee consumption, this latter hypothesis would have reinforced our results. The intake of coffee was based on self-reported questionnaire, which is sensitive to recall and response biases. We did not monitor the true coffee consumption during the long-video-EEG monitoring, an information which would have validated the patients' declarative coffee consumption. We did not have access to the true caffeine intake, which could only be

approximated through the measurement of the coffee consumption. Coffee consumption was measured as number of cups per day or week without considering the size of the cups. A study reported variations of caffeine content from 29 to 176 mg per cup [16]. Biological composition of coffee varies across brands and preparation methods. This is particularly true for the caffeine concentration, but also for the other bioactive components [17]. However, the details about the coffee brands consumed by each patient, including caffeine concentration, were not collected. We could not exclude that some patients reported coffee consumption without excluding use of decaffeinated coffee, especially in patients who indicated coffee intake in the evening. Lastly, other sources of caffeine including tea, soft drinks and energizing drinks have not been considered. Caffeine content in a cup of tea or soft drink is not negligible but remains lower than caffeine content in a cup of coffee [16; 18], whereas data showed that caffeine exposure from energy drinks has increased [19].

Our results are consistent with preclinical data which showed that chronic exposure of low doses (6 to 20 mg/kg) of caffeine decreased seizure susceptibility in young and adult rodents [11; 20; 21]. In humans, data about the link between epilepsy and caffeine intake are limited. In a case report, a patient with newly-diagnosed epilepsy reported drastic amelioration of seizure frequency when he stopped drinking 2L of ice tea per day [22]. Inaugural seizures have also been reported in young non epileptic women receiving oral or intravenous caffeine for post-lumbar puncture syndrome [23–25]. Based on available data, some authors have advised against coffee consumption in patients with epilepsy. While our results also suggest that coffee consumption might favour the occurrence of FBTCS at high dose (more than 4 cups a day), moderate consumption might have a protective effect. Among the few large-scale studies that have investigated the link between epilepsy and coffee, two also showed reassuring findings. An observational study of 174 patients hospitalized for epileptic seizures evaluated caffeine consumption on days with seizures compared with seizures free days [26]. No difference was

found between the caffeine intake 24 h prior to the seizure and the habitual consumption or the consumption on a seizure-free day. However, in the 121 patients diagnosed with epilepsy, there was a trend towards less caffeine ingestion prior to seizures as compared to the habitual intake. Another prospective study examined the association between caffeine intake and risk of seizure or epilepsy among women registered nurses [27]. Among 105 941 participants, long-term average intake of 400 mg of caffeine/day compared with <200 mg/day was not associated with greater risk of seizures or epilepsy.

Pathophysiological mechanisms potentially underlying the effect of coffee on seizures remain unclear, especially when considering opposite effects of acute and chronic caffeine administrations. Many studies have demonstrated that chronic exposure to caffeine leads to an upregulation of adenosine A1 receptor, possibly providing decreased neuronal excitability [28; 29]. It has also been shown that chronic oral caffeine consumption, as well as acute caffeine injection in rats increase plasma adenosine concentration suggesting a receptor-mediated regulation of the plasma adenosine concentration [30]. Caffeine consumption-related plasticity of the adenosine pathway might also play a role in limitation of seizure propagation, underlying our observation that moderate coffee consumption did not modulate the monthly frequency of all seizure types but showed a trend with decreased rate of FBTCS only. However, the very own effect of coffee can be difficult to appreciate since coffee intake is sometimes associated with other seizure precipitants as it may cause impaired sleep and emotional tension [1; 26]. In addition, we could not exclude a confounding effect of ASMs. Greater FBTCS rate is usually associated with more ASMs burden, which could result in more side effects such as fatigue possibly leading to more coffee consumption. On the other hand, we did not observed relation neither between number of ongoing ASMs and coffee consumption nor between the Adverse Event Profile total score and coffee consumption. Finally, either other bioactive components of coffee [1] or other compounds, which can be added to coffee by patients, might also have an

effect on seizure frequency. Preclinical studies suggested an anticonvulsant effect of steviol glycoside, natural constituents of stevia. Usual addition of sugar or sweeteners into coffee by patients was not collected in our study [31].

In a mouse model of SUDEP, it has been found that survival time was increased with caffeine administration after seizure, suggesting that seizure-related adenosine release might have a deleterious effect on respiratory function [32]. Adenosine is also involved in the control of autonomic function and can alter cardiovascular and respiratory functions through increased activation of brainstem adenosine receptors [33]. Interestingly, a recent study reported an association between usual coffee consumption and the risk of peri-ictal respiratory dysfunction in patients with drug-resistant focal epilepsy, with reduction of the peri-ictal hypoxemia with the increase in the amount of coffee consumed [15]. According to these data and the results of the present study, specifically investigating the potential relation of coffee consumption and risk of SUDEP might be important. To address this issue, long-term prospective epidemiological data with detailed collection of caffeine intakes, including consumption of coffee and/or other caffeine-containing beverages, will be needed. In addition, self-report questionnaires should be combined with plasma and/or urine monitoring of caffeine levels.

CONCLUSION

As observed in animal models of epilepsy, our data suggest that effect of coffee consumption on seizures might depend on the dose, with potential benefits on frequency of FBTCS at moderate doses in comparison with both lower and higher doses. Considering the number of people who regularly drink coffee, this observation might be important to integrate in the information discussed with patients about the external factors that might modulate seizure frequency. Based on our data and those reported previously, patients can be reassured and there

is no reason to contraindicate coffee consumption in patients with focal epilepsy. However, the level of consumption might be important to discuss in some patients. Because of the potential association between increased FBTCS frequency and high coffee consumption, patients with FBTCS may be advised to limit their coffee consumption to less than 4 cups per day. However, because of the methodological limitations of our study, formal association between coffee consumption and seizure frequency could not be established and a dedicated prospective study is required to confirm our observations.

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Figure 1. Average monthly frequency distributions of all seizures and FBTCSs.

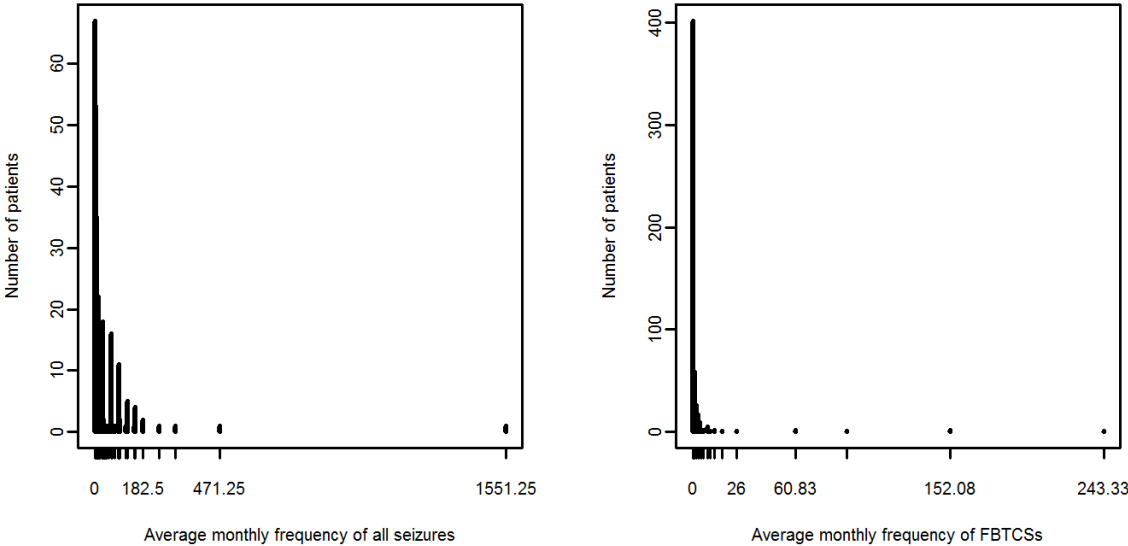


Figure 2: Association between coffee consumption and number of FBTCS over the past year.

Odds ratio (95%CI) were calculated using ordinal logistic regression, with moderate coffee consumption as reference.

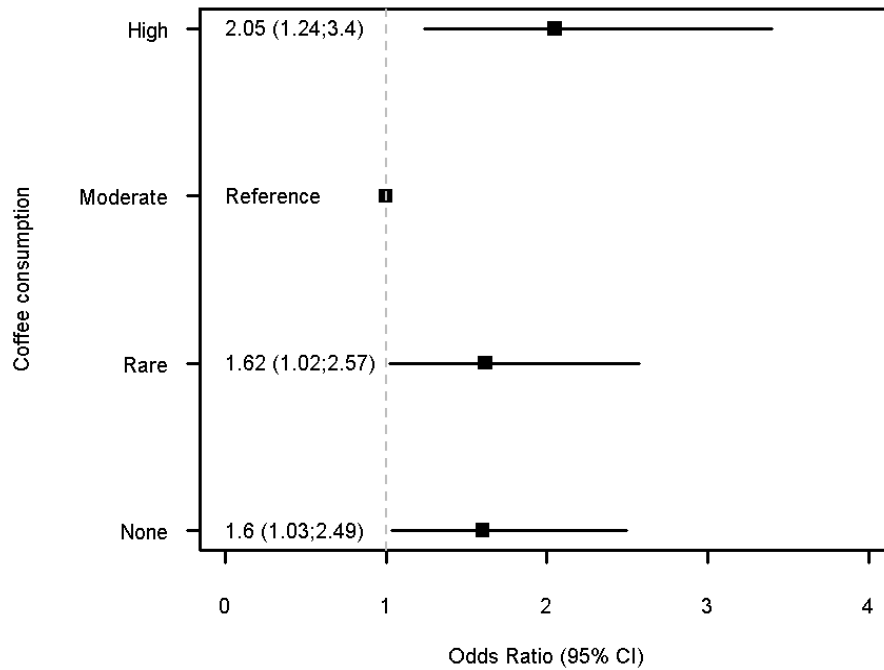


Table 1. Included and excluded patient's characteristics.

	Included patients		Excluded patients	
	n		n	
Age (years)	619	36.1 ± 11.6	228	35.5 ± 12.5
Gender (n.%)	619		228	
Male		285 (46)		114 (50)
Female		334 (54)		114 (50)
Coffee consumption (n.%)	619		93	
None		193 (31%)		35 (38%)
Rare		149 (24%)		23 (25%)
Moderate		177 (29%)		26 (28%)
High		100 (16%)		9 (10%)
Monthly seizure frequency	619	19.2 ± 71.6	53	21.5 ± 37.8
FBTCS	619		202	
none		402 (65)		174 (86)
1-3 per year		60 (10)		10 (5)
> 3 per year		157 (25)		18 (9)

Table 2: Ongoing antiseizure medications

	Patients	
	n	%
Lamotrigine	226	36%
Levetiracetam	213	34%
Lacosamide	197	32%
Carbamazepine	143	23%
Perampanel	117	19%
Clobazam	110	18%
Zonisamide	99	16%
Eslicarbazepine acetate	84	14%
Valproic acid	78	13%
Oxcarbazepine	63	10%
Topiramate	56	9%
Clonazepam	23	4%
Phenobarbital	23	4%
Pregabalin	16	3%
Phenytoin	7	1%
Vagabatrín	4	1%
Diazepam	3	0%
Gabapentin	3	0%
Brivacetam	1	0%
Ethosuximide	1	0%
Felbamate	1	0%
Primidone	1	0%
Retigabine	1	0%
Rufinamide	1	0%
Tigabine	1	0%

Table 3: Factors associated with coffee consumption

ASMs: antiseizure drugs. CBZ: Carbamazepine. TPM: topiramate. KW : Kruskal Wallis test

	N	Coffee consumption								p value (test)
		None		Rare		Moderate		High		
Number of patients (n.%)	619	193	31.2	149	24.1	177	28.6	100	16.2	-
Gender (n.%)	619									<0.001 (Chi2)
Male		66	23.2	77	27	78	27.4	64	22.5	
Female		127	38	72	21.6	99	29.6	36	10.8	
Age at epilepsy onset (years)	607	15.7 ± 9.6		18.3 ± 12.1		19.2 ± 12.8		19.1 ± 11.9		0.035 (KW)
Epilepsy duration (years)	607	16.0 ± 10.5		18.5 ± 11.2		19.2 ± 13.1		19.7 ± 13.1		0.065 (KW)
Number of ASMs (n.%)	616									0.349 (KW)
0		4	33.3	4	33.3	3	25	1	8.3	
1		27	37.5	19	26.4	17	23.6	9	12.5	
2		85	32.2	60	22.7	74	28	45	17	
3		60	30.0	52	26	61	30.5	27	13.5	
4		14	23.7	10	16.9	18	30.5	17	28.8	
5		3	37.5	4	50	1	12.5	0	0	
6		0	0	0	0	1	100	0	0	
Seizure Focus (n.%)	616									0.564 (Fisher)
Temporal		103	29.8	88	25.4	98	28.3	57	16.5	
Frontal		20	27.4	13	17.8	27	37	13	17.8	
Parietal		6	37.5	1	6.3	7	43.8	2	12.5	
Occipital		2	33.3	0	0	3	50	1	16.7	
Insula		10	41.7	4	16.7	5	20.8	5	20.8	
Multifocal		7	35	7	35	4	20	2	10	
Unknown		44	33.6	36	27.5	32	24.4	19	14.5	
Tobacco consumption (n.%)	619	22	18.2	22	18.2	46	38	31	25.6	<0.001 (Chi2)
Current use of CBZ (n.%)	619	36	25.2	33	23.1	52	36.4	22	15.4	0.101 (Chi2)
Current use of TPM (n.%)	619	17	30.4	13	23.2	16	28.6	10	17.9	0.986 (Chi2)
NDDIE	563	12.1 ± 4.0		12.0 ± 4.6		12.4 ± 4.2		12.2 ± 4.3		0.682 (KW)

Table 4. Factors associated with monthly frequency of all types of seizures in univariate analyses

ASMs: antiseizure drugs. CBZ: Carbamazepine. TPM: topiramate

	N	≤2 per month		2 to 5 per month		5 to 13 per month		> 13 per month		OR (CI95%)	p value of the ordinal logistic regression
Number of patients (n.%)	619	170	27.5	172	27.8	137	22.1	140	22.66	-	-
Coffee consumption (n.%)	619										
None		58	30.1	50	25.9	43	22.3	42	21.8	0.89 (0.61;1.28)	0.902
Rare		39	26.2	41	27.5	35	23.5	34	22.8	1 (0.68;1.48)	
Moderate		44	24.9	57	32.2	32	18.1	44	24.9	1	
High		29	29	24	24	27	27	20	20	0.92 (0.60;1.43)	
Gender (n.%)	619										
Male		76	26.7	83	29.1	61	21.4	65	22.8	1	0.916
Female		94	28.1	89	26.6	76	22.8	75	22.5	0.98 (0.2;1.22)	
Age at epilepsy onset (years)	607	16.8 ± 11.4		20.0 ± 12.5		17.6 ± 10.6		16.7 ± 11.6		0.97* (0.86;1.1)	0.619
Epilepsy duration (years)	607	18.0 ± 12.2		17.9 ± 12.5		18.2 ± 11.5		18.5 ± 11.5		1.02* (0.9;1.15)	0.688
Number of ASMs (n.%)	616									1.18 (1.02;1.38)	0.025
0		2	16.7	4	33.3	3	25	3	25		
1		19	26.4	19	26.4	17	23.6	17	23.6		
2		81	30.7	80	30.3	56	21.2	47	17.8		
3		57	28.5	51	25.5	42	21	50	25		
4		10	16.9	15	25.4	18	30.5	16	27.1		
5		0	0	2	25	0	0	6	75		
6		0	0	0	0	1	100	0	0		
Seizure Focus (n.%)	616										0.001
Temporal		95	27.5	98	28.3	88	25.4	65	18.8	1	
Frontal		11	15.1	18	24.7	15	20.5	29	39.7	2.26 (1.42;3.6)	
Parietal		4	25	4	25	2	12.5	6	37.5	1.57 (0.6;4.12)	
Occipital		0	0	2	33.3	2	33.3	2	33.3	2.57 (0.66;10.97)	
Insula		4	16.7	7	29.2	5	20.8	8	33.3	1.76 (0.84;3.75)	
Multifocal		5	25	5	25	7	35	3	15	1.08 (0.49;2.38)	
Unknown		49	37.4	38	29	18	13.7	26	19.8	0.7 (0.48;1.01)	
Tobacco consumption (n.%)	619	35	28.9	31	25.6	27	22.3	28	23.1	0.99 (0.69;1.42)	0.961
Current use of CBZ (n.%)	619	30	21	42	29.4	33	23.1	38	26.6	1.38 (0.99;1.93)	0.058
Current use of TPM (n.%)	619	12	21.4	14	25	14	25	16	28.6	1.44 (0.88;2.37)	0.143
NDDIE	563	11.8 ± 4.0		12.7 ± 4.7		12.4 ± 4.2		11.9 ± 4.1		1 (0.97;1.04)	0.798

*OR for 10 years

Table 5. Factors associated with annual number of FBTCS in univariates analyses.
ASMs: antiseizure drugs. CBZ: Carbamazepine. TPM: topiramate

	N	0	1-3 per year	> 3 per year	OR (CI95%)	p value of the ordinal logistic regression
Number of patients (n.%)	619	402 64.9	60 9.7	157 25.4	-	-
Coffee consumption (n.%)	619					
None		124 64.3	13 6.7	56 29	1.6 (1.03;2.49)	0.029
Rare		92 61.7	20 13.4	37 24.8	1.62 (1.02;0.57)	
Moderate		130 73.4	13 7.3	34 19.2	1	
High		56 56	14 14	30 30	2.05 (1.24;3.4)	
Gender (n.%)	619					
Male		176 61.8	33 11.6	76 26.7	1	0.18
Female		226 67.7	27 8.1	81 24.3	0.8 (0.58;1.11)	
Age at epilepsy onset (years)	607	17.9 ± 11.9	17.7 ± 10.2	17.8 ± 11.4	0.99* (0.86;1.14)	0.876
Epilepsy duration (years)	607	18.8 ± 12.4	17.7 ± 11.4	16.4 ± 10.9	0.86* (0.74;0.99)	0.0322
Number of ASMs (n.%)	616				0.88 (0.73;1.04)	
0		9 75	0 0	3 25	0.136	
1		46 64	7 9.7	19 26.4		
2		160 60.6	33 12.5	71 26.9		
3		136 68	13 6.5	51 25.5		
4		41 69.5	7 11.9	11 18.6		
5		7 87.5	0 0	1 12.5		
6		1 100	0 0	0 0		
Seizure Focus (n.%)	616					
Temporal		232 67.1	30 8.7	84 24.3	1	0.145
Frontal		47 64.4	8 11	18 24.7	1.1 (0.65;1.83)	
Parietal		7 43.8	2 12.5	7 43.8	2.54 (0.96;6.72)	
Occipital		4 43.8	2 33.3	0 0	0.75 (0.11;3.32)	
Insula		20 83.3	0 0	4 16.7	0.43 (0.12;1.17)	
Multifocal		12 60	0 0	8 40	1.61 (0.61;4.02)	
Unknown		77 58.8	18 13.7	36 27.5	1.35 (0.9;2)	
Tobacco consumption (n.%)	619	71 58.7	15 12.4	35 28.9	1.35 (0.9;2)	0.141
Current use of CBZ (n.%)	619	109 76.2	9 6.3	25 17.5	0.51 (0.33;0.77)	0.001
Current use of TPM (n.%)	619	36 64.3	3 5.4	17 30.4	1.11 (0.62;1.94)	0.713
NDDIE	563	12.2 ± 4.2	11.3 ± 4.0	12.5 ± 4.5	1 (0.94;1.05)	0.827

*OR for 10 years

Appendix 1: Authors' contributions

Name	Location	Contribution
Julie Bourgeois-Vionnet	Hospices Civils de Lyon. France	Acquisition of data. Analyzed and interpreted the data. Drafted the manuscript for intellectual content
Philippe Ryvlin	Centre Hospitalo-Universitaire Vaudois. Lausanne. Switzerland	Design and conceptualized the SAVE study. Ensured the national co-coordination of the SAVE study. Drafted the manuscript for intellectual content
Mad-Hélénie Elsensohn	Hospices Civils de Lyon. France	Statistical analysis. Revised the manuscript for intellectual content
Véronique Michel	Hôpital Pellegrin. Bordeaux. France	Major role in the acquisition of data. Ensured the coordination of the SAVE study in respective center. Revised the manuscript for intellectual content
Luc Valton	University Hospital of Toulouse. France	Major role in the acquisition of data. Ensured the coordination of the SAVE study in respective center. Revised the manuscript for intellectual content
Philippe Derambure	Lille University Medical Center. Lille. France	Major role in the acquisition of data. Ensured the coordination of the SAVE study in respective center. Revised the manuscript for intellectual content
Valerio Frazzini	Assistance Publique-Hôpitaux de Paris. France	Major role in the acquisition of data. Ensured the coordination of the SAVE study in respective center. Revised the manuscript for intellectual content
Edouard Hirsch	University Hospital of Strasbourg. Strasbourg. France	Major role in the acquisition of data. Ensured the coordination of the SAVE study in respective center. Revised the manuscript for intellectual content
Louis Maillard	University Hospital of Nancy. Nancy. France	Major role in the acquisition of data. Ensured the coordination of the SAVE study in respective center. Revised the manuscript for intellectual content
Fabrice Bartolomei	Timone Hospital. Marseille. France	Major role in the acquisition of data. Ensured the coordination of the SAVE study in respective center. Revise the manuscript for intellectual content
Julien Biberon	University Hospital of Tours. Tours. France	Major role in the acquisition of data. Ensured the coordination of

		the SAVE study in respective center. Revised the manuscript for intellectual content
Jérôme Petit	La Teppe Epilepsy Center. Tain l'Hermitage. France	Major role in the acquisition of data. Ensured the coordination of the SAVE study in respective center. Revised the manuscript for intellectual content
Arnaud Biraben	University Hospital of Rennes. France	Major role in the acquisition of data. Ensured the coordination of the SAVE study in respective center. Revised the manuscript for intellectual content
Arielle Crespel	Epilepsy Unit. Montpellier. France	Major role in the acquisition of data. Ensured the coordination of the SAVE study in respective center. Revised the manuscript for intellectual content
Pierre Thomas	University Hospital of Nice. Nice. France	Major role in the acquisition of data. Ensured the coordination of the SAVE study in respective center. Revised the manuscript for intellectual content
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Philippe Convers	University Hospital of Saint-Etienne. Saint-Etienne. France	Major role in the acquisition of data. Ensured the coordination of the SAVE study in respective center. Revised the manuscript for intellectual content
Mathilde Leclercq	Hospices Civils de Lyon. France	Ensured the national co-ordination of the SAVE study. Revised the manuscript for intellectual content
Sébastien Boulogne	Hospices Civils de Lyon. France	Major role in the acquisition of data. Revised the manuscript for intellectual content
Pascal Roy	Hospices Civils de Lyon. France	Statistical analysis. Revised the manuscript for intellectual content
Sylvain Rheims	Hospices Civils de Lyon. France	Design and conceptualized study. major role in the acquisition of data. Ensured the national co-ordination of the SAVE study. Reviewed and analyzed the data. performed the statistical analyses. Drafted the manuscript for intellectual content

Appendix 2: List of co-investigators of the SAVE study

Name	Location	Role	Contribution
Philippe Ryvlin	Centre Hospitalo-Universitaire Vaudois. Lausanne. Switzerland	Scientific co-coordinator of the SAVE study	Study design and data analysis.
Sylvain Rheims	Hospices Civils de Lyon. France	Scientific co-coordinator of the SAVE study. Site PI	Study design and data analysis. Leads and coordinates communication and data acquisition among sites. Local coordination of the study. Patients' recruitment and data acquisition
Pascal Roy	Hospices Civils de Lyon. France	Member of steering committee	Statistical analysis
Catherine Mercier	Hospices Civils de Lyon. France	Member of steering committee	Statistical analysis
Mathilde Leclercq	Hospices Civils de Lyon. France	Project manager	Ensured the national co-ordination of the SAVE study
Marie de Montaudoin	University Hospital of Bordeaux	Site PI	Local coordination of the study. Patients' recruitment and data acquisition
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Lidia Afonso Delgado	University Hospital of Bordeaux	Site investigator	Patients' recruitment and data acquisition
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William Szurhaj	University Hospital of Lille	Site investigator	Patients' recruitment and data acquisition
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