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Abstract

Purpose:

The aim of this study was to investigate the relationship between alcohol use and seizures in acutely hospitalized patients, both isolated seizures as well as in diagnosed epilepsy. We wished to study the extent of the problem as well as the clinical characteristics of people with alcohol-related seizures in various seizure disorders, including their drinking pattern.

Method:

In this prospective observational case cross-over study, a semi-structured interview took place after admission in 134 consecutive patients (epilepsy 92, isolated seizures 42). Alcohol use was assessed by the Alcohol Use Disorders Identification Test (AUDIT) and daily alcohol unit consumption was recorded during the six days prior to the seizure. Sleep-time was recorded for the last three dates. The Hospital Anxiety and Depression Scale (HADS) was also applied. In 30 patients with epilepsy, non-adherence was assessed by therapeutic drug monitoring (TDM) at admission compared to a routine drug concentration/dose (CD) ratio when no seizure had occurred. C/D ratio <50% at admission was defined as non-adherence.

A follow-up telephone interview (alcohol intake/sleep) covering the same weekday was performed on a seizure-free day at least four weeks later.

Results:

28% of patients had AUDIT score ≥8 (hazardous drinking), 22% in epilepsy, 43% in isolated seizures (p=0.012). Alcohol consumption, non-focal seizures and HADS anxiety subscores were increased in isolated seizures, suggesting a withdrawal mechanism. A high percentage of binge drinkers had epilepsy (61%). In the 58 epilepsy patients with social drinking (excluded hazardous drinking/binging>10 units in one day), the alcohol intake was not different prior to seizure compared to follow-up, downgrading the role of modest alcohol intake as a seizure precipitant in epilepsy. However, in 10 of the 19 patients with idiopathic generalized epilepsy (IGE), binge drinking had occurred within the last two days prior to seizure.

Sleep loss prior to the seizure was associated with hazardous dinking. Non-adherence was present in 13 of 30 patients with TDM; 8 were hazardous drinkers (75%). In the 22 with AUDIT<8, non-adherence was present in 7 (32%) (n.s.).

Conclusion:

Alcohol is a major seizure precipitant in the context of hazardous drinking and withdrawal. Occasional social drinking in people with predominantly focal epilepsy is an uncommon cause of seizure breakthrough, but binge drinking prior to seizure admissions in IGE is common. In people with epilepsy, alcohol, sleep loss and non-adherence often occur in combination prior to a seizure. Alcohol alone should not always be blamed.

Preface

In the course of writing this student thesis, we have gotten a great introduction into the world of medical scientific work. Not only have we experienced the crushing feeling of learning that a result was derived from the wrong set of numbers and having to do the calculations all over again, but we have also experienced the joy of discovery and feeling of accomplishment after finally getting it (presumably) right. We have gotten a new understanding of the amount of work behind a scientific paper, and consequently gained a greater respect for medical research and the people behind it.

We would like to thank Dr. Christian Samsonsen, for providing us with the data used in this student thesis, as well as for guiding us in analyzing it, and for being an all-around great guy.

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Tåle Strindler and Harald Myklebust

1 Introduction

Despite having been investigated in several studies during the last decades, the relationship between alcohol consumption, seizures and epilepsy is still not sufficiently explored.

An epileptic seizure is a transient occurrence of signs or symptoms due to abnormal and excessive neuronal activity in the brain, whereas epilepsy is a disease of the brain characterized by repeated unprovoked seizures and the neurobiological, cognitive, psychological and social consequences of this condition (Fisher et al., 2005). The unprovoked seizures that characterize epilepsy must be distinguished from acute symptomatic seizures, which is a separate entity that has a precipitating factor with a close temporal relationship to the seizure that makes it possible to establish a likely causality (Beghi et al., 2010). The precipitating factor can be metabolic, toxic, structural, infectious or due to inflammation, and among them are alcohol abuse (Beghi et al, 2010). However, the same events that in their extreme form lead to acute symptomatic seizures, may in even small doses lead to seizures in people with epilepsy (Ferlisi & Shorvon, 2014; Nakken et al., 2005). Thus, the border between provoked and unprovoked seizures may sometimes be blurred in clinical practice, which makes it a challenge to distinguish between the two.

The management of seizure disorders aims to avoid further seizures. It can be divided into pharmacological and non-pharmacological options and should be tailored to the individual patient. Pharmacological treatment is focused on preventing the pathological hypersynchronized activation of neurons by using antiepileptic drugs (AEDs) to modulate excitatory and inhibitory functions in the brain, thus effectively raising the threshold for seizures. Nonpharmacological treatment options include the efforts to identify and reduce seizure precipitating factors (Aird, 1983; Nakken et al., 2005). Factors contributing to triggering of a seizure varies from patient to patient, and are in many instances unknown. Alcohol is a major seizure precipitant, which has been known since the times of Hippocrates (Lloyd, 1978).

The relationship between alcohol and seizures is complex (Bråthen, 1999; Hillbom, 2003). Alcohol has a direct impact on the two main systems of neurotransmitters in the CNS (Rang et al, 2011; Faingold et al, 1998):

1. *The glutamate system*: Alcohol inhibits ionotropic receptors, especially the NMDA-receptor at lower concentrations.

2. *The GABA-system*: Alcohol exerts an agonistic effect, mainly by affecting the GABA-alpha receptor subunit delta

The influence of alcohol on these two systems effectively leads to an alteration in the balance of excitatory and inhibitory impulses in the brain. The acute effects lower the seizure threshold, whereas the chronic effect may cause an opposite effect. Prolonged alcohol consumption leads to the development of tolerance and physical dependence. Compensatory functional changes lead to down-regulation of GABA receptors and increased expression of NMDA receptors. Thus, glutamate levels increase to maintain transmitter-homeostasis in the central nervous system. Withdrawal of alcohol may unmask these changes by causing a rapid excess of glutamate and a decline of the tonic inhibitory effect of the GABAergic delta subunits. The ensuing neuronal overactivity may lead to seizures and neuropsychiatric and autonomic complications in the form of delirium tremens (Jesse et al., 2016). Withdrawal seizures are usually of the generalized tonic–clonic type, but focal onset seizures may also be triggered by the same mechanism (Bråthen et al, 1999). They usually occur 6-48 hours after cessation of alcohol consumption (Rogawski, 2005).

Withdrawal seizures in the context of acute symptomatic seizures (Figure 1) have received much more scientific attention than the potential seizure precipitating effect of alcohol in people with established epilepsy. Notwithstanding, the association between epilepsy and substance use disorders is high. In a large Norwegian population-based study based on ICD-10 coding, the proportion of people with epilepsy registered with alcohol use disorders was 5.7 % compared to 1.3% in the population without epilepsy (relative risk 4.4). A high clinical awareness of this increased comorbidity is needed. It has also been suggested that weekend binge drinking and even a single dose of alcohol may increase the seizure susceptibility in vulnerable individuals with epilepsy (Hillbom, 1980). The safety of social alcohol consumption in people with epilepsy has been much debated. Some studies on this subject

show no effect of moderate consumption on seizure precipitation (Höppener et al., 1983; Gordon and Devinsky, 2001).

The aim of this study was to investigate the relationship between alcohol use and seizures in people acutely admitted to our hospital, both isolated seizures as well as in diagnosed epilepsy. We wished to study the extent of the problem as well as the clinical characteristics of people with alcohol-related seizures in various seizure disorders, including their drinking pattern.

2 Methods

2.1 Study design

Prospective observational case cross-over study

2.2 Patient material

Patients admitted for seizures and able to cooperate were consecutively included in the project. A semi-structured admission interview took place at a time when patients were clinically considered to be cognitively restored after the seizure. A follow-up interview by telephone was performed at least four weeks later at a time when there had been no seizure for >3days.

Interviews took part in a total of 179 admissions, but after exclusion of repeated admissions in the same patient, 169 unique patients were left for inclusion.

2.3 Data recorded at the interviews

2.3.1 Admission interview

Alcohol use was assessed by the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993) (Appendix I) and recording of daily alcohol unit consumption during the six days prior to the seizure (day 0 = seizure day and day -1, -2, -3, -4, -5). A standard alcohol unit was defined according to the Norwegian Directorate of Health as 12 -15 g of pure alcohol representing the amount of alcohol in a small bottle of beer, a glass of wine or a small liquor drink (Mørland, 2005). Hazardous drinking has been defined as AUDIT ≥8.

Total sleep-time on the date of the seizure and the last three days and nights before were recorded in a sleep diary by the interviewer.

Drugs ingested during the last week were recorded to identify agents which might influence the seizure threshold.

Additionally, the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983) was applied during the admission interview and anxiety and depression subscale-scores were calculated (Appendix II). A person can score between 0 and 21 for either anxiety or

depression. A cut-off point of 8/21 has been identified for both anxiety and depression (Bjelland et al., 2002).

The patients were also asked to score potential seizure precipitants for the present seizure on a visual analogue scale (VAS).

2.3.2 Follow-up interview

The following elements of the admission interview were repeated: alcohol use during the last six days prior to the interview (including the seizure day), a sleep record for the last four nights, as well as the history of medications used during the last week. The follow-up interview covered the same weekdays as the admission interview.

2.4 Definitions of drinking patterns

2.4.1. Hazardous drinking

Subjects with AUDIT scores $\geq$8 (AUDIT positive) were identified as hazardous drinkers. For this cut-off both specificity and sensitivity are considered greater than 90% (Conigrave et al. 1995, MacKenzie et al., 1996, Bråthen et al. 1999)

2.4.2. Alcohol abstainers

We identified abstainers by using the first question of the AUDIT-questionnaire (Appendix I).

2.4.3. Withdrawal seizures

An operational definition of the term withdrawal seizure was applied to seizures occurring in people with hazardous drinking (AUDIT positive) with last alcohol intake within the last two days prior to seizures (48-72h, day-1- and -2) (Bråthen et al., 1999).

2.4.4 Binge drinking

Binge drinking has been defined as a drinking pattern that brings blood alcohol concentration levels above 0.08 gram percent. In the average adult, this responds to ≥4 standard drinks for women, and ≥5 drinks for men in a single drinking occasion (during a 2 hour period). (National institute on alcohol abuse and alcoholism, 2004). In our material, the period of alcohol intake could not be precisely assessed. Hence, we defined binge drinking as an intake of ≥4 and 5 alcohol units in one or more of the five study days prior to seizure for men and women, respectively. To ensure an episodic drinking pattern, we excluded subjects from this group if they had reported a habitual intake of alcohol ≥4 days a week in the AUDIT questionnaire. Individuals with a diagnosed alcohol use disorder were also excluded.

2.4.5. Social drinking

Social drinking was defined as alcohol consumption in individuals without hazardous drinking and no binge drinking > 12 alcohol units/day during the study periods.

2.5 Seizures and epilepsy classification

We have endeavored to adopt the recent revisions of the classification of seizures and epilepsies by the International League Against Epilepsy (ILAE) (Fisher et al, 2017; Scheffer et al., 2017). For practical purposes we modified the seizure classification for use in this study. Focal onset seizures were defined as seizures with focal clinical features and in addition we included bilateral tonic-clonic seizures without perceived or observed focal onset when distinct localized findings were identified in EEG recordings and/or in brain imaging. Tonic-clonic seizures were considered generalized when occurring in the context of generalized epilepsy syndromes and/or associated with generalized epileptiform EEG discharges. Onset was classified as unknown in the absence of a diagnosed epilepsy syndrome and no localized EEG and imaging findings and no apparent focal onset presented by history. For this study, seizures with generalized and unknown onset were categorized together as non-focal onset seizures.

Patients using or starting AEDs for the prophylactic treatment of seizures during the admission were considered to have epilepsy.

2.6 Screening for treatment non-adherence

In patients using AEDs, serum concentrations were drawn in the emergency room and compared with drug-fasting control values at least two weeks later. Definite non-adherence was defined as a concentration dose ratio (C/D ratio) on admission of 50% or lower compared to the control C/D-ratio (Samsonsen et al. 2014).

2.7 Statistics

Statistical analyses were performed using SPSS, and the significance of observed crude differences between groups were determined using independent Student's t-test. Paired Student's t-test was used to determine differences between admission and control interviews. Chi-square test was used to compare proportions in between groups and between our study group and the general population.

3 Results

3.1 Patient overview

The number of admissions excluded or lost to follow-up is shown in Figure 1. A follow-up interview was performed in 152 patients, but due to missing alcohol data, only 144 admissions were left for analysis. Out of these, 140 patients had paired alcohol consumption data during the study periods. A total of 137 patients had complete AUDIT-data, whereas 134 patients had both paired consumption data and complete AUDIT-data. In the patients with paired consumption data, the mean age was 40.7 (SD 16.9), 82 were male (59%) and 58 were female (41%). Hazardous drinking (AUDIT ≥8) was found in 38 patients (28%); 33 were binge drinkers (25 %). Ten individuals had a diagnosis of alcohol use disorder at admission, and out of them, three had a diagnosis of epilepsy. Seventeen patients (13%) reported themselves as alcohol abstainers.

Non-AED medications with the potential to influence seizure propensity were used in eight patients (benzodiazepines 7, tramadol 1). Doses were low or stable, and their effects were considered negligible. The use of hypnotic drugs (predominantly alimemazine and zopiclone) was similar at admission and follow-up.

3.2 AUDIT characteristics

Table 1 shows the distribution of AUDIT-positive and AUDIT-negative patients among the patient groups, as well as the distribution of abstainers. The frequency of hazardous drinking was slightly higher in people with previously diagnosed epilepsy (24%) compared to new onset epilepsy (20%). The proportion of hazardous drinkers was significantly higher in the group with isolated seizures (43%, p=0.026)

Table 2 describes the characteristics of patients by AUDIT-category. Hazardous drinkers had higher HADS scores than AUDIT negative patients.

Table 3 shows the habitual alcohol consumption reported in the three first questions of the AUDIT questionnaire (AUDIT-Consumption).

3.3. Classification of seizures and epilepsy

Focal onset seizures were identified in 57% and non-focal seizures in 43%.

Table 4 shows the distribution of seizure types in relation to AUDIT status. No significant differences were demonstrated.

Among patients with epilepsy, generalized idiopathic (genetic) epilepsies were identified in 28 patients: 22 had epilepsy with generalized tonic-clonic seizures only, 3 had juvenile myoclonic epilepsy and 3 had absence epilepsies.

3.4 Epilepsy versus isolated seizures

Table 5 compares patients with epilepsy to patients with isolated seizures. Age and gender distribution was similar, but non-focal seizures were much more common in isolated seizures. Prior to seizure, the alcohol consumption was significantly higher in the group with isolated seizures. HADS scores were also higher. The difference in alcohol intake during the five days prior to follow-up and the in-group difference of consumption prior to seizure versus control were not significant.

3.5 Withdrawal seizures

As many as 24 (63%) of AUDIT positive seizures were classified as withdrawal seizures. Half of them were of focal type, and the other half non-focal. Withdrawal seizures were present in 12% of patients with epilepsy and in 28% of patients with isolated seizures ($p=0.02$). Table 6 compares withdrawal seizures to non-withdrawal seizures in the groups with epilepsy and isolated seizures. In the isolated seizure group 75% of withdrawal seizures were non-focal, whereas in epilepsy 75% were classified with focal onset.

3.6 Binge drinkers

Binge drinking was identified in 33 patients. As many as 20 (61%) were diagnosed with epilepsy, whereas 13 (39%) had isolated seizures. Of the bingers, 27% fulfilled the criteria for a withdrawal seizure, 2/3 were non-focal.

Twenty patients were binging during the two last days prior to admission. Among these, 14 had a diagnosis of epilepsy; 8 of them were diagnosed with a generalized epilepsy syndrome; six in other types of epilepsy (p=0.017). Of the 8 patients with generalized epilepsy syndromes, 6 had new onset epilepsy.

Table 7 shows the characteristics of binge-drinkers among patients with epilepsy and isolated seizures. Several significant differences were found between bingers and non-bingers in the epilepsy group. Binge-drinkers were younger than non-bingers, and non-focal seizures occurred more frequently. Mean alcohol intake in bingers with epilepsy was significantly higher in the five days prior to both admission and follow-up, but there was still a significant reduction of alcohol consumption from seizure to follow-up in contrast to non-bingers. Perceived impact of alcohol on seizure precipitation was higher in bingers than in non-bingers.

No significant differences between bingers and non-bingers were found in the isolated seizure group.

3.7 Weekday distribution of seizures

As many as 25% of seizures in all groups combined occurred on Monday (Table 8).

In the epilepsy group, seizures peaked on Monday (23%) and Sunday (21%). The highest alcohol intake was on Friday. In the isolated seizure group, the highest occurrence of seizures was on Monday (29%), whereas alcohol intake peaked on Saturday.

Among binge drinkers, the proportion of seizures on Sunday and Monday together was 52%, but the difference was not significant compared to non-bingers, p=0.23 (Table 9). The intake was increased during the weekend with a peak on Saturdays.

3.8 Anxiety and depression

The HADS-depression score was higher in the group with isolated seizures compared to the epilepsy group. No difference in anxiety score was found (Table 4). HADS-anxiety or depression scores were not different when comparing the abstainer group and the drinker group in patients with epilepsy (Table 10). When comparing bingers to non-bingers in the epilepsy and isolated seizure groups, no significant differences were found (Table 7). Among bingers there was a significantly higher VAS score on psychological stress among patients with isolated seizures compared to the epilepsy group. In the isolated seizure group, patients with AUDIT $\geq$ 8 had a higher perceived impact of psychological stress (VAS) on seizure precipitation (**p=0.042**) Table 10). In both the epilepsy and isolated seizure groups, patients with a HADS-anxiety score $\geq$ 8, perceived psychological stress (VAS) as a significantly more important seizure precipitating factor (p=0.001 and p=0.002, respectively) (table 10).

3.9 Drinking patterns prior to seizure and follow-up in various seizure groups

In figures 2-6 we compare the alcohol consumption during the five days prior to the admission and follow-up, in Fig 2 the overall intake in patients with epilepsy, in Fig 3 in social drinkers with epilepsy, in Fig 4 social drinking in the subgroup with generalized epilepsies, in Fig 5 the total intake in patients with isolated seizures, and in Fig 6 in binge drinkers.

Social drinking (alcohol consumers excluded hazardous drinkers) was present in 58 patients with epilepsy (Fig 3) and is analyzed in table 12.1. There was no significant difference for any period prior to admission and follow-up (-5 days, -2 days and -1 day). In patients with previously diagnosed epilepsy the consumption was similar prior to admission and follow-up. In the newly diagnosed patients who started AED treatment after the seizure, there was slightly less intake prior to follow-up. For the smaller group with generalized epilepsy syndromes (Fig 4), the intake was higher during the two days prior to seizure (Table 12.2).

For patients with isolated seizures mean intake was steady during each of the study periods (Fig 5), but significantly higher in the five days prior to seizure (Table 12.3). For bingedrinkers the consumption was also significantly different in the five-day period (p=0.006) (Table 12.4) with a peak on day -2 prior to seizure (Fig 6).

3.10 Other seizure precipitating factors

3.10.1 Sleep

Sleep time was not different between patients with epilepsy and isolated seizures in the three days before seizure or control (Table 5). However, the in-group difference in total sleep time three days prior to seizure versus control was significant in the epilepsy group (p=0.029).

Among patients with epilepsy no significant difference in sleep time prior to seizure was found between non-drinkers and drinkers, and no difference was found in sleep time prior to control (Table 11). No significant difference was noted in the abstainer group when comparing sleep prior to seizure vs control, whilst there was a significant difference in the drinker group from seizure to control (p=0.012).

Non-bingers in the epilepsy group slept significantly more the three days preceding follow-up compared to the three days prior to seizure (p=0.032) (Table 7). No significant difference was found in the binger group.

3.10.2 Antiepileptic drug non-adherence

A total of 43 patients with epilepsy used AEDs at admission. Paired serum concentrations of AEDs were available in 30 (Table 13). In 13, the values were consistent with non-adherence. Six of the patients with AUDIT$\geq$8 showed non-adherence (75%); all had serum concentrations <50% of control values (definite non-adherence), whereas seven with AUDIT <8 (32%) were non-adherent (p=0.11). Five of the six AUDIT positive patients with non-adherence were males.

4 Discussion

Alcohol is a neurotoxic agent that has been known as a major seizure precipitant for decades. The seizure inducing effect is evident in the context of chronic abuse, but the acute effects of partying or binge drinking are less clear and the influence of modest social drinking in people with epilepsy has largely been obscure.

The present student thesis elucidates the role of alcohol as a seizure precipitant in a clinical setting by using patients admitted to hospital for seizures as their own controls. Because alcohol intake rarely occurs alone, but rather in combination with a range of other potential seizure-promoting circumstances, its independent effect is sometimes difficult to sort out. The entire spectrum of admitted seizures was included in this study as the border between spontaneous and provoked seizures often is blurred, and we endeavored to assess the role of alcohol use and misuse in various seizure disorders.

4.1 Classification of patients by alcohol use

Nearly 30% of patients acutely admitted for seizures were hazardous drinkers (AUDIT $\geq$8). This is slightly less than in a previous study performed at our department approximately two decades ago (35%), but in that study a lower fraction of patients with diagnosed epilepsy were included (Bråthen et al., 1999). However, AUDIT scores $\geq$ 8 were considerably more prevalent compared to a recent population-based survey in Norway (17.5%) (Halkjelsvik et al., 2015).

In patients diagnosed with epilepsy, the percentage of hazardous drinkers was slightly above 20%, whereas it was nearly twofold in those with isolated seizures not fulfilling the diagnostic criteria for epilepsy, suggesting a high frequency of acute symptomatic seizures related to alcohol use in that group.

Abstainers constituted 13 % of those admitted for seizures, similar to the prevalence in the general Norwegian population (13%) (Halkjelsvik et al., 2015). This proportion was somewhat higher in subjects with previously diagnosed epilepsy (15%) and twofold compared to those with new onset epilepsy and isolated seizures. The percentage of abstainers among patients with known epilepsy was substantially lower than in the material

collected by Bråthen et al in the same area in the 1990s (27%) (Bråthen et al, 2000). Patients with epilepsy have previously been routinely advised to refrain from alcohol consumption, but these recommendations may have been less strictly applied during recent years to avoid unnecessary restrictions in the lives of these people.

4.2 Seizure classification

This study highlights practical problems of using the recently introduced and purely semiological ILAE classification (Fisher et al., 2017). The majority of epileptic seizures acutely admitted to hospital are bilateral tonic-clonic, but precise information about clinical details is rarely available. In addition to manifest semiological features, we have retained distinct focal EEG and brain imaging findings as signs of focal onset. We have lumped generalized seizures and seizures with unknown clinical onset together with bilateral tonic-clonic seizures without localized EEG and/or imaging features as non-focal seizures. As result, we categorized 57% as focal onset seizures and 43% as non-focal seizures. In AUDIT positive seizures, there were more non-focal seizures, whereas in AUDIT negative seizures the majority was focal, but the difference did not reach statistical significance. There was a significant difference in seizure distribution when comparing patients with epilepsy to patients with isolated seizures, with a markedly higher proportion of non-focal seizures in the group without epilepsy (Table 5).

4.3 The alcohol withdrawal seizure

The withdrawal seizure is a symptom mainly occurring during the early phase of withdrawal. The vast majority of seizures occur within 48 h of cessation of prolonged drinking (Victor and Brausch, 1967; Bråthen et al, 1999, Rogawski 2005). Seizures frequently occur as the first obvious sign of withdrawal prior to autonomic, motor and neuropsychiatric symptoms of the withdrawal syndrome (Figure 7). More than half of the individuals present with repeated seizures, and in up to 5% they may progress to status epilepticus (Rathlev et al, 2006). Untreated, withdrawal seizures represents a strong risk factor for progression into a severe withdrawal state with development of delirium tremens in up to 30% of cases (Victor and Brausch, 1967).

In the present material 63% of seizures in AUDIT positive individuals were classified as withdrawal seizures. The withdrawal seizure has been considered the prototype of a generalized onset tonic clonic seizure due to the pathophysiological mechanism of a widespread disruption of the balance between GABA and glutamate receptor function in the brain. Nevertheless, only half of withdrawal seizures was of non-focal type, whereas the other half was considered to be of focal onset type. This is in line with previous studies; up to 50% of alcohol withdrawal seizures have been associated with concurrent endogenous or exogenous risk factors, such as previous epilepsy, structural brain lesions or use of drugs with neurotoxic or withdrawal mechanisms (Rathlev et al, 2006, Bråthen et al., 1999, Jesse et al., 2017). Conceivably, vulnerable individuals may develop withdrawal seizures with a lower threshold than people with completely unaffected brains.

There was a significantly higher proportion of AUDIT-positive patients in the non-epilepsy group (Table 1). We also found a significantly higher alcohol intake in the five days prior to seizure in the non-epilepsy group, and a significant reduction in the mean consumption between the five days prior to seizure and the period prior to follow-up (Fig 5, table 12.3). This is suggestive of a high proportion of non-focal withdrawal seizures in patients with hazardous drinking.

4.4 Binge drinking

The majority of binge-drinkers had epilepsy (61%). This finding is important, as it suggests that binging more frequently provokes seizures in epileptic brains, whereas an occasional binge is less common prior to isolated seizures (Table 7). In bingers in the non-epilepsy group, hazardous drinking was present in the majority of patients, suggesting a withdrawal mechanism, whereas most patients with epilepsy were AUDIT negative. Unsurprisingly, the threshold for alcohol-provoked seizures appears to be lower in people with epilepsy who are characterized by an enduring predisposition to develop seizures.

The peak of the mean alcohol intake on the day prior to the seizure in binge drinkers is demonstrated in Fig 6. Of 20 the patients who were binging during the last two days prior to the seizure, 10 had idiopathic generalized epilepsy syndromes, corroborating the vulnerability to this effect in these patients. Moreover, binge-related seizures were

significantly associated with younger age. These findings confirm common clinical experience and provides a firm base for appropriate patient counselling.

4.5 Weekday variation

More seizures occurred on Mondays compared to any other days of the week. A total of 25% of seizures occurred on Mondays (Table 8). The clustering of seizures on Mondays, as well as a lower proportion of seizures during the weekend is conceivably partly related to the Scandinavian cultural norm of weekend binge drinking followed by a seizure on the first working day. In people with alcohol overuse, seizures usually occur with some latency within 48 hours after cessation of drinking (Rogawski, 2005; Jesse et al., 2017). However, 74% of all seizures on Mondays were AUDIT-negative, suggesting that other factors may be at play. Only six out of 34 people (18%) with seizures on Monday were binge drinkers. Other weekend-related factors, including a disrupted sleep pattern might be relevant. Similar findings were reported by Bråthen and coworkers in a previous study (Bråthen et al., 2000).

In the isolated seizure group, the highest occurrence of seizures was on Monday (29%), whereas alcohol intake peaked on Saturday (Table 8).

Among binge drinkers, more than 50% of seizures occurred on Sunday and Monday, while there was a quite low incidence on Friday and Saturday (Table 9). Conceivably, ongoing drinking protects against seizures while stopping drinking releases epileptic activity. Binge drinkers had a declining tendency to seizures throughout the week with a nadir at the weekend, whereas in the epilepsy groups the frequencies were fluctuating, but relatively stable through the workdays, then peaking during the weekend. This may account for partly different mechanisms. The withdrawal mechanism is obvious at play for isolated seizures, whereas other and partly obscure factors may be more relevant for seizure breakthrough in epilepsy.

4.6 Mood and anxiety

There is a bilateral neurobiological interaction between depression and epilepsy. People with epilepsy often develop depression, and depression is a risk factor for developing

epilepsy. The same is true for anxiety (Hesdorffer et al., 2012). Surprisingly, rather low mean HAD scores were found in patients admitted for seizures in this study (Table 2). Only for the anxiety subscores in patients with isolated seizures, we identified a mean value (8.2) above cutoff (8.0). This appeared to be related to hazardous drinking, (8.9), and was more pronounced in those with withdrawal seizures (10.3) as well as binge drinking (9.2). These findings could indicate that subjects with higher intake of alcohol had higher levels of anxiety. However, the results do not allow for any conclusion as to what might be the cause and effect.

Our hypothesis was that binge drinking could be related to mood and anxiety in opposite ways, either positively in joyful and unconcerned party people or negatively in miserable and worried individuals. Such a differentiation would obviously be important for the therapeutic approach to these patients. Mean HADS depression and anxiety scores did not differ between bingers and non-bingers and the standard deviations were not larger in the binge-drinking group. Thus, we found no evidence for a wider or two-peaked distribution in support of this hypothesis.

Mood and anxiety as measured by HADS did not appear to be significant factors in this study.

Only in the group with isolated seizures there was a significant difference in perceived effect of psychological stress on seizure precipitation between hazardous drinkers and social drinkers. Increased anxiety was associated with a higher perceived impact of stress.

4.7 Alcohol use in people with epilepsy

A surprisingly large proportion of patients with epilepsy admitted for seizures were identified with hazardous drinking, more than 20%, and with a similar distribution between focal and non-focal seizures. The prevalence of hazardous drinking was higher than in the general adult Norwegian population (18%), in spite of the common advice of considerable caution concerning alcohol intake. Remarkably, the frequency was even higher in people with previously diagnosed epilepsy (24%) compared to new onset epilepsy (20%).

The association between alcohol misuse and epilepsy is a substantial problem that needs more clinical and scientific attention. Alcohol use disorder is present in nearly 6% in the Norwegian adult population with epilepsy (Bakken et al., 2014). The risk of developing an alcohol use disorder is more than fourfold in people with epilepsy. The comprehensive management of these comorbid individuals is a multidisciplinary challenge. It includes careful counselling and information about the seizure precipitating effect of alcohol, particularly the concurrent withdrawal of alcohol and AEDs. These patients may receive inadequate assessment of their seizure disorder in substance abuse treatment facilities. They may also receive inappropriate care in epilepsy treatment settings due to an irregular lifestyle and poor adherence to both clinical appointments and prescribed AED treatment. It has been advised that prophylactic AED treatment should be limited to patients with recurrent epileptic seizures clearly unrelated to alcohol intake (Bråthen et al., 2005). The association between alcohol overuse and epilepsy needs more attention in clinical practice.

4.7.1 How much alcohol can a patient with epilepsy safely consume?

One previous clinical trial (Höppener et al., 1983) has addressed this particular issue; an intake of one to three drinks each containing 9.9 g ethanol twice a week did not increase seizure susceptibility in treated patients with predominantly focal epilepsy. This study was an innovative and interesting undertaking, but its scientific value is debated. The randomized and controlled crossover design was scientifically good, but the true effect of blinding was rather dubious. Other studies have suggested a seizure risk proportional to the alcohol intake level (Heckmatt et al., 1990; Mattson et al., 1990).

Sensitivity to seizure precipitants may vary between epilepsy syndromes. Generalized epilepsies, first of all juvenile myoclonic epilepsy, may be particularly prone to seizure precipitation by alcohol, commonly in combination with other factors, such as lack of sleep and stress (Pedersen and Petersen, 1998; da Silva Sousa, 2005; Syvertsen et al., 2014). Accordingly, the overall alcohol intake during the five days prior to admission was somewhat higher than prior to control in the unselected group of epilepsy patients (Fig 2)

It has been suggested that an intake of one to three standard alcohol units up to a couple of times per week is safe in the majority of people with well controlled focal epilepsy and in the

absence of any history of alcohol overuse (Bråthen et al., 2005). Our study supports the notion that modest social drinking is safe in most patients with epilepsy. In the 58 patients with social drinking (number adjusted for hazardous drinking and abstainers), alcohol consumption prior to seizure and follow up was not different (Fig 3, Table 12.1) (mean 0.5 compared to 0.4 unit). One obvious confounder in that analysis is that a large proportion of these patients represented new onset epilepsy and had started AED treatment prior to follow-up, influencing the tendency to seizures. In the subgroup with previously diagnosed epilepsy and ongoing treatment, alcohol consumption was practically identical prior to seizure and follow-up indicating that social drinking at least up to 2-3 alcohol units is safe for most patients (Table 11.1). Given that many people with epilepsy already are living with severe restrictions in their lives, it stands to reason that recommendations preferably should be grounded on evidence.

However, in patients with generalized epilepsy syndromes there was an intake peak the day prior to admission and the mean consumption was significantly higher in the two days prior to seizure (mean 1.0 compared to 0.5 unit) (Fig 4, Table 11.2). Although the number of patients was small, this finding nicely illustrates that people with idiopathic generalized epilepsy syndromes appear to be more susceptible to the seizure precipitating effects of alcohol. As already mentioned (4.4.), patients with generalized epilepsy were overrepresented in subjects with binge drinking prior to the seizure. Subgroups of people with idiopathic generalized epilepsy syndromes are burdened by psychosocial maladjustment (Camfield & Camfield, 2010). Caution is warranted for this particular group. An adverse personality profile, including impulsivity related to sleep/wake rhythm, decision-making and even substance and alcohol abuse have been reported, particularly in juvenile myoclonic epilepsy (Syvertsen et al, 2014).

4.8 Multifactorial seizure precipitation related to alcohol use

Epileptic seizures are often precipitated by a combination of factors. Alcohol intake may be associated with a range of such factors. Particularly in young people, binge drinking is frequently associated with intense partying, late nights and excitement, often with an

excessive array of stimuli, including disco flashing lights, non-alcoholic energy drinks and recreational drugs. The interaction between these various factors is difficult to disentangle.

4.8.1 Sleep

The relationship between sleep, seizures and alcohol is intricate. Significant differences between sleep time prior to seizure and follow-up was demonstrated in this study. Subjects with isolated seizures as well as patients with epilepsy slept less prior to admission, although this difference was only significant for patients with epilepsy. Insomnia is a core symptom of the alcohol withdrawal syndrome which is characterized by central nervous excitation, including autonomic symptoms of sympathetic overactivity, restlessness and anxiety (Jesse et al., 2017). It has been shown that even a single alcohol dose has a considerable influence on sleep architecture (Ebrahim et al., 2013). A recent study has demonstrated that alcohol ingestion and sleep loss are independent seizure precipitants in spite of being very frequently linked (Samsonsen et al, 2016).

4.8.2 Non-adherence to antiepileptic drug treatment

Unsurprisingly, non-adherence was more prevalent among patients with hazardous alcohol consumption. Definite non-adherence was identified in 2/3 of patients in this group by means of therapeutic drug monitoring, but the findings were not significant, conceivably due to the low number of subjects with available paired drug levels.

Non-adherence is a major cause of seizure breakthrough in people with epilepsy. Many patients are unaware of missed drug intake (Samsonsen et al., 2014). Alcohol consumption might certainly cause poor medication-taking behavior, together with coping difficulties of the seizure disorder, immature attitudes, and irregular lifestyle. When pseudo-drug resistant epilepsy is suspected, all these factors need clinical attention (Brodtkorb et al, 2016).

Drug intake lapses must of course be suspected in patients with epilepsy who have been drinking, particularly in young men. The alcohol alone should not always be blamed.

When a patient is hit by several seizure provoking factors at the same time, the risk for severe, recurrent and prolonged seizures is increased. Non-adherence has been identified as the single most common cause of status epilepticus in people with epilepsy (Lie et al., 2015), but the role of alcohol is very often obscure and should be explored.

4.9 Strengths and imitations of the study

A strength of this study is that all patients hospitalized for epileptic seizures in the present catchment area are admitted to one single neurological department. Nevertheless, a selection bias cannot be excluded as only patients able and willing to complete interviews and questionnaires could participate. Particular care was taken to interview patients as soon as possible after restoration of postictal cognitive symptoms in order to facilitate the ability to recall events prior to admission, but the optimal timing was sometimes difficult to assess.

The memory of the exact alcohol consumption in the preictal period may have been impaired by some degree of postictal confusion, benzodiazepine treatment or a hang-over effect. Reporting increasingly lower alcohol intake backward in time is natural as memory becomes increasingly blurred, but might lead to a wrong impression of increased consumption just prior to admission. Nevertheless, we consider that the intake peak on the days just prior to admission (Figures 2-4) is more likely to be related to weekday/weekend than a recall bias for the days more distant to the seizure, as in isolated seizures with probable withdrawal, there was no such peak (Fig 5). Unwillingness to share habitual excessive alcohol intake with the clinician is possible, but the case cross-over design should render this effect to be similar at admission and at follow-up. Moreover, a recent Swedish population-based validity study of AUDIT has shown excellent performance in identifying dependency, risk drinking and alcohol use disorder (Lundin et al., 2015)

5 Conclusion

The present prospective observational case cross-over study corroborates that alcohol is a major seizure precipitant in the context of hazardous drinking and withdrawal. In this study, hazardous drinking was identified in nearly 30% of patients acutely hospitalized with seizures. Withdrawal seizures are typically of non-focal type, but the withdrawal mechanism is often at play even in focal onset seizures.

The study indicates that binge drinking frequently is associated with loss of seizure control in people with epilepsy, even outside hazardous drinking, particularly in patients with idiopathic generalized epilepsies, Occasional social drinking in people with predominantly focal epilepsy (< 2-3 alcohol units) appears to be an uncommon cause of seizure breakthrough.

The seizure inducing effect of alcohol is well known and occurs commonly, but is often unrecognized in clinical practice. Alcohol intake is often trivialized by the patient, and may be left unexplored in the emergency setting due to postictal blunting of the patient which hampers a detailed history of recent events.

However, it is important to bear in mind that several seizure precipitants often occur in concert. Along with alcohol, non-adherence to AED treatment and sleep loss should receive attention. Blaming modest alcohol intake in people with epilepsy might be unjustified and may lead to undue restrictions of the individual’s social life.

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7 Tables

Table 1 Drinking patterns in patients with complete alcohol data

	Total (N=134)	**AUDIT <8 (N=96)**	**AUDIT ≥8 (N=38)**	**Mean AUDIT score**	**Abstainers (N=17)**
Epilepsy	92	72 (78%)	20 (22%)	4.5 (SD 3.9)	14 (15.2%)
- Previous epilepsy	*41*	*31 (76%)*	*10 (24%)*	*4.7 (SD 4.7)*	*10 (24.4%)*
- New onset epilepsy	*51*	*41 (80%)*	*10 (20%)*	*4.4 (SD 3.1)*	*4(7.8%)*
Isolated seizures	42	24 (57%)	18 (43%)*	9.8 (SD 8.5)	3 (7.1%)
		P=0.012*		P<0.001*	n.s.

AUDIT – Alcohol Use Disorder Identification Test

*Epilepsy vs isolated seizures

Table 2 Characteristics by AUDIT category in patients with complete alcohol data (n=134)

	AUDIT <8 (N=96)	**AUDIT ≥8 (N=38)**	**p**
Age	39.8 (SD 17.0)	40.5 (SD 15.5)	n.s.
Male	54 (56%)	25 (66%)	n.s.
AUDIT (n=134)	3.2 (SD 2.2)	13.7 (SD 6.9)	P<0.001
HADS depression (n=136)	3.2 (SD 3.0)	5.7 (SD 4.1)	P=0.001
HADS anxiety (n=136)	6.2 (SD 3.8)	8.9 (SD 4.6)	P=0.001
Perceived impact of alcohol on seizure precipitation (VAS 0-100) (n=121)	10.7 (SD 20.1)	47.0 (SD 36.2)	P<0.001
Perceived impact of psychological stress on seizure precipitation (VAS 0-100) (N=121)	39.0 (SD 34.4)	49.9 (SD 32.5)	n.s.
Mean intake 5 days prior to seizure	0.5 (SD 0.8)*	2.6 (SD 3.9)**	P=0.002
Mean intake 5 days prior to follow-up	0.3 (SD 0.5)*	2.4 (SD 4.5)**	P=0.009
Total sleep time 3 days prior to seizure	24.4 (SD 4.3)***	21.9 (SD 5.5)****	P=0.009
Total sleep time 3 days prior to follow-up	25.0 (SD 3.4)***	22.8 (SD 6.9)****	n.s.

AUDIT – Alcohol Use Disorder Identification Test

HADS - Hospital Anxiety and Depression Scale

VAS – Visual Analogue Scale

*****Paired t-test seizure vs follow-up p=0.041

****** Paired t-test seizure vs follow-up n.s.

*******Paired t-test seizure vs follow-up n.s.

****Paired t-test seizure vs follow-up n.s.

Table 3 Habitual alcohol use as self-reported in the three first questions of the AUDIT questionnaire in patients with and without epilepsy (N=137*)

Questions	Epilepsy (n=93)			Isolated seizures n=44	p All epilepsy vs isolated seizures
	All	Established (n=42)	New onset (n=51)		
1. How often do you have a drink containing alcohol?					
Never	14 (15%)	10 (24%)	4 (8%)	3 (7%)	n.s.
<= Monthly	30 (32%)	10 (24%)	20 (39%)	9 (21%)	n.s.
2-4 times/month	36 (39%)	17 (40%)	19 (37%)	19 (43%)	n.s.
2-3 times/week	10 (11%)	5 (12%)	5 (10%)	7 (16%)	n.s.
>=4 times/week	3 (3%)	0 (0%)	3 (6%)	6 (8%)	n.s.
2 How many drinks containing alcohol do you have on a typical drinking day?					
1-2	36 (39%)	19 (45%)	17 (33%)	10 (23%)	n.s.
3-4	28 (30%)	9 (21%)	19 (37%)	9 (21%)	n.s.
5-6	18 (19%)	8 (19%)	10 (20%)	18 (41%)	P=0.008
7-9	10 (11%)	5 (12%)	5 (10%)	2 (4%)	n.s.
>= 10	0 (0%)	0 (0%)	0 (0%)	5 (11%)	P=0.0009
3 How often do you have six or more drinks on one occasion?					
Never	48 (52%)	24 (57%)	24 (47%)	15 (34%)	n.s.
<Monthly	29 (31%)	9 (21%)	20 (39%)	18 (41%)	n.s.
Monthly	13 (14%)	6 (14%)	7 (14%)	8 (18%)	n.s.
Weekly	1 (1%)	1 (2%)	0 (0%)	2 (5%)	n.s.
Daily or almost daily	0 (0%)	0 (0%)	0 (0%)	1 (2%)	n.s.

*All patients with AUDIT-data.

Table 4 Seizure types in relation to AUDIT status

	AUDIT <8	AUDIT ≥8
All (N=134)	**N=96**	**N=38**
Focal onset	58 (60%)	18 (47%)
Non-focal	38 (40%)	20 (53%)
Subgroup: Epilepsy (N=92)	**N=72**	**N=20**
Focal onset	51 (71%)	14 (70%)
Non-focal	21 (29%)	6 (30%)
Subgroup: Isolated seizures (N=42)	**N=24**	**N=18**
Focal onset	7 (29%)	4 (22%)
Non-focal	17 (71%)	14 (78%)

AUDIT- Alcohol Use Disorders Identification Test

Table 5 Characteristics of patients with epilepsy and isolated seizures

	Epilepsy (N=97)	**Isolated seizures (N=43)**	**p**
Age	41.4 (SD 17.3)	39.3 (SD 16.1)	n.s.
Male	56 (58%)	26 (61%)	n.s.
Focal onset seizure	69 (71.1%)	11 (25.6%)	P<0.001
Non-focal onset seizure	28 (28.9%)	32 (74.4%)	P<0.001
AUDIT (n=134)	4.5 (SD 3.9)	9.8 (SD 8.5)	P<0.001
HADS depression (n=136)	3.4 (SD 3.1)	5.5 (SD 4.3)	P=0.006
HADS anxiety (n=136)	6.5 (SD 3.6)	8.2 (SD 5.1)	n.s.
Perceived impact of alcohol on seizure precipitation (VAS 0-100) (n=121)	17.0 (SD 25.8)	28.9 (SD 37.2)	n.s.
Average. intake 5 days prior to seizure	0.6 (SD 1.0)*	2.1 (SD 3.7)**	P=0.01
Average intake 5 days prior to control	0.5 (SD 1.0)*	1.7 (SD 4.3)**	n.s.
Total sleep time 3 days prior to seizure	23.9 (SD 4.4)***	23.1 (SD 5.4)****	n.s.
Total sleep time 3 days prior to control	24.6 (SD 4.0)***	24.2 (SD 6.4)****	n.s.

AUDIT – Alcohol Use Disorder Identification Test

HADS - Hospital Anxiety and Depression Scale

VAS-Visual Analogue Scale

*****Paired t-test seizure vs control n.s.

****** Paired t-test seizure vs control n.s.

*******Paired t-test seizure vs control p=0.029

****Paired t-test seizure vs control n.s.

Table 6 Characteristics of patients with withdrawal vs non-withdrawal in relation to seizure group

	Epilepsy (N=97)		**p**	**Isolated seizures (N=43)**		**P**
	Withdrawal (N=12)	***Not Withdrawal (N=85)***		***Withdrawal (N=12)***	***Not Withdrawal (N=31)***	
Age	41.3 (SD 14.9)	41.4 (SD 17.7)	n.s.	45.1 (SD 16.4)	37.0 (SD 15.7)	n.s.
Male	7 (58%)	49 (58%)	n.s.	7 (58%)	19 (61%)	n.s.
Focal onset seizures	9 (75%)	60 (71%)	n.s.	3 (25%)	8 (26%)	n.s.
Non-focal onset seizures	3 (25%)	25 (29%)		9 (75%)	23 (74%)	
AUDIT score (n=134)	9.7 (SD 2.1)	3.7 (SD 3.5)	P<0.001	18.3 (SD 9.2)	6.5 (SD 5.5)	P=0.001
HADS-depression	3.7 (SD 2.6)	3.3 (SD 3.1)	n.s.	8.1 (SD 4.3)	4.4 (SD 3.9)	P=0.010
HADS-anxiety	6.8 (SD 2.9)	6.4 (SD 3.8)	n.s.	10.3 (SD 6.1)	7.4 (SD 4.5)	n.s.
Perceived role of alcohol (VAS 0-100)	41.6 (SD 30.9)	13.1 (SD 22.9)	P<0.001	67.6 (SD 28.6)	14.6 (SD 29.1)	P<0.001
Mean alcohol intake 5 days prior to seizure	1.9 (SD 1.7)	0.4 (SD 0.7)	P=0.010	5.2 (SD 5.8)	0.9 (SD 1.2)	P=0.029
Mean alcohol intake 5 days prior to follow-up	1.0 (SD 0.8)	0.5 (SD 1.0)	n.s.	4.2 (SD 7.3)	0.7 (SD 1.6)	n.s.
Total sleep time 3 days prior to seizure	21.4 (SD 5.5)	24.2 (SD 4.2) *	P=0.045	22.6 (SD 6.2)	23.3 (SD 5.1)	n.s.
Total sleep time 3 days prior to follow-up	21.1 (SD 5.2)	25.2 (SD 3.5) *	P=0.001	28.1 (SD 5.1)	23.1 (SD 6.4)	n.s.

AUDIT – Alcohol Use Disorder Identification Test

HADS - Hospital Anxiety and Depression Scale

VAS-Visual Analogue Scale

*****p=0.014

Table 7 Characteristics of binge vs non-binge drinkers in patients with epilepsy and isolated seizures

	Epilepsy (N=97)		**p**	**Isolated seizures (N=43)**		**P**
	Binger (N=20)	***Not Binger (N=77)***		***Binger (N=13)***	***Not Binger (N=30)***	
Age	34.0 (SD 16.5)	43.3 (SD 17.1)	P=0.032	33.3 (SD 12.3)	41.8 (SD 17.1)	n.s.
Male	8 (40%)	48 (62%)	n.s.	9 (69%)	17 (57%)	n.s.
Focal onset seizures	10 (50%)	59 (77%)	P=0.019	2 (15%)	9 (30%)	n.s.
Non-focal onset seizures	10 (50%)	18 (23%)		11 (85%)	21 (70%)	
AUDIT (n=134)	6.9 (SD 3.0)	3.9 (SD 3.9)	P=0.004	12.9 (SD 8.7)	8.5 (SD 8.3)	n.s.
AUDIT-positive (n=134)	7 (41%)	13 (17%)	P=0.039	8 (62%)	10 (35%)	n.s.
HADS-depression	2.1 (SD 2.3)	3.6 (SD 3.1)	n.s.	6.5 (SD 3.7)	5.0 (SD 4.5)	n.s.
HADS-anxiety	6.4 (SD 3.0)	6.5 (SD 3.8)	n.s.	9.2 (SD 4.5)	7.7 (SD 5.3)	n.s.
Perceived role of alcohol (VAS 0-100)	43.5 (SD 31.5)	10.6 (SD 19.7)	P=0.001	44.9 (SD 38.4)	21.2 (SD 34.8)	n.s.
Mean alcohol intake 5 days prior to seizure	1.7 (SD 0.9)**	0.3 (SD 0.7)	P<0.0001	3.0 (SD 2.0)	1.7 (SD 4.2)	n.s.
Mean alcohol intake 5 days prior to follow-up	1.0 (SD 1.0)**	0.4 (SD 0.9)	P=0.013	4.2 (SD 7.2)	0.6 (SD 1.1)	n.s.
Total sleep time 3 days prior to seizure*	24.9 (SD 4.6)***	23.6 (SD 4.4)****	n.s.	21.3 (SD 6.3)	23.8 (SD 4.9)	n.s.
Total sleep time 3 days prior to follow-up*	24.6 (SD 3.8)***	24.6 (SD 4.0)****	n.s.	23.6 (SD 9.3)	24.4 (SD 4.9)	n.s.

AUDIT – Alcohol Use Disorder Identification Test**,** HADS - Hospital Anxiety and Depression Scale

VAS-Visual Analogue Scale

*****paired data obtained in 17 binge drinkers and in 69 non-binge drinkers with epilepsy, and 12 bingers and 26 non-bingers with isolated seizure

******p=0.006

***n.s.

****p=0.032

Table 8 Weekly distribution of seizure occurrence. Total and mean alcohol consumption by weekday.

	Epilepsy (N=97)	Mean alcohol units	Isolated seizures (N=43)	Mean alcohol units	Total (N=140)
Monday	23 (24%)	0.3	12 (28%)	0.9	35 (25%)
Tuesday	11 (11%)	0.4	7 (16%)	0.9	18 (13%)
Wednesday	8 (8%)	0.5	7 (16%)	1.5	15 (11%)
Thursday	13 (13%)	0.6	4 (9%)	1.3	17 (12%)
Friday	10 (10%)	0.9	5 (12%)	1.4	15 (11%)
Saturday	11 (11%)	0.7	4 (9%)	3.3	15 (11%)
Sunday	21 (22%)	0.4	4 (9%)	1.5	25 (18%)

Table 9: Binge drinking and seizure occurrence by weekday

	No binge drinking (N=107)	Mean alcohol units (SU)	Binge drinking (N=33)	Mean alcohol units (SU)	Total (N=140)
Monday	28 (26%)	0.2	7 (21%)	1.0	35 (25.0%)
Tuesday	13 (12%)	0.2	5 (15%)	0.8	18 (13%)
Wednesday	9 (8%)	0.6	6 (18%)	0.4	15 (11%)
Thursday	15 (14%)	0.5	2 (6%)	0.5	17 (12%)
Friday	14 (13%)	0.6	1 (3%)	1.2	15 (11%)
Saturday	13 (12%)	0.9	2 (6%)	4.7	15 (11%)
Sunday	15 (14%)	0.4	10 (30%)	1.8	25 (18%)

Table 10 Comparison of perceived impact of psychological stress on seizure precipitation (VAS) by HADS-anxiety score and AUDIT-category

	HADS-anxiety ≥ 8	**HADS-anxiety < 8**	**p**
Epilepsy (N=85)	53.7 (SD 32.7)	27.1 (SD 32.2)	p=0.001
Isolated seizures (N=40)	68.4 (SD 26.1)	40.3 (SD 27.0)	p=0.002
	AUDIT ≥ 8	**AUDIT < 8**	**p**
Epilepsy (N=94)	35.2 (SD 29.5)	36.5 (SD 36.1)	n.s.
Isolated seizures (N=40)	65.5 (SD 28.6)	46.1 (SD 28.6)	p=0.042

AUDIT – Alcohol Use Disorder Identification Test VAS – Visual analogue scale

Table 11 Alcohol abstainers vs consumers among patients with epilepsy

	Alcohol abstainers (N=13)	**Alcohol consumers (N=79)**	**p**
Age	46.7 (SD 17.0)	39.8 (SD 16.9)	n.s.
Male	8 (62%)	46 (58.2%)	n.s.
Focal onset seizure	11 (84.6%)	54 (68.4%)	n.s.
Non-focal onset seizure	2 (15.4%)	25 (31.6%)	n.s.
AUDIT (n=134)	0	5.2 (SD 3.7)	P<0.0001
HADS-depression	4.5 (SD 3.6)	3.1 (SD 2.8)	n.s.
HADS-anxiety	6.3 (SD 3.9)	6.4 (SD 3.6)	n.s.
Perceived impact of alcohol on seizure precipitation*	6.2 (SD 13.7)	18.5 (SD 26.8)	P=0.033
Mean intake of alcohol 5 days prior to seizure	0	0.7 (SD 1.0)	P<0.0001
Mean intake of alcohol 5 days prior to follow-up	0	0.6 (SD 1.1)	P<0.0001
Total sleep time three days prior to seizure**	25.8 (SD 4.1)	23.6 (SD 4.5)***	n.s.
Total sleep time three days prior to follow-up**	24.6 (SD 2.1)	24.5 (SD 4.0)***	n.s.

AUDIT – Alcohol Use Disorder Identification Test

HADS - Hospital Anxiety and Depression Scale

*data obtained in 10 abstainers and 73 consumers

**paired data obtained in 11 abstainers and 71 consumers

*** p=0.012

Tables 12 Drinking patterns prior to seizure and follow-up in relation to patient groups

Table 12.1 Social drinking in patients with epilepsy (n=58)

		Seizure	Follow-up	p
	Mean alcohol units in the preceding 5 days	0.46	0.38	0.299
	2 days	0.60	0.43	0.159
	1 day	0.56	0.40	0.324
Established epilepsy (n=21)	Mean alcohol units in the preceding 5 days	0.36	0.36	1.000
	2 days	0.73	0.67	0.822
	1 day	0.69	0.76	0.837
Newly diagnosed (n=37)*	Mean alcohol units in the preceding 5 days	0.52	0.40	0.234
	2 days	0.53	0.30	0.056
	1 day	0.49	0.19	0.090

*All patients were treated with an AED at follow-upl

Table 12.2 Social drinking in the subgroup with generalized epilepsy syndromes (n=19)

	Seizure	Follow-up	p
Mean alcohol units in the preceding 5 days	0.56	0.38	0.180
2 days	1.03	0.47	0.026
1 day	1.23	0.42	0.059

Table 12.3 Alcohol intake prior to seizure and follow-up in patients with isolated seizures (n=21)

	Seizure	Follow-up	p
Mean alcohol units in the preceding 5 days	0.82	0.43	0.048
2 days	0.60	0.19	0.157
1 day	0.67	0.24	0.388

Table 12.4 Alcohol intake prior to seizure and follow-up in binge drinkers (n=20)

	Seizure	Follow-up	p
Mean alcohol units in the preceding 5 days	1.73	1.01	0.006
2 days	2.58	1.58	0.179
1 day	3.05	1.65	0.178

Table 13 AUDIT and AED-adherence in 30 patients with paired therapeutic drug monitoring at admission and follow-up

AUDIT	Non-adherence	Adherence
≥8 (N=8)	75% (6)	25% (2)
<8 (N=22)	32% (7)	68% (15)

AUDIT – Alcohol Use Disorder Identification Test

AED – Anti-epileptic Drug

8 Figures

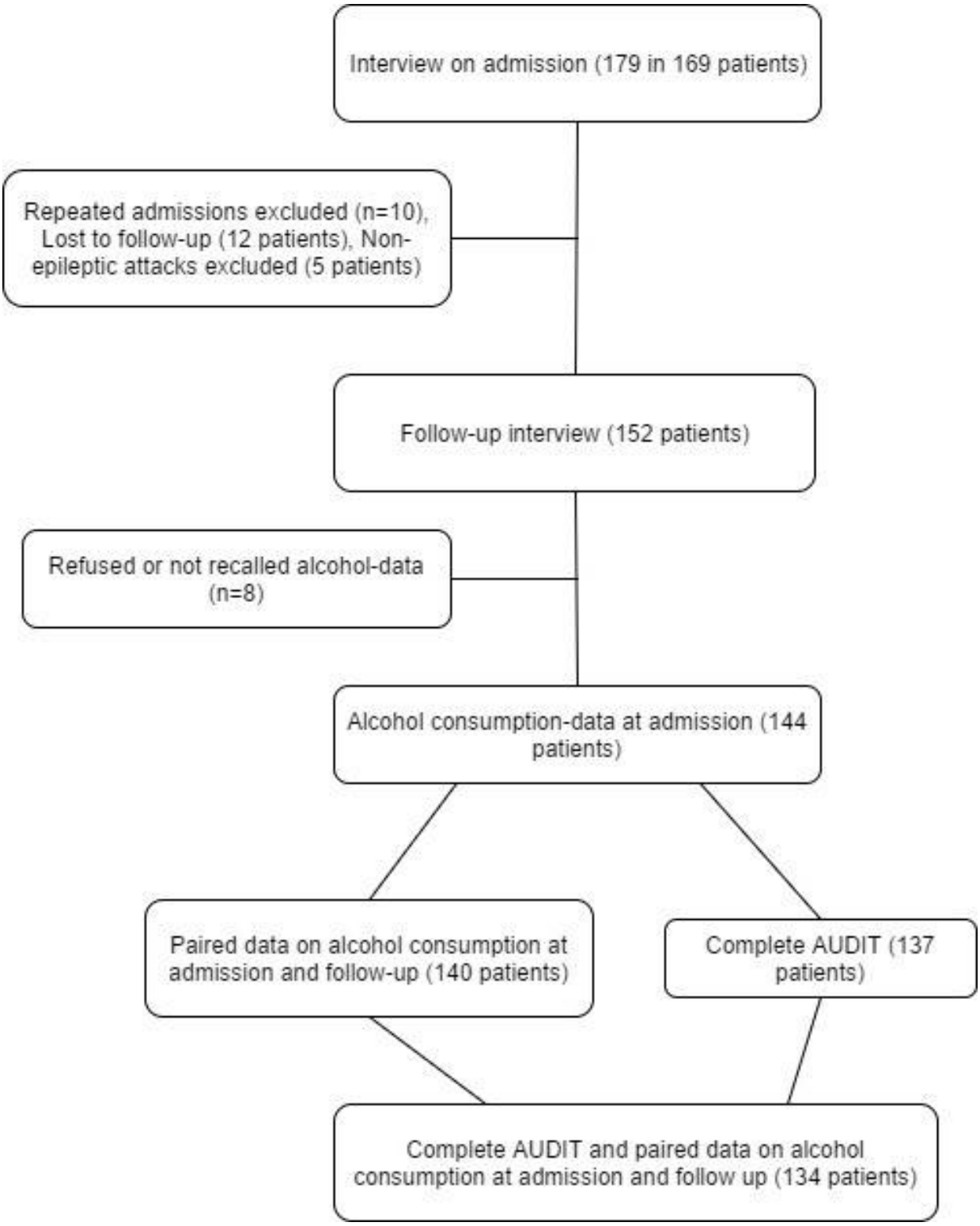
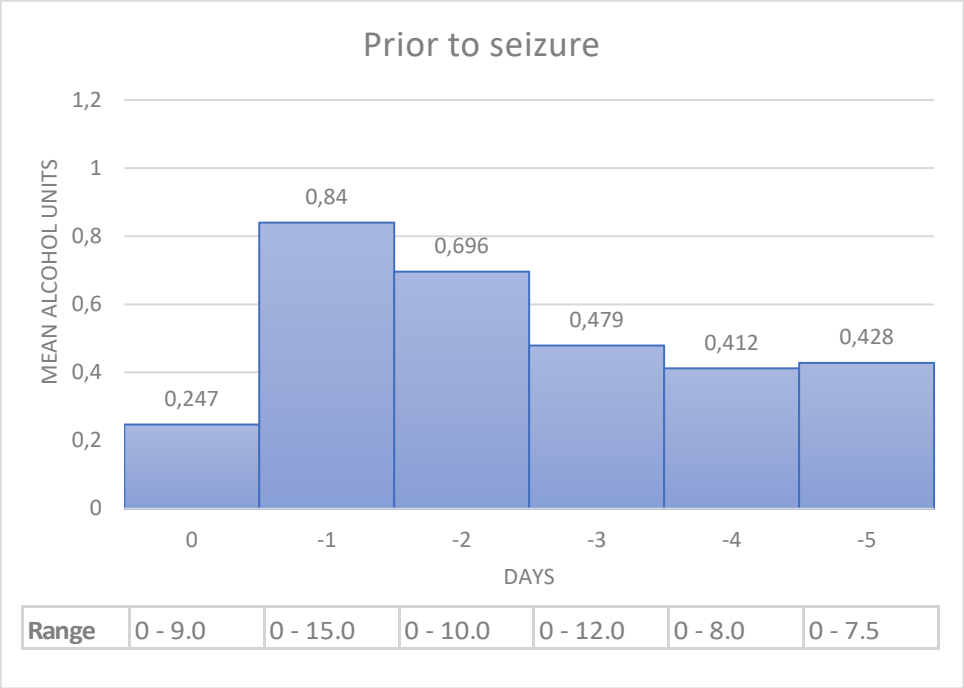


Figure 1. Inclusion flow chart



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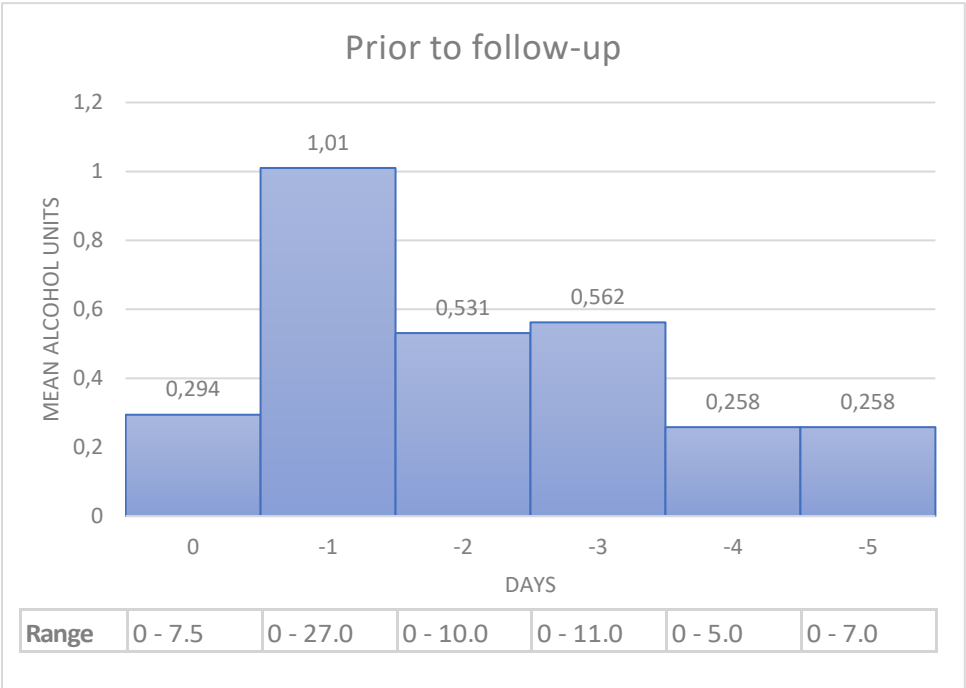
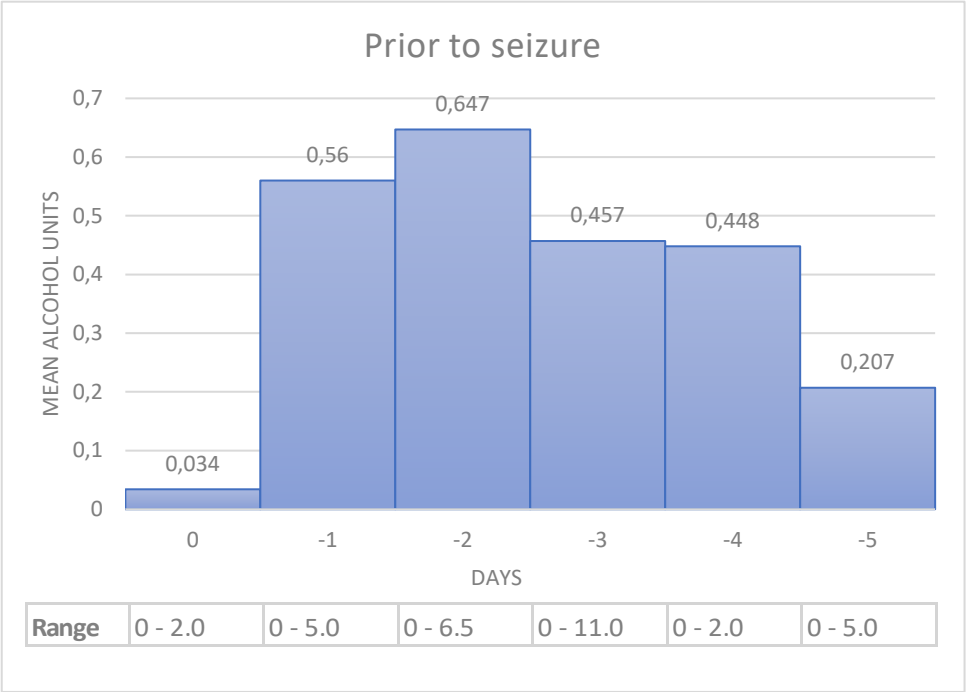


Range	0 - 7.5	0 - 27.0	0 - 10.0	0 - 11.0	0 - 5.0	0 - 7.0

Figure 2 Alcohol intake prior to seizure and follow-up in all patients with epilepsy (N=97)



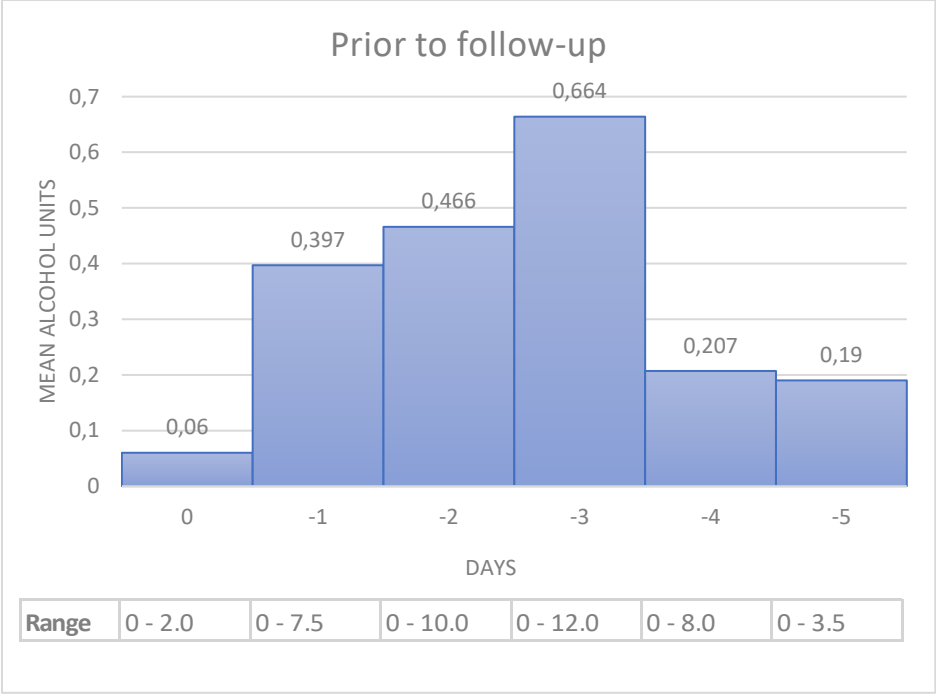
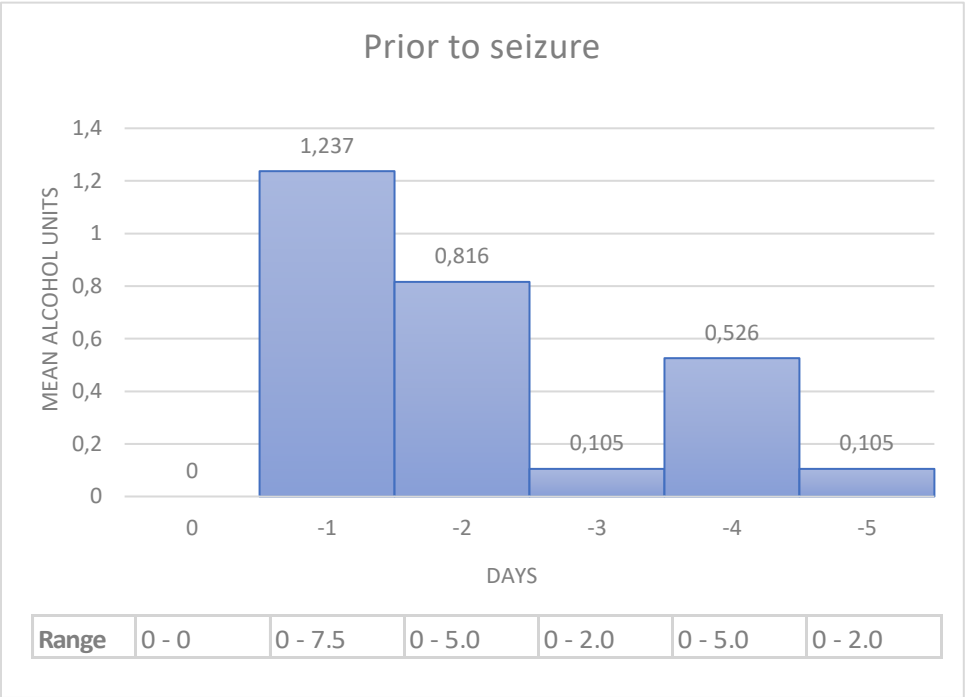
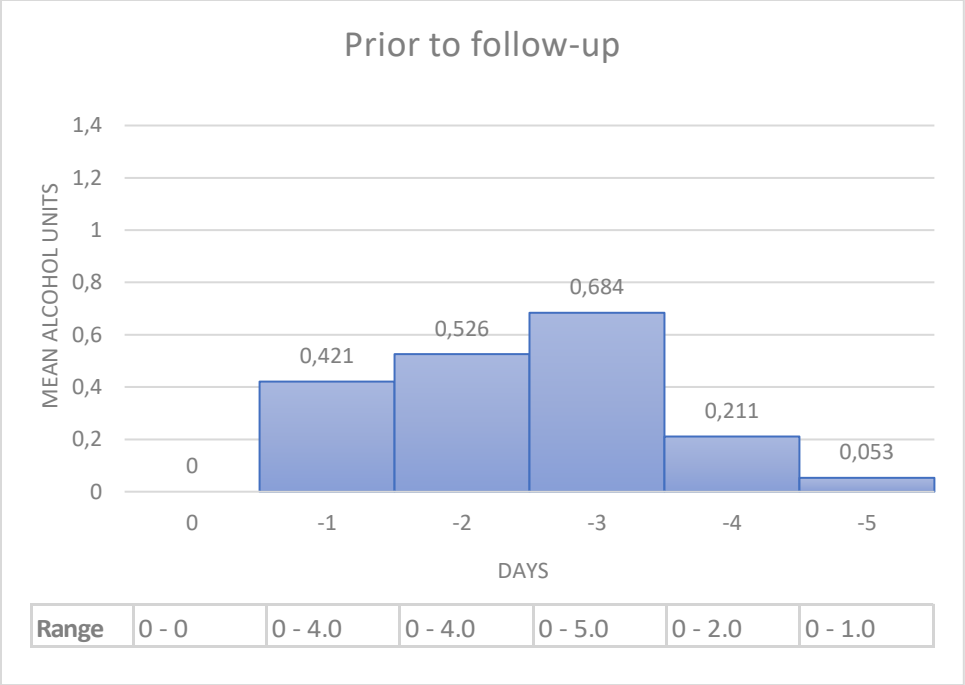


Figure 3 Social drinking prior to seizure and follow-up in patients with epilepsy (N=58)

(14 abstainers and 20 patients with a hazardous drinking excluded)

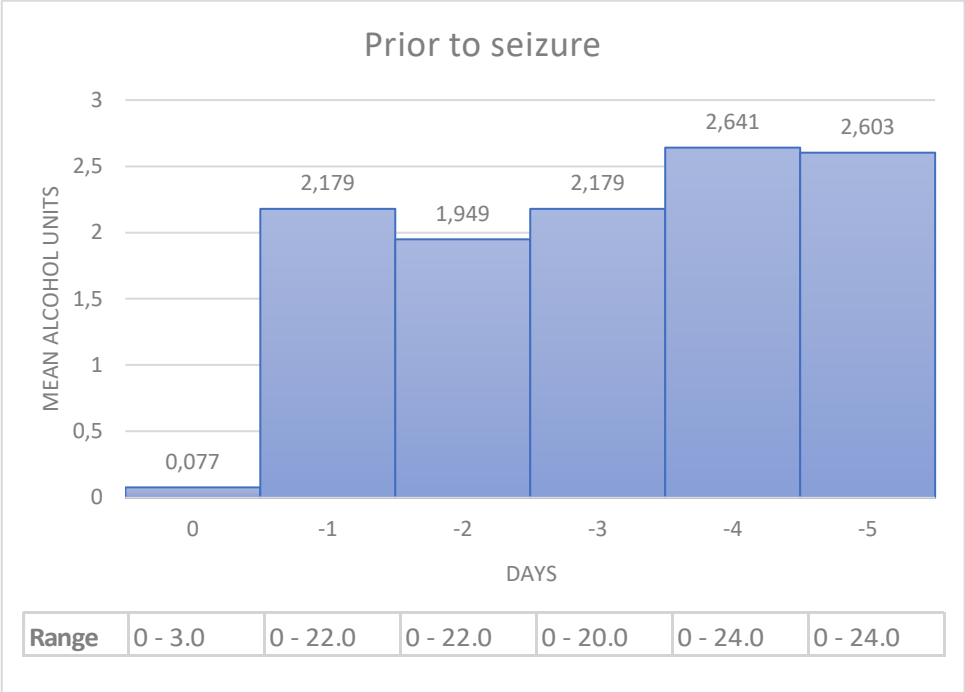


Range	0 - 0	0 - 7.5	0 - 5.0	0 - 2.0	0 - 5.0	0 - 2.0



Range	0 - 0	0 - 4.0	0 - 4.0	0 - 5.0	0 - 2.0	0 - 1.0

Figure 4 Social drinking prior to seizure and follow-up in patients with generalized epilepsy syndromes (N=19) (One with missing AUDIT-data, two abstainers and six patients with hazardous drinking excluded)



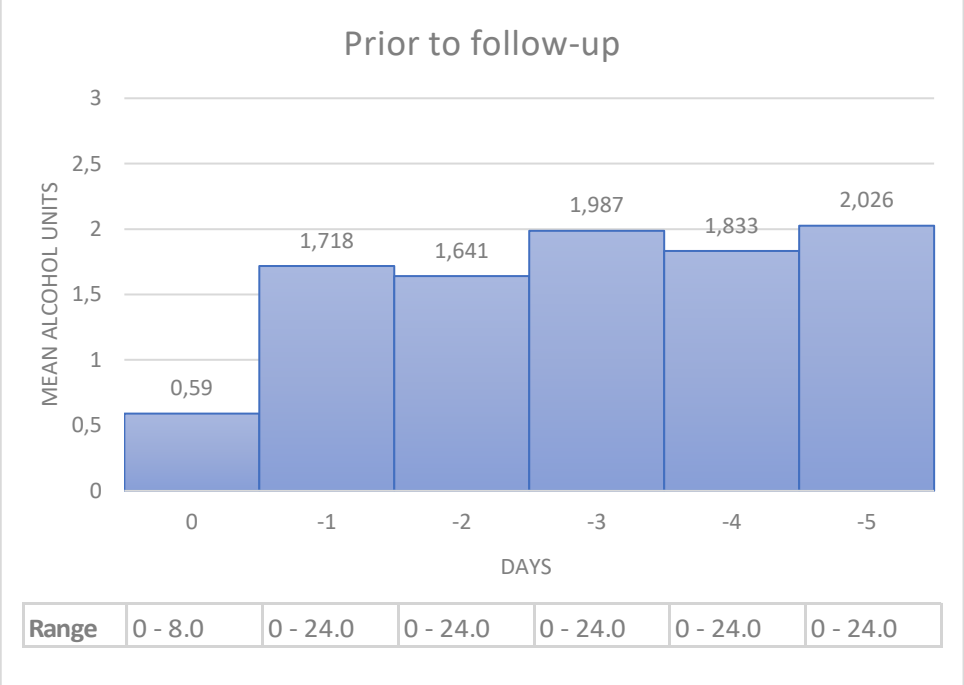
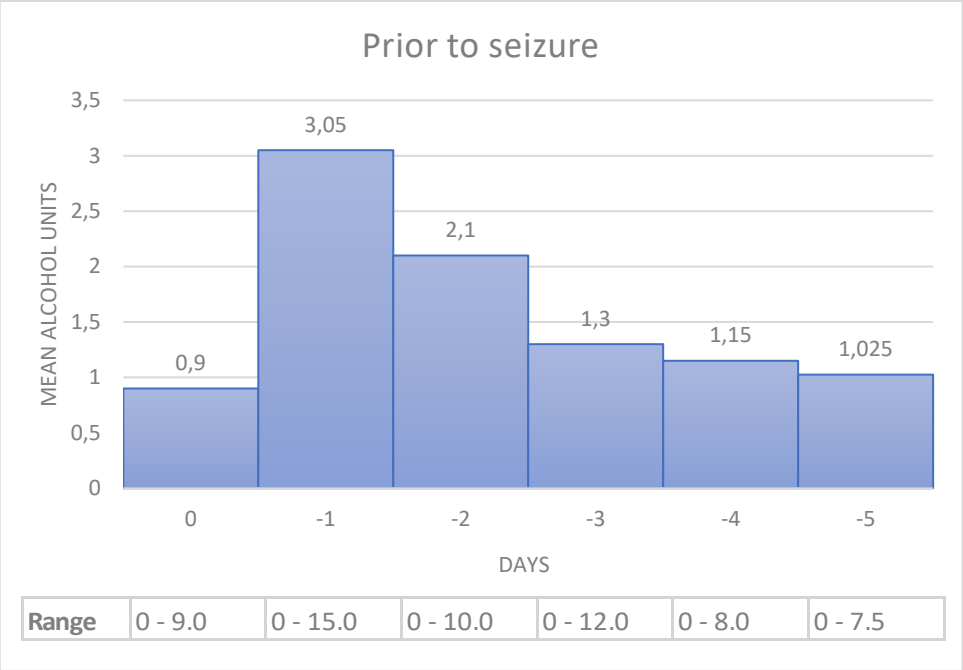


Figure 5 Alcohol intake prior to seizure and follow-up in patients with isolated seizures (N=39)

(Three abstainers excluded)



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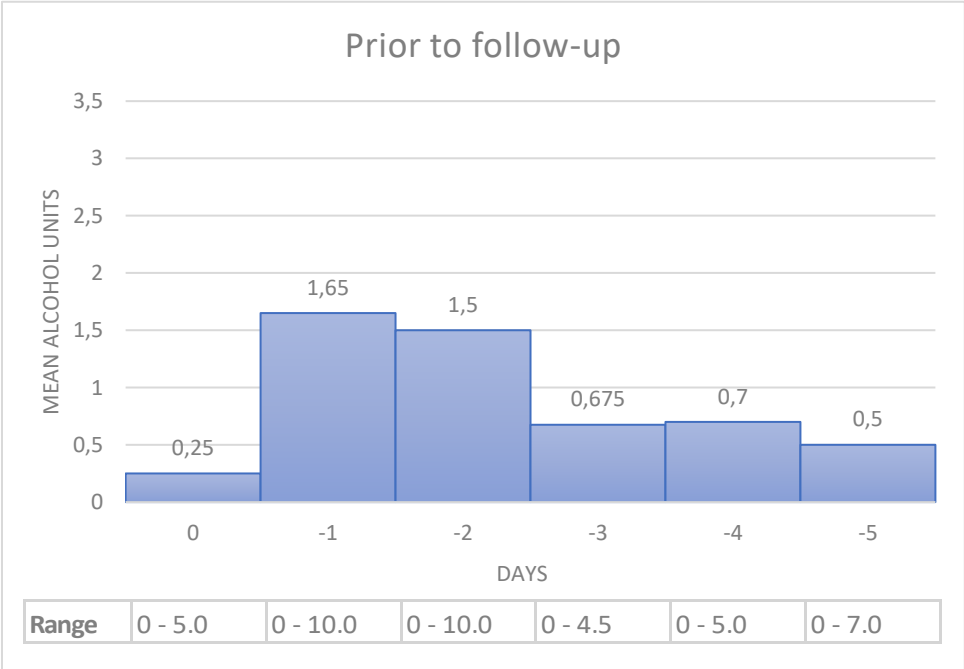

Range	0 - 5.0	0 - 10.0	0 - 10.0	0 - 4.5	0 - 5.0	0 - 7.0

Figure 6 Alcohol intake prior to seizure and follow-up in binge drinkers with epilepsy (N=20)*

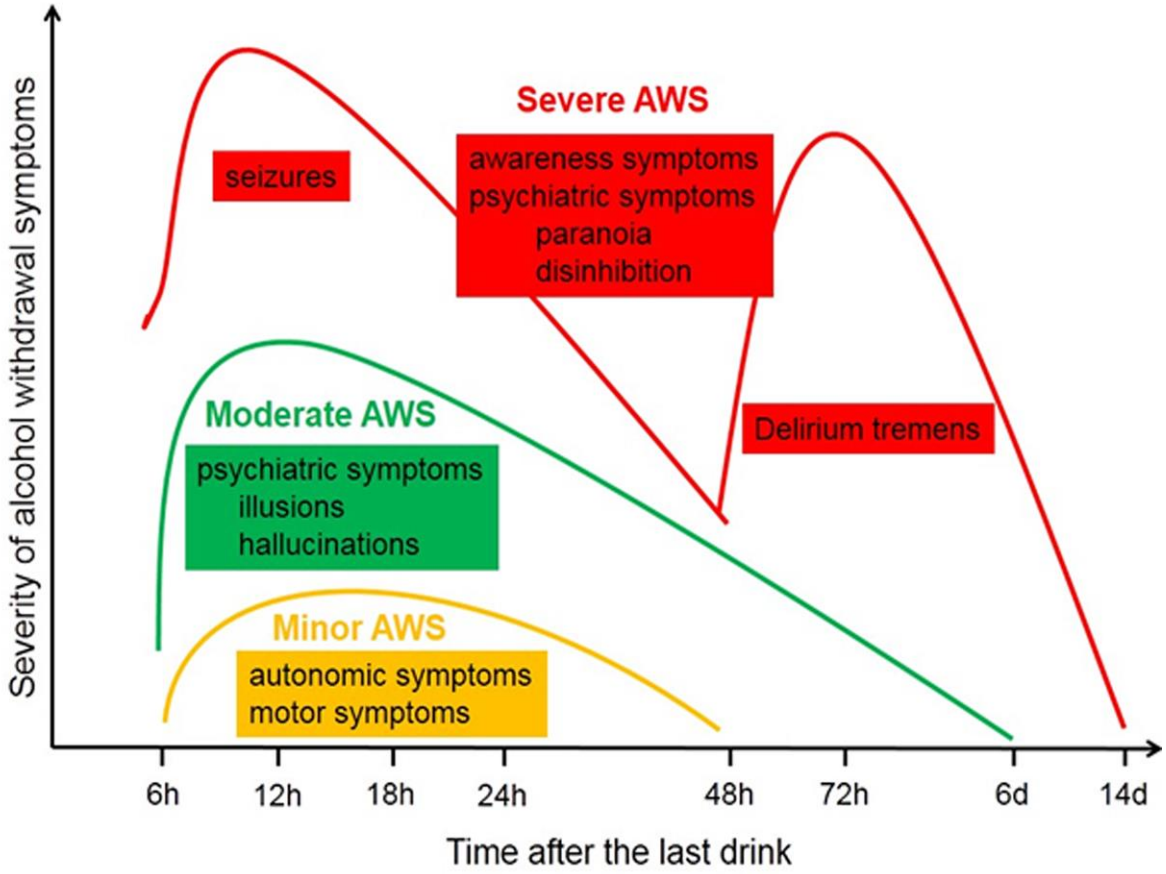

Figure 7: Chronological development of symptoms related to Alcohol Withdrawal Syndrome (Jesse et al. 2016)

9 Appendix

Appendix 1: Alcohol Use Disorders Identifying Test (AUDIT) questionnaire

Questions	0	1	2	3	4	
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4 or more times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	
					Total	

Appendix 2: Hospital Anxiety and Depression Scale (HADS) questionnaire

I feel tense or 'wound up':	**A**		**I feel as if I am slowed down:**	**D**	
Most of the time	3		Nearly all of the time	3	
A lot of the time	2		Very often	2	
Time to time, occasionally	1		Sometimes	1	
Not at all	0		Not at all	0	
I still enjoy the things I used to enjoy:	**D**		**I get a sort of frightened feeling like 'butterflies in the stomach':**	**A**	
Definitely as much	0		Not at all	0	
Not quite so much	1		Occasionally	1	
Only a little	2		Quite often	2	
Not at all	3		Very often	3	
I get a sort of frightened feeling like something awful is about to happen:	**A**		**I have lost interest in my appearance:**	**D**	
Very definitely and quite badly	3		Definitely	3	
Yes, but not too badly	2		I don't take as much care as I should	2	
A little, but it doesn't worry me	1		I may not take quite as much care	1	
Not at all	0		I take just as much care as ever	0	
I can laugh and see the funny side of things:	**D**		**I feel restless as if I have to be on the move:**	**A**	
As much as I always could	0		Very much indeed	3	
Not quite so much now	1		Quite a lot	2	
Definitely not so much now	2		Not very much	1	
Not at all	3		Not at all	0	
Worrying thoughts go through my mind:	**A**		**I look forward with enjoyment to things:**	**D**	
A great deal of the time	3		A much as I ever did	0	
A lot of the time	2		Rather less than I used to	1	
From time to time but not too often	1		Definitely less than I used to	3	
Only occasionally	0		Hardly at all	2	
I feel cheerful:	**D**		**I get sudden feelings of panic:**	**A**	
Not at all	3		Very often indeed	3	
Not often	2		Quite often	2	
Sometimes	1		Not very often	1	
Most of the time	0		Not at all	0	
I can sit at ease and feel relaxed:	**A**		**I can enjoy a good book or radio or TV programme:**	**D**	
Definitely	0		Often	0	
Usually	1		Sometimes	1	
Not often	2		Not often	2	
Not at all	3		Very seldom	3	