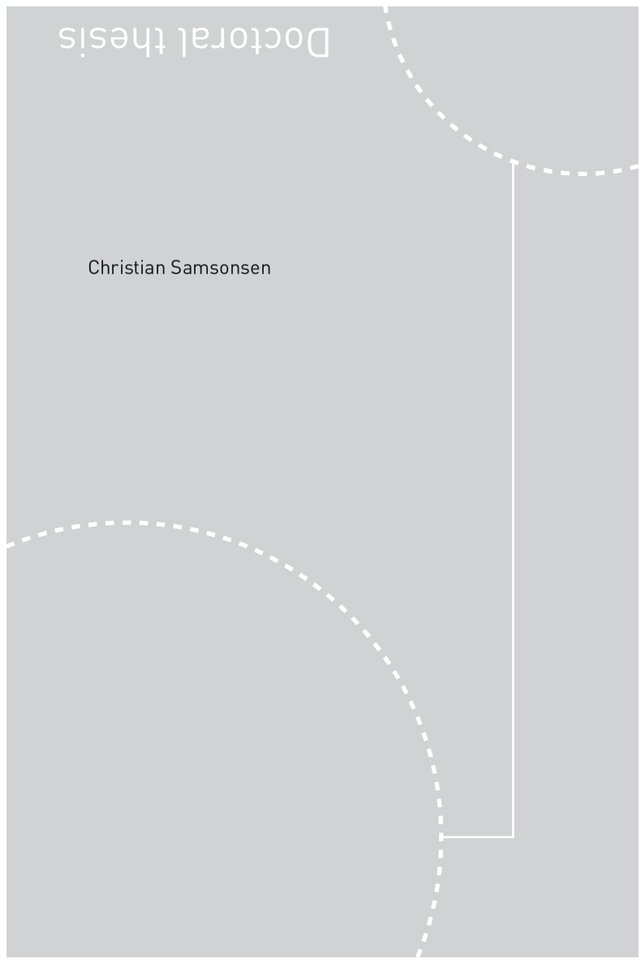
Doctoral theses at NTNU, 2017:214

Christian Samsonsen

Seizure Precipitants



ISBN 978-82-326-2500-0 (printed ver.)
ISBN 978-82-326-2501-7 (electronic ver.)
ISSN 1503-8181

NTNU
Norwegian University of
Science and Technology

Doctoral theses at NTNU, 2017:214

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of neuromedicine and Movement
Science

NTNU
Norwegian University of
Science and Technology

Christian Samsonsen

Seizure Precipitants

Thesis for the Degree of Philosophiae Doctor

Trondheim, August 2017

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of neuromedicine and Movement Science

NTNU
Norwegian University of
Science and Technology

NTNU
Norwegian University of Science and Technology

Thesis for the Degree of Philosophiae Doctor

Faculty of Medicine and Health Sciences
Department of neuromedicine and Movement Science

ISBN 978-82-326-2500-0 (printed ver.)
ISBN 978-82-326-2501-7 (electronic ver.)
ISSN 1503-8181

Doctoral theses at NTNU, 2017:214

Printed by NTNU Grafisk senter

Norsk sammendrag

Helhetlig forebyggende epilepsibehandling dreier seg både om medikamentell behandling og kartlegging av anfallsutløsende faktorer hos den enkelte pasient. Anfall oppstår ofte etter at pasienter er utsatt for flere samtidige og påfølgende faktorer som er avhengig av hverandre og forsterker hverandre.

Denne studien kartlegger anfallsutløsende årsaker hos pasienter innlagt ved Avdeling for nevrologi og klinisk nevrofysiologi, St. Olavs Hospital, fra juli 2006 til februar 2010, hvor funnene er beskrevet i tre artikler.

I den første artikkelen ser vi på mengden koffein inntatt før anfall sammenlignet med inntak i anfallsfri periode. Dyrestudier har vist at store doser koffein kan forårsake epileptiske anfall og en rekke kasuistikker beskriver anfall etter høyt koffeininntak. Det har derfor hersket usikkerhet om hvilke råd man skal gi mennesker med epilepsi i forhold til kaffedrikking. Vi fant at det ikke hadde vært endringer i koffeininntak i forkant av anfallene.

Det er kjent at svikt i medikamentinntak er en vanlig årsak til tap av anfallskontroll hos mennesker med epilepsi, men det har vært vanskelig å kartlegge omfanget. I den andre artikkelen brukes serumkonsentrasjonsmålinger hvor man sammenligner konsentrasjon/dose ratio ved anfall med medisinfastende målinger i en anfallsfri periode. Det viser seg at med denne metoden påvises en sikker eller sannsynlig svikt i inntaket før anfall hos 39%. Det må legges mer vekt på å hjelpe pasientene til et regelmessig medikamentinntak.

Den tredje artikkelen ser på sammenhengen mellom søvn og epileptiske anfall. Mange epilepsipasienter rapporterer at lite søvn kan utløse anfall, men søvnmangel er ofte assosiert med en rekke andre anfallsutløsende faktorer. Vi fant at søvnmangel er en uavhengig anfallsutløsende faktor når man kontrollerer for variabler som alkoholinntak, depresjon/angst, stress og medikamenter.

Candidatus medicinae Christian Samsonsen
Institutt for nevromedisin og bevegelsesvitenskap, Norges teknisk-naturvitenskapelige universitet (NTNU)

Hovedveileder: Eylert Brodtkorb, NTNU; biveileder: Geir Bråthen, NTNU

Table of contents

Acknowledgements

The work presented in this thesis was carried out at the Department of Neurology and Clinical Neurophysiology, St Olav's Hospital, Trondheim University Hospital, while working as a neurologist. The finishing work was financed by the Department of Neuromedicine and Movement Science, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, spring 2017.

First of all, I would like to thank my main supervisor Eylert Brodtkorb. He got me interested in the field of epilepsy and has guided and inspired me in an excellent way through these years. His unparalleled enthusiasm and extensive knowledge has been invaluable. My co-supervisor Geir Bråthen and Arne Reimers, have both been continuously supportive and given constructive feedback during the whole process. Trond Sand has contributed eminently, especially in the statistical analyses.

Grethe Helde is a key member of the epilepsy group at St Olav's Hospital and has been working tirelessly on this project from the very beginning. Her support has been unlimited and I owe her greatly for the completion of this thesis.

I would like to express my sincere gratitude to all patients who generously gave their time to take part in this study and to all of my colleagues at the Department of Neurology and Clinical Neurophysiology and Department of Neuromedicine and Movement Science for encouraging me in my research efforts.

Finally, I would like to thank my family. My parents, Møyfrid and Jan, and parents-in-law, Mabel and Svein, have all been interested in my research, even when life turns unexpectedly. Most of all I am deeply grateful to my wonderful wife Marit's patience and encouragement and to our beautiful children Erle, Magnus and Sondre for joyful afternoons with soccer, track and field, handball, gymnastics and skiing, and for reminding me every day that there is more to life than work.

List of papers

PAPER I - Samsonsen C, Bråthen G, Reimers A, Helde G, Brodtkorb E. Is dietary caffeine involved in seizure precipitation? Epilepsy Behav. 2013; 28:147-50.

PAPER II - Samsonsen C, Reimers A, Bråthen G, Helde G, Brodtkorb E. Nonadherence totreatment causing acute hospitalizations in people with epilepsy: an observational, prospective study. Epilepsia. 2014; 55:125-8.

PAPER III - Samsonsen C, Sand T, Bråthen G, Helde G, Brodtkorb E. The impact of sleep loss on the facilitation of seizures: A prospective case-crossover study. Epilepsy Res. 2016; 127:260-266.

Acronyms and abbreviations

AED – Anti-epileptic drug

AUDIT - Alcohol Use Disorder Identification Test

C/D – Concentration/dose

GTC – Generalized tonic-clonic

HADS – Hospital Anxiety and Depression Scale

ILAE – International league against epilepsy

TDM – Therapeutic Drug Monitoring

VAS – Visual analogue scale

WHO – World Health Organization

Definitions

*Seizur*e (Fisher et al., 2005)

A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

Epilepsy – conceptual definition (Fisher et al., 2005)

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.

Epilepsy – practical/operational definition (Fisher et al., 2014)

Epilepsy is a disease of the brain defined by any of the following conditions

1. At least two unprovoked (or reflex) seizures occurring >24 h apart

2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years

3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Summary

In the comprehensive management of epilepsy, both preventive pharmacological treatment and awareness of possible seizure precipitating factors are important. The true cause of seizure generation is often hard to disentangle, as triggers often are obscure and occur in concert. This dissertation examines possible seizure precipitants in patients admitted to Department of Neurology and Clinical Neurophysiology, St Olav's Hospital, Trondheim University Hospital, July 2006-February 2010, soon after a seizure.

The results from the study are presented in three papers.

In paper I, preictal caffeine intake was compared to consumption in a seizure free period as animal models and case reports have suggested caffeine to contribute to seizure development. Dietary caffeine intake 24h prior to the seizure was not different compared to habitual intake or compared to intake in a seizure free period. Therefore, caffeine does not seem to be a common seizure precipitant in a clinical setting, and patients should be accordingly advised.

Non-adherence persists as a major obstacle to optimal epilepsy treatment, but its magnitude has been difficult to determine. In paper II, patients with epilepsy acutely admitted for seizures were included, and concentration/dose ratios of AEDs at admission were compared with the patient's own steady-state, drug-fasting control values. Non-adherence was seen in 39%, and was more common in younger patients. Many patients seem to be unaware of missed drug intake. AED serum concentrations should be part of the emergency care. Efforts to improve treatment adherence is an important part of comprehensive epilepsy management.

Sleep-time in the 24h prior to the seizure was assessed in paper III, and was found to be lower when compared to follow-up. Anxiety and depression did not correlate with differences in sleep time, but the interaction between alcohol and sleep was high. However, sleep loss stood out as an independent trigger.

This study demonstrates that epileptic seizures usually seem to be precipitated by a combination of clinical factors.

1. Introduction to study

1.1 Background

The broader management of epilepsy comprises more than prescribing pills and counting seizures. Health professionals often exclusively focus on the medical aspects of the disorder. Less awareness has been given to the multifaceted and reciprocal impact of epilepsy on everyday life and that of lifestyle factors on the occurrence of seizures. Comprehensive epilepsy service has for many years been a focus of scientific interest to the Epilepsy Research Group at St. Olav's Hospital. Seizure precipitating factors have received particular attention. In 2001 Geir Bråthen wrote his thesis about alcohol-related seizures (Bråthen, 2001). Later, research nurse Grethe Helde led a randomized controlled trial on the effect of a structured educational program for patients with uncontrolled epilepsy (Helde et al., 2003 and 2005). In this context, the included patients were interviewed about seizure precipitating factors. This part of the study became the topic of a medical student thesis in 2005 (Vedeld, 2005). Table 1 gives an overview of the most commonly reported seizure precipitants in 113 patients with uncontrolled seizures.

Table 1. Frequency of seizure precipitants in 113 patients (Vedeld, 2005)

Precipitant	Reported spontaneously	Selectable in questionnaire
Lack of sleep	22%	66%
Stress	61%	54%
Forgotten AED	4%	40%
Alcohol	12%	37%
Disturbance in sleep pattern	1%	35%
Physical activity	7%	20%
Menstruation	4%	18%
Light	5%	17%
Computer use	1%	12%
Fever	1%	5%

However, many questions remained unanswered. The exact role of various seizure-provoking factors is difficult to decipher as many of them occur in combination and receive little attention from the patients themselves. Knowledge on these issues is still insufficient. Inadequate information about the disorder and poor professional support has been common. Accordingly, the importance of providing appropriate education and counseling to people with chronic disorders and their relatives is now recognized through legislation in Norway. There has been an incentive to focus more on self-management issues in people with uncontrolled epilepsy (Helde et al., 2003 and 2005; Helmers et al., 2017).

In the present thesis we selected three life-style factors with potential seizure inducing effects that previously have been insufficiently explored: caffeine ingestion, non-adherence to treatment and sleep loss.

1.2 General concepts

Normal brain neuronal activity occurs in a nonsynchronous manner with groups of neurons inhibited and excited sequentially. 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 chronic neurological disorder characterized by repeated unprovoked seizures (Fisher et al., 2005). Unprovoked seizures should be distinguished from acute symptomatic seizures, which occur in close temporal relationship with acute structural, inflammatory, toxic or metabolic insults to the brain, including drug or alcohol intoxication and withdrawal (Beghi et al., 2010). The term "situation-related seizures" has fallen into discredit, as it is a vague concept (Beghi et al., 2010). It includes seizures associated with transient extraordinary non-lesional precipitating factors, comprising strong psychological strain, sleep deprivation and drug and alcohol effects, often in combination. In milder forms, these events may merely occur as occasional daily life stressors, which may contribute to the generation of seizures in the context of epilepsy (Ferlisi and Shorvon, 2014; Nakken et al., 2005). Thus, the borders between unprovoked and provoked seizures are sometimes blurred and may be difficult to evaluate in clinical practice.

Moreover, epileptic seizures are referred to as reflex if they are objectively and consistently modulated, precipitated or inhibited by a specific stimulus that almost immediately results in a

seizure (Koepp et al., 2016), in contrast to reactive or situation-related if they occur in association with non-specific triggers (Blume, 2001). The type of reflex epilepsy is named after the stimulus necessary to provoke a seizure. Typically, the lateral sensorimotor- and visual cortex is involved, e.g.: primary reading epilepsy, photosensitive occipital lobe epilepsy, other visual-sensitive epilepsies, and startle epilepsy (Berg et al., 2010; Engel, 2001). Auditory provoked seizures may take the form of telephone-induced seizures (Michelucci et al., 2004) or speech-induced seizures in LGI1-related autosomal dominant temporal lobe epilepsy (ADTLE) (Brodtkorb et al., 2005).

A number of mechanisms play directly or indirectly upon the crucial balance of excitation and inhibition within the central nervous system. In the classic study by Aird, circumstances that temporarily lower the seizure threshold were called seizure-inducing factors, while stimuli that are capable of precipitating a seizure, were referred to as seizure-triggering factors (Aird, 1983). Together, they are called seizure precipitants. The ILAE Glossary of Descriptive Terminology defines a provocative factor as a transient and sporadic endogenous or exogenous element capable of augmenting seizure incidence in persons with chronic epilepsy and evoking seizures in susceptible individuals without epilepsy (Blume et al., 2001). Burdette (1992) describes seizure precipitating factors in a more every-day language as "those circumstances that precede the onset of an epileptic attack and are considered by both patient and neurologist to be a possible explanation for why the seizure happened when it did, and not earlier or later". This means that the patients may have a perception of what initiates a seizure. Patients with epilepsy often try to find a connection between their seizures and external or internal events that give them a feeling of predictability (Spatt et al., 1998). However, in a clinical setting, the true nature of seizure precipitation is often hard to disentangle with certainty. Precipitants are sometimes ill defined and frequently within physiological limits. Nevertheless, in people with epilepsy, patterns where seizures are more likely to occur can sometimes be identified. Acute symptomatic, reflex, provoked and precipitated seizures may be seen as a continuum towards the seemingly spontaneous seizure.

Lack of sleep, alterations in sleep rhythm, abrupt awakening, non-adherence to prescribed drug regimens, alcohol, stress, fever, menstruation and physical activity, are all examples of reported precipitants (Table 1) (Nakken et al., 2005; Tan et al., 2005). These factors, however, often occur in concert, and may have different impact according to the type of epilepsy or

epileptic syndrome involved (Frucht et al., 2000). In some patients, the use of medications may induce seizures by a direct neurotoxic effect (Kumlien and Lundberg, 2010), whereas seizures due to alcohol- and benzodiazepine abstinence are also common (Stimmel and Dopheide, 1996). Several recreational drugs and stimulants, even intake of energy drinks containing caffeine, are believed to induce seizures (Bonhila and Li, 2004).

Awareness of these factors is probably an underestimated part of the self-management of epilepsy (Nakken et al., 2005), and information about the principles of prophylactic drug treatment, as well as the knowledge of potential seizure precipitating factors, is important. In the study by Aird, 43 % of patients reported benefit from increased awareness on precipitants, in 17% it was thought to have substantial impact on seizure control (Aird, 1983). On the other hand, it seems to be a common problem that patients often are aware of possible seizure precipitants, while believing that the precipitants are unavoidable (da Silva Sousa, 2005).

The principal goal in the management of seizure disorders is to avoid further seizures. The comprehensive approach can be divided into pharmacological and non-pharmacological options and should be tailored to the individual patient.

This thesis aims to examine the unsettled role of caffeine consumption, non-adherence to recommended AED regimens by means of therapeutic drug monitoring (TDM), as well as the complex interaction between sleep, stress, depression, anxiety and alcohol as seizure precipitants in a clinical setting.

1.3 Caffeine

Caffeine is widely used as a stimulant and has complex pharmacological actions. Modern energy drinks containing high amounts of caffeine and typically other additives, such as taurine, herbal supplements, vitamins and guarana, may compound the stimulant effects of caffeine (Mattson, 2013). Animal models (Chu, 1981; Cutrufo, 1992; Gomes et al., 1999) and case reports suggest that excessive caffeine intake may precipitate seizures (Bonhila and Li, 2004; Calabrò et al., 2012; Cleary et al., 2012; Haller et al., 2005; Iyadurai and Chung, 2007; Kaufman and Sachdeo, 2003; Mortelmans et al., 2008; Röggla and Moser, 2007; Trabulo et al., 2011). Caffeine binds to presynaptic adenosine receptors, but unlike adenosine, the final

breakdown product of adenosine triphosphate, which slows down neuronal firing when the cells run low on energy, caffeine allows continued neuronal stimulation (Ferre et al., 1991; Fredholm and Dunwiddie, 1988). In other words, adenosine's protective action is antagonized by caffeine. In vulnerable networks, this is theoretically thought to contribute to the cascade of events leading to a seizure. Caffeine has for a long time been used as therapy for apnea in prematurity; safety in terms of possible seizure induction is not conclusive so far (Aranda et al., 1977). However, theophylline, commonly used in treatment of pulmonary diseases, binds to the adenosine receptor in a similar manner as caffeine, and is a well-known seizure precipitant (Zwillich et al., 1976).

Interestingly, the use of adenosine as an anticonvulsant is currently in early stages of development as a potential AED (Bialer et al., 2017). Adenosine seems to affect mechanisms important to prevent epileptogenesis (Williams-Karnesky et al., 2013).

However, whether dietary caffeine intake is involved in seizure precipitation in a clinical setting, is controversial. Unclear recommendations have so far been given based on animal studies and the few available case reports suggesting seizure-inducing effects of excessive intake of new energy drinks containing caffeine. Hence, we wished to assess whether a fluctuating intake of dietary caffeine might contribute to the generation of seizures.

1.4 Non-adherence

Prophylactic pharmacological treatment of epilepsy is mainly focused on preventing the pathological hypersynchronised activation of neurons by using antiepileptic drugs (AEDs) to modulate excitatory and inhibitory functions in the brain, thus effectively raising the threshold for seizures. Stable concentrations of AEDs are necessary in order to prevent seizures from occuring. However, "drugs don't work in patients who don't take them" (Osterberg and Blaschke, 2005). The term adherence has replaced compliance in the meaning of the implementation, i.e. the initiation and execution of an agreed medical treatment (Brodtkorb et al., 2016). Non-adherence to AED treatment is a major obstacle for successful outcome in epilepsy (Cramer et al., 2002; WHO, 2003). Knowledge of, and the extent of non-adherence, has not been given the attention needed (Commission on Antiepileptic Drugs ILAE, 1993; Tomson, 1995).

Non-adherence causes an increase in the number and severity of seizures, emergency department visits and hospitalizations. It reduces quality of life for the patients and results in higher healthcare cost (Davis et al., 2008; Ettinger et al., 2009; Faught et al., 2009; WHO, 2003). Thus, adequate patient education on the principles of prophylactic treatment is a fundamental part of the comprehensive management of seizure disorders (Cramer and Russel, 1988; Faught, 2012; Garnett, 2000; Helde et al., 2005; Paschal et al., 2008; Smithson et al., 2012).

The causes of suboptimal AED treatment may be complex and difficult to recognize (Hao et al., 2013). Non-adherence may be intentional or non-intentional. It may be related to the healthcare system, to the condition itself, to therapy, or to socio-economic- and patient-related factors. AED treatment is preventive, and when seizure-free, people with epilepsy are often not reminded of the need for drug treatment (Loiseau, 1998). Side-effects, and fear of side-effects, may cause reluctance to follow the prescribed regimen. Increase of AED doses are often made after seizures without taking non-adherence into consideration. Specht and colleagues studied adherence in young patients with epilepsy and emphasized that TDM immediately after a seizure is a useful tool to assess non-adherence (Specht et al., 2003), in order to avoid excessive AED dosing. Increasing the dose on false premises may accentuate side-effects and lead to poor adherence.

Recently, the International League against Epilepsy (ILAE) defined drug-resistant epilepsy as uncontrolled seizures in spite of adequate trials of at least two tolerated, appropriately chosen and appropriately used AED schedules (Kwan et al., 2010). Hence, non-adherence was acknowledged, but not further addressed. Uncontrolled epilepsy is not necessarily the same as drug-resistant epilepsy. Appropriate use is often taken for granted, but missed AED intake as a cause of pseudo-resistant epilepsy is probably underestimated (Brodtkorb et al., 2016). The extent of the problem has been difficult to assess (WHO, 2003).

Several different methods of measuring adherence are available. They can be subjective or objective, and have direct or indirect approaches. All have advantages and limitations. Patient self-reports and questionnaires rely on the patient's own perception of adherence, whereas pill counts and prescription refill rates are objective, but indirect, as they do not necessarily reflect

intake (Faught, 2012; Paschal et al., 2008; Smithson et al., 2012; WHO, 2003;). Therapeutic drug monitoring (TDM) is direct and objective, part of the routine in many countries and easy to understand. However, shortcomings are costs, pharmacokinetic variability, interactions, diurnal variation and the need for control values. Combined methods are probably useful, and may enhance the recognition of non-adherence, but the true extent of the problem has been left obscure. By comparing serum concentrations of AEDs in the emergency room at admission for acute seizures and controlling for routine values, we wished to assess the magnitude of this problem in people with uncontrolled seizures admitted to our hospital.

1.5 Sleep, alcohol, stress, anxiety, depression

Sleep loss, alterations in sleep rhythm and abrupt awakening is frequently reported as a seizure precipitant by patients (Frucht et al., 2000; Nakken et al., 2005). However, lack of sleep is closely intertwined with a range of possible confounding factors, including alcohol, stress and mood. There are still no conclusive clinical data showing to what extent and magnitude each of these factors trigger seizures. (Aird, 1983; Antebi and Bird, 1993; Ferlisi and Shorvon, 2014; Gunderson et al., 1973; Lawn et al., 2014; Méndez and Radtke, 2001; Spector et al., 2000; Tan et al., 2005; Wassenaar et al., 2014). Although sleep deprivation has been found to activate epileptiform EEG in several studies (Fountain et al., 1998), it has been debated whether isolated sleep loss promotes seizures (Malow, 2004). In a much cited study on patients with uncontrolled focal seizures who underwent long-term EEG monitoring, sleep deprived subjects did not demonstrate increased seizure frequency compared to those who had slept normally. It was suggested that in an inpatient situation free of the stress of everyday life, sleep deprivation does not significantly affect seizure frequency (Malow et al., 2002).

Alcohol is a major seizure precipitant by itself (Bråthen et al., 1999), which has been known since the times of Hippocrates (Bråthen et al., 2005). The pathophysiological mechanisms of alcohol induced seizures are not yet fully understood as the effect of alcohol on the central nervous system is complex, and affect several systems of neurotransmitters, most notably the GABA-/ and glutamate systems (Faingold et al., 1998, Jesse et al., 2016). In patients with a first-time seizure, alcohol appeared to be a contributing factor in more than 30% of admissions (Bråthen et al., 1999). Awareness of seizures due to alcohol withdrawal is important, as prophylactic AED treatment is usually not indicated in these patients.

Specifically, the association between alcohol misuse and epilepsy is a substantial problem that needs more clinical and scientific attention. In a recent Norwegian population-based registry study based on ICD-10 codes in specialist care, alcohol use disorder was present in 5.7% among people diagnosed with epilepsy, compared to 1.3% in patients without epilepsy (Bakken et al., 2014). The comprehensive management of these comorbid individuals is a multidisciplinary challenge. It includes careful counselling and information about the seizure precipitating effects of alcohol, particularly the concurrent withdrawal of alcohol and AEDs.

Lin and colleagues reviewed the occurrence of psychiatric comorbidity in epilepsy that add further burden to these patients (Lin et al., 2012). Bidirectional relationships are well established between epilepsy and depression (Ettinger et al., 2004, Ottman et al., 2011), and epilepsy and anxiety (Ottman et al., 2011; Tellez-Zenteno et al., 2007), whereas the connection to bipolar disease is less convincing. Living with epilepsy has obvious implications on mental health in many patients. One study examined the effect of stress on the risk of having seizures, where high stress levels were associated with more frequent seizures for most participants. However, some of the patients might have been stressed due to the occurrence of seizures itself (Temkin and Davis, 1984). Additionally, perceived stress and its association to sleep loss have not been studied thoroughly in terms of seizure precipitation. Nevertheless, countermeasures to lower the level of stress seem to reduce seizure frequency in some patients (Aird and Gordon, 1993; Dahl et al., 1992; Frucht et al., 2000; Loiseau, 1997; Spector et al., 2000).

As shown in Table 1, lack of sleep crowns the list of self-reported seizure precipitants (Frucht et al., 2000; Nakken et al., 2005). It is frequently associated with other clinical circumstances mentioned above. We wished to find out whether sleep loss is an independent seizure provoking factor.

2. Aims of study

The overall aim of the study was to examine the occurrence of potentially seizure-precipitating factors in patients hospitalized after a seizure.

The specific aims for each individual paper were as follows:

Paper I

To study the role of caffeine as a seizure precipitant in a clinical setting.

Paper II

To study the role of nonadherence to pharmacological treatment as a precipitant of seizures by means of therapeutic drug monitoring (TDM) and to explore the clinical characteristics of patients affected by this problem.

Paper III

To study the sleep related circumstances that may facilitate the generation of an epileptic seizure. Specifically, we wished to assess whether lack of sleep is an independent seizure-provoking factor in a clinical setting.

3. Methods

3.1 Material

In this observational, prospective study, we included consecutive, adult patients (age >16) who were hospitalized soon after a seizure at the Department of Neurology and Clinical Neurophysiology, St Olav's Hospital, Trondheim University Hospital, Norway, between July 2006 and February 2010.

Gender, age, date and weekday of the seizure, marital-, living- (with or without companions) and occupational status were recorded, together with medical comorbidity.

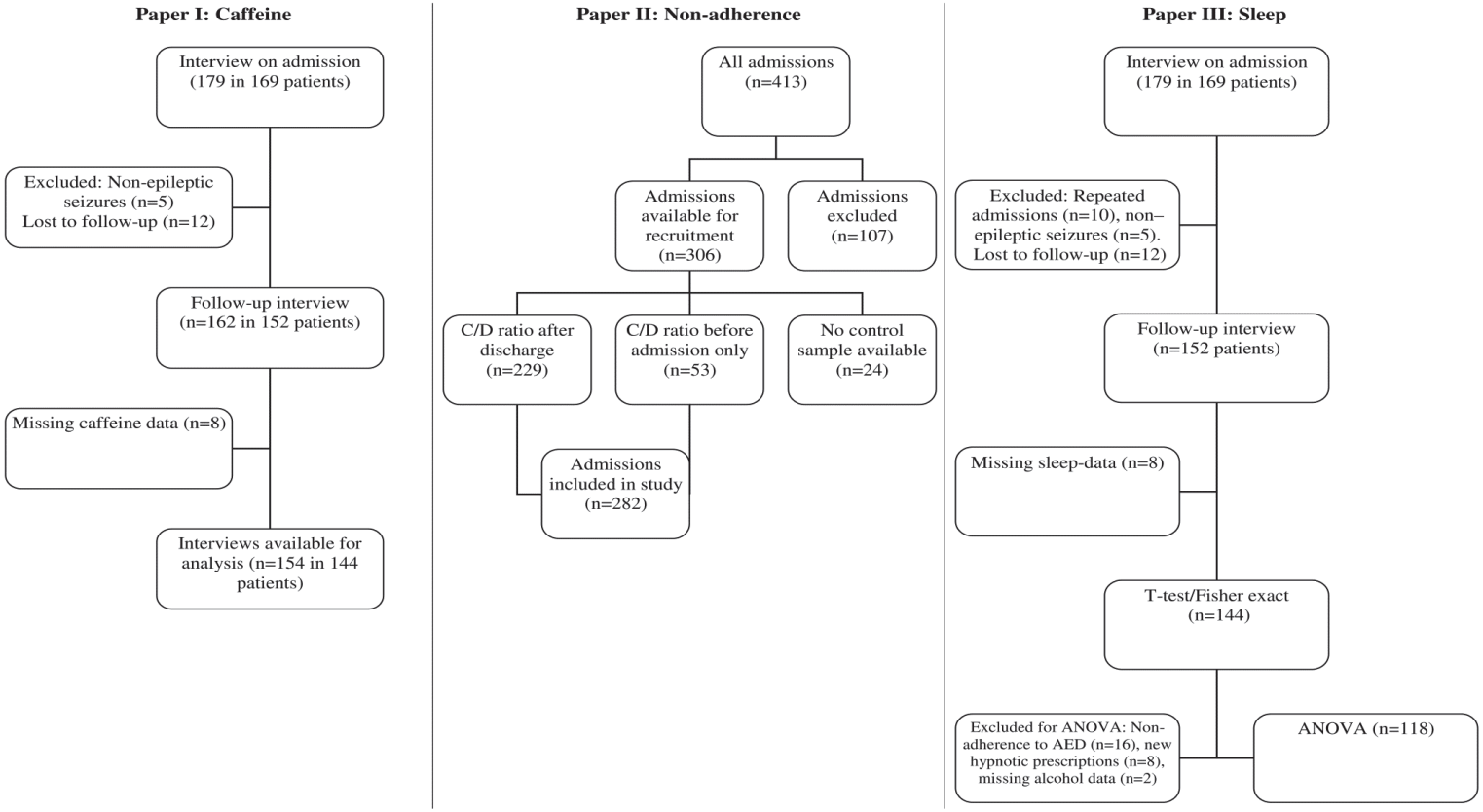
Various data given in paragraphs 3.2-3.10 were recorded.

A follow-up interview by telephone was performed at least four weeks after seizure admission at a time when there had been no seizure for >3days. The follow-up interview covered the same weekdays as in the admission interview of each patient.

The following elements of the admission interview were repeated: a sleep record, alcohol use, as well as the history of medications used during the last week and the caffeine consumption during the last 24 h. Repeated admissions were used in the statistical analyses in paper I and II, whereas only the first admission was used in paper III.

The number of patients included, excluded and lost to follow up in the various studies, are given in Figure 1.

Figure 1: Summary of patient recruitment



3.2 Seizure and epilepsy classification

Seizures and epilepsies were categorized according to classifications by the International League Against Epilepsy (ILAE) at the time of the studies (Berg et al., 2010, Thurman et al., 2011). Focal onset seizures were defined as seizures with localized clinical onset and/or focal findings in brain imaging and EEG. Tonic-clonic seizures were considered generalized in onset when occurring in the context of generalized epilepsy syndromes and/or associated with generalized epileptiform EEG discharges, or if EEG and imaging was normal and no focal onset was presented by history.

3.3 Caffeine

Patients were asked to estimate their caffeine intake during the last 24 hours prior to the seizure, as well as their habitual 24 h caffeine consumption. Interviews took place at a time when the patients were clinically considered to be cognitively restored after the seizure. A follow-up interview was performed at least four weeks later. The caffeine consumption was recorded on the same day of the week and at a time when no seizure had occurred within the last 24 hours. The patients served as their own controls.

Beverages containing caffeine (coffee, tea, colas) were recorded as standard units defined as one cup of coffee, two cups of tea or three caffeinated soft-drinks, according to their different caffeine contents (Heckman et al., 2010).

The caffeine intake was roughly categorized into four groups: 1) no caffeine, (2) low consumption (≤3 units), 3) moderate consumption (>3 - ≤6 units), and 4) high consumption (>6 units).

3.4 Adherence

On admission, blood was drawn from the patients for TDM of relevant AEDs. Blood analyses were performed with routine in-house methods. Time of last AED intake and time for blood sampling, as well as concomitant medications were recorded. Concentration/dose (C/D) ratios were calculated. Each patient served as his/her own control. Steady-state, drug-fasting, control

C/D ratios were obtained at scheduled outpatient appointments and controlled for co-medication. The first post-discharge value was preferred; if not available, the last value prior to admission was used.

Non-adherence was defined as probable when the C/D ratio at admission was 50 to 75% of the control C/D ratio, and as definite when it was less than 50%. Patients using multiple AEDs were assessed according to the drug with the lowest C/D ratio. The medical records were reviewed for information on the patients' own history of recent adherence.

3.5 Sleep

Total sleep-time during the last 24 h prior to the seizure was recorded in a sleep diary by the interviewer. The time of seizure occurrence, as well as its relation to sleep and awakening, was also recorded. Seizure-related sleep deprivation was defined as total sleep time <50% during the last 24h prior to admission compared to follow-up.

3.6 Alcohol

Alcohol use was assessed by the Alcohol Use Disorders Identification Test (AUDIT). The AUDIT was developed by the WHO as a simple method of screening for excessive drinking; to determine if a person may be at risk of alcohol abuse (Saunders et al., 1993).

The daily number of alcohol units consumed was recorded for each of the six days prior to the seizure. 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).

3.7 Other medications/drugs

Prescription- and illegal drugs ingested during the last week were recorded to identify agents that might influence the seizure threshold.

3.8 Anxiety and depression

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.

HADS is commonly used by doctors to determine the levels of anxiety and depression that a patient is experiencing. The HADS is a fourteen-item scale that generates ordinal data. Seven of the items relate to anxiety; the other seven relate to depression. Every item on the questionnaire is scored from 0-3. A cut-off point of 8/21 for both anxiety and depression is most often used (Bjelland et al., 2002).

3.9 Visual analogue scale

Patients were also asked to score the perceived role of various precipitants for the present seizure on a visual analogue scale (VAS) 100mm in length with scores ranging from 0 to 100 accordingly.

VAS is a psychometric response scale which can be used in questionnaires (Huskisson, 1974). It is a measurement instrument for subjective characteristics or attitudes that cannot be directly measured. When responding to a VAS item, respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points.

The patient's own evaluation of common seizure precipitants, including stress, physical activity, lack of sleep, irregular rhythm, alcohol, photostimulation, TV/screenplay, menstruation, fever and others, was marked on the scale. The precipitants chosen were the most frequently reported in previous studies (Nakken et al., 2005; Vedeld, 2005). Only perceived stress from the VAS was included for the present thesis.

3.10 Epilepsy knowledge (not included in the present papers)

Patients were asked to complete the 34-item medical knowledge sub-scale of the Epilepsy Knowledge Profile – General (Jarvie et al., 1993). The questionnaire has been translated into Norwegian. Correct answers are given one point, wrong answers zero point. The maximum

total score is 34.

3.11 Statistics

IBM Statistical Package for the Social Sciences (SPSS) versions 17-23 and Excel were used for statistical analysis.

A p value <0.05 was considered statistically significant. A p value <0.01 was considered highly significant.

Paper 1:

Statistical analyses were performed using Wilcoxon's signed-ranks test.

Paper 2:

Fisher's exact test was used for statistical analysis.

Paper 3:

Paired Student's t-test and two-group Student's t-test was used for determination of the significance of crude differences.

Categorical 2x2 data were assessed with Fisher exact test or paired McNemar's test for symmetry.

Pearson correlation was used for exploring associations between main outcome variables and background variables.

A supplementary repeated measures ANOVA model was created in order to control for the effects of AED and alcohol consumption change.

3.12 Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics

(approval number 420061611). Participants taking part in the interviews gave their informed written consent. The Regional Committee for Medical and Health Research Ethics (reference 2009/1672-2), approved serum concentrations drawn from all patients to be studied in this project, without consent being given.

4. Results – overview of papers

Paper 1:

Samsonsen C, Bråthen G, Reimers A, Helde G, Brodtkorb E. *Is dietary caffeine involved in seizure precipitation?* Epilepsy Behav. 2013; 28:147-50.

Caffeine acts as a central nervous stimulant by blocking A1 and A2A adenosine receptors. Its effect on seizures is complex. Animal studies and case reports indicate that acute caffeine exposure may induce seizures, whereas chronic exposure might have an opposite effect. We wished to study the role of caffeine as a seizure precipitant in a clinical setting.

Patients acutely hospitalized for seizures (n=174) were asked for their consumption of caffeinated beverages 24 h prior to admission as well as their habitual caffeine intake. 24-h caffeine consumption was also recorded in a later telephone interview on a seizure free day (n=154). Thus, the patients served as their own controls. Categorized data were analysed using the Wilcoxon's signed-ranks test.

No difference was found between the 24-h intake of caffeine prior to the seizure and the habitual consumption (p=0.37), or the consumption on a seizure free day (p=0.13).
We concluded that dietary caffeine does not appear to be a common seizure precipitant.

Paper 2:

Samsonsen C, Reimers A, Bråthen G, Helde G, Brodtkorb E. *Nonadherence to treatment causing acute hospitalizations in people with epilepsy: an observational, prospective study.* Epilepsia. 2014; 55:125-8.

Poor adherence to treatment with AED persists as a major obstacle to optimal epilepsy care. We aimed to assess the clinical relevance of this problem by means of TDM, and to investigate the clinical characteristics of patients prone to AED non-adherence.

Consecutive patients with epilepsy acutely admitted to hospital for seizures were included. Non-adherence was defined as having a serum concentration/dose ratio at admission of <75 % of the patient's own control value (probable non-adherence: 50-75%; definite: <50%).

A large proportion of patients (39%) was non-adherent to AED treatment (definitely: 24%; probably: 15%). Non-adherence was more common in patients with generalized seizures compared to those with focal onset seizures (p=0.021), and in patients <30 years compared to older patients (p=0.006).

We concluded that non-adherence is a common cause of seizure breakthrough in patients with epilepsy, particularly in adolescents and young adults, and in those with generalized epilepsies. Prompt measurements of AED serum concentrations should be available as part of the emergency care for patients acutely hospitalized for seizures to permit this issue to be thoroughly addressed prior to discharge.

Paper 3:

Samsonsen C, Sand T, Bråthen G, Helde G, Brodtkorb E. *The impact of sleep loss on the facilitation of seizures: A prospective case-crossover study.* Epilepsy Res. 2016; 127:260-266.

The relationship between sleep and seizures is intricate. The aim of this study was to assess whether sleep loss is an independent seizure precipitant in a clinical setting.

In this prospective, observational cross-over study, 179 consecutive hospital admissions for epileptic seizures were included. A semi-structured interview regarding several seizure precipitants was performed. The sleep pattern prior to the seizure, as well as alcohol, caffeine and drug use, were recorded. The same interview was repeated by telephone covering the same weekday at a time when there had been no recent seizure. The Hospital Anxiety and Depression Scale (HADS) and a visual analogue scale for perceived stress was applied at admission. Student t test, Fisher exact test and ANOVA were used for statistical analyses.

Complete data for analysis were retrieved in 144 patients. Sleep time during the 24 h prior to

the seizure was lower compared to follow-up ($p<0.0005$). Caffeine consumption and use of relevant non-AEDs were not different. HADS and stress scores at admission did not correlate with sleep time difference. ANOVA considering sleep time, alcohol consumption and AED use could be applied to 120 patients. In this model, sleep time difference remained significant ($p=0.008$). The interaction with alcohol intake was high, but not significant when controlled for high consumption (> average 2 units per day during 6 days).

Epileptic seizures are often precipitated by a combination of various clinical factors, but sleep loss stands out as an independent seizure trigger.

5. Discussion

5.1 Main findings of the thesis

This thesis explores the significance of potential seizure precipitating factors and attempts to assess the circumstances and settings in which they occur.

Increased dietary caffeine did not appear to be associated with increased occurrence of seizures, in spite of the fact that ingestion of caffeine-containing beverages may often be associated with lack of sleep.

By means of TDM we have demonstrated that non-adherence to AED treatment is a major cause of pseudo drug-resistant epilepsy, particularly in young adults. Non-adherence was even present in many patients who were not aware of missed drug intake, as well as in patients with intellectual disability receiving their drugs from caregivers.

The relationship between sleep and seizures is intricate. Sleep-time was significantly lower prior to a seizure than at follow-up, but the interaction between sleep loss and alcohol use was high. Nevertheless, sleep loss appears to be an independent seizure trigger.

Seizure precipitants are often multiple and combined. Awareness of these factors and their interactions are important. However, fear of seizure-inducing situations causes concerns and restrictions in the lives of people with seizure disorders. Advice and interventions should not be based on myths and beliefs.

5.2 The burden of the enduring susceptibility of having seizures

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate seizures and by the neurobiological, cognitive, psychological and social consequences of the disorder (Fisher et al., 2005). The prevalence of epilepsy increases in children and adolescents reaching a plateau level during the age between 20 and 30 years (Syvertsen et al., 2015). Crucial elements in the management of this disorder is the balance between wanted and unwanted effects of the treatment, as well as the balance between avoidance of seizure precipitating factors and the risk related to seizures. These aspects are particularly important

in the young patient moving towards an independent life. In general, chronic disorders and their treatment may have negative implications for peer relationships and evoke a feeling of being different, for which adolescents may be more susceptible than older patients (Kyngäs, 2000).

Patients with epilepsy may suffer from stigma, exclusion, restrictions, overprotection and isolation. Poor seizure control may in particular have deleterious consequences in young people, as it frequently affects educational performance and social adjustment. The enduring potential for seizure recurrence may not only have an impact on the patients, but also on their families. Hence, the burden of having epilepsy is now included as part of the conceptual definition of the condition (Fisher et al., 2005), thus underscoring the need for comprehensive and multiprofessional management of epilepsy.

Seizure precipitation by lifestyle factors is very common in the young age group, conceivably due to immature attitudes. Young patients are especially prone to stimulant and illegal drug use, as well as uncontrolled use of alcohol and irregular sleep rhythm (Leach et al., 2012). This particularly pertains to juvenile myoclonic epilepsy (Syvertsen et al., 2014). In this common electroclinical syndrome, lifestyle is an extremely important part of the treatment, which should be thoroughly discussed with the patient (Crespel et al., 2013).

5.3 The impact of caffeine on seizure control

Currently, an increasing number of admissions to hospitals are thought to be related to the intake of energy drinks containing large amounts of caffeine (Mattson, 2013). A range of case reports have been published, exclusively in young people (up to age 28 years) (Calabro et al., 2011; Iyadurai and Chung, 2007; Röggla and Moser, 2007; Trabulo et al., 2011). Confounders, particularly psychosocial circumstances, including sleep loss and the intake of other seizure-inducing agents should generally receive ample attention in such anecdotal reports. Limited caffeine consumption has been advised for people with epilepsy by some authors (Kasteleijn-Nolst Trenité et al., 2013; Kaufman et al., 2003), but evidence-based clinical findings supporting such recommendations are lacking. Hence, undocumented restrictions should be avoided.

Even though caffeine is commonly used as a stimulant to restore alertness after sleep deprivation, the amount of pre-ictal dietary caffeine was not increased in our study, thus indicating that caffeine is not a common contributor to the events leading to a seizure. However, none of the patients included in Paper I had used energy drinks. The question concerning the role of caffeine in large doses combined with various additives commonly used in these beverages is thus left unanswered. Individuals without prior daily exposure to caffeine might be more vulnerable to a possible seizure-inducing effect of excessive ingestion (Boison, 2011; Jacobson et al., 1996). As a digression in this context, life-long caffeine consumption is thought to protect against neurological conditions like cognitive decline, stroke, and Alzheimer's and Parkinson's disease. It should therefore not without reason be discouraged as part of a healthy balanced diet (Nehlig, 2016).

5.4 Treatment adherence

We detected non-adherence to AEDs in a very large proportion of patients with epilepsy admitted to hospital for seizures. That the highest proportion of 46% definite and probable non-adherent patients was found in the cohort under 30 years is particularly worrying, but the predominance in young people is perhaps not very surprising. We believe that the number of patients identified in the present hospital-based findings merely represent the "tip of the iceberg" of this problem, as only a part of patients with established epilepsy are admitted to hospital when a seizure occurs.

The study on seizure precipitants performed as a student thesis in patients with uncontrolled seizures in our outpatient clinic (Vedeld, 2005) provided intriguing findings (Table 1). The patients were first asked to write down factors that they believed could precipitate seizures. Only 4 % spontaneously reported missed drug intake, whereas it was reported in as many as 40% when ticked in a questionnaire. This discrepancy prompts the need to increase the awareness of this problem among the patients.

When patients themselves suspect missed drug intake as the cause of seizures, they may be less inclined to seek emergency care. On the other hand, patients with non-adherence may suffer from more severe or multiple seizures, resulting in acute admission. In a study in young adults, generalized tonic-clonic seizures occurred more often than other seizure types when

the relapse was caused by noncompliance (Specht et al., 2003). We have recently also studied non-adherence in status epilepticus (Lie et al., 2015) using TDM. In this retrospective study, 38% of admissions for status epilepticus in patients with epilepsy had serum concentration/dose ratios <75% of a drug fasting control value, indicating missed drug intake (Lie et al., 2015). In line with these findings, current guidelines for the management of status epilepticus recommend that patients on prophylactic treatment should receive a bolus dose of their AEDs as part of the initial treatment (Brophy et al., 2012). Status epilepticus related to non-adherence is usually treatment responsive, but may still be critical in patients with comorbidities and multihandicaps (Lie et al., 2015). Among recurrent episodes of status epilepticus, AED withdrawal has been identified as the leading cause (Tsetsou et al., 2015).

Moreover, non-adherence appeared to be more prevalent among admissions of patients with generalized epilepsies compared to those with focal epilepsies. In juvenile myoclonic epilepsy low medication adherence has specifically been pointed out as a very important cause of pseudo-drug resistance (Crespel et al., 2013).

Even if there was a trend towards better adherence among patients with intellectual disability, it is noteworthy that 12% of admissions in this group was associated with definite non-adherence. Being residents of sheltered housing with supervised drug ingestion, the causes of missed doses may be different from independently living people with epilepsy, e.g. swallowing dysfunction or behavioural problems. High awareness of adherence must continue even in this group. Non-educated assistant carers may sometimes be poorly informed about the principles of prophylactic AED treatment. The present findings highlight the importance of training and supervision of all health care professionals who are in charge of these patients.

Complex regimens have always been thought to be troublesome. Although some authors report a significantly better degree of adherence in patients on monotherapy (Bryant and Ereshefsky, 1981; Specht et al., 2003), we found no difference between monotherapy and polytherapy (Cramer et al., 2002; Sweileh et al., 2011). Easy-to-follow medication regimens and few adverse effects are considered important factors for good adherence (Faught, 2012). On the other hand, patients on polytherapy more frequently have uncontrolled epilepsy, and may therefore have more focus on following strict medication routines. They are also more likely to be seen regularly at outpatient clinics where concerns can be dealt with.

As a whole, we found no difference in treatment adherence between patients on monotherapy compared to those on polytherapy. However, patients using levetiracetam was identified as having lower adherence compared to those using valproate, carbamazepine and lamotrigine (p=<0.001). Interestingly, definite non-adherence was present in 63% (17 of 27 patients) of admissions with levetiracetam in polytherapy. In these 17 admissions, 19 of 20 C/D ratios of AEDs combined with levetiracetam were also consistent with non-adherence. Our findings suggest that patients treated with levetiracetam had a higher rate of non-adherence, as defined in this study, compared to other commonly used AEDs. This is probably caused by its short plasma half-life (6-8 h). In polytherapy, non-adherence was determined by the drug with the lowest C/D ratio; thus levetiracetam appears to be a more sensitive indicator of irregular intake than many other AEDs.

The pharmacokinetic variability of serum concentrations between and within patients is well known and frequently discussed (Johannessen Landmark et al., 2012). Our definition of non-adherence (C/D ratio on admission <75% compared to drug fasting control) was used to reduce the impact of this phenomenon. Importantly, the control values could of course vary as well. In the most extreme scenario where all C/D ratios on admission are at their lowest (e.g. 75% of average ratio) and all controls at their highest (125% of average ratio), the ratio will still be 0.6. As presented in our study, 24% of all patients had a ratio <0.5.

Rapid identification of non-adherence is essential. Prompt measurements of AED serum concentrations should be part of the emergency care for patients acutely hospitalized for seizures to permit this issue to be thoroughly addressed prior to discharge. Dose increase on false premises will certainly not improve adherence.

5.5 Sleep loss, alcohol and associated seizure precipitants

Our study elucidates the role of sleep loss as a seizure precipitant in a clinical setting. As with non-adherence, young people seem to be especially at risk of lack of sleep prior to seizures. However, the various seizure precipitants complicating to sleep deprivation seems to be particularly difficult to decipher. Sleep deprivation and alcohol are intertwined in late night party settings, with the implication that when seizures occur after sleep loss, the role of

alcohol should be explored as well and *vice versa*. The alcohol withdrawal seizure is a symptom mainly occurring primarily during the early phase of withdrawal, which is also characterized by insomnia, restlessness and autonomic symptoms. However, seizures may occur in the absence of other signs of the alcohol withdrawal syndrome, which often rather occur in the postictal phase. More than 90% of seizures emerge within 48h of cessation of prolonged drinking. More than half of the individuals present with repeated seizures, and in up to 5% they may progress to status epilepticus. More than 50% of withdrawal seizures are associated with concurrent risk factors such as prior epilepsy, structural brain lesions or use of other drugs (Jesse et al, 2016).

Subjects with established epilepsy may have a much lower threshold for the seizure-inducing effect of alcohol. It may usually occur on the day after alcohol intake, often after "binge" drinking (Kasteleijn-Nolst Trenité et al., 2013), but frequently outside the setting of alcohol abuse and the alcohol withdrawal syndrome. Surprisingly, this common, practical problem is insufficiently explored. Only one randomized clinical trial (Höppener et al., 1983) has addressed this particular issue; an intake of one to three drinks each containing approximately 10 g of ethanol twice a week in an inpatient setting did not alone increase seizure susceptibility in treated patients with predominantly focal epilepsy. Alcohol sensitivity may vary among epileptic disorders. Genetic generalized epilepsies, particularly juvenile myoclonic epilepsy, seem to be more vulnerable to alcohol and sleep deprivation, particularly the combination of the two factors (Pedersen and Petersen, 1998).

Poor sleep, as well as alcohol use, is also associated with psychosocial adverse events and psychiatric disorders. These interactions may also be complicated and difficult to sort out. It should be borne in mind that the relationship between epilepsy and psychiatric disease may be bidirectional; psychiatric disease may precede the onset of epilepsy and *vice versa.* Furthermore, a range of neuroactive drugs may lower the seizure threshold, particularly antipsychotics (Bakken et al., 2014; Kanner and Hesdorffer, 2012; Kumlien and Lundberg, 2010).

It has been stated that "happiness is a very powerful anticonvulsant" (Fenwick, 1990); the opposite may be true for unhappiness. Nevertheless, in our study we found no association between sleep loss and depression or anxiety as measured by the HADS score or with

perceived stress according to the visual analogue scale. Conceivably, the reason might be that these factors partly were outweighed by party or other merry social settings in young people or possibly by a weakness of the instruments. Bjelland identified a cut-off point of 8/21 for both anxiety and depression, giving a specificity of 0.78 and a sensitivity of 0.9 for anxiety and a specificity of 0.79 and a sensitivity of 0.83 for depression (Bjelland et al., 2002). Although no significant difference in HADS anxiety was found comparing the sleep deprived to those with adequate sleep in our study; the mean score was fairly high in both groups (7.95 and 6.86 respectively). The score is at least partly likely to be influenced by a recent seizure. Nevertheless, appropriate attention to sleep patterns in epilepsy patients with psychiatric comorbidity should be given. Psychiatric diseases are often associated with episodic emotional stress, sleep disturbances, resignation and disregard of life-style recommendations.

The independent role of sleep loss as a seizure trigger has been debated (Malow et al., 2002), but we found evidence for poor sleep hygiene being an independent seizure-precipitating factor. This enhances the understanding and awareness of the intricate role of sleep in the cascade of events that leads to a seizure and may improve patient care. The finding corroborates that people with epilepsy, in particular those with brittle seizure control, should be advised to avoid sleep deprivation.

5.6 Additional seizure precipitants to be considered

As underscored in the preceding discussion on sleep loss, seizure precipitants often occur in combination forming multifaceted clinical circumstances that should be analysed in detail. It is worth mentioning that the impact of photostimulation is often complex (Shoja et al., 2007). Computer games often extend into the nights with a sense of excitement, stress and sleep deprivation. Energy drinks may be blamed, sometimes unwarranted (Fisher et al., 2005; Loiseau, 1997; Piccioli et al., 2005; Singh et al., 2001). In clinical studies, 3-17% of patients report photostimulation as a precipitant (Frucht et al., 2000; Hayden et al., 1992; Spatt et al., 1998; Spector et al., 2000). Young people with genetic generalized epilepsies such as juvenile myoclonic epilepsy and other photosensitive epilepsies, including Jeavon's syndrome (Panayiotopoulos, 2010), are particularly vulnerable to these situations. These settings may also be associated with non-adherence to AEDs. Furthermore, physical activity, fatigue, changes in sleep and mental stress are important cofactors to consider. (Ferlisi and Shorvon,

2014; McKee and Privitera, 2017; Nakken, 1999).

Of course, the well-established concept of catamenial epilepsy should be considered. Menstruation may be associated with a range of ill-defined symptoms that may aggravate other seizure triggers (Foldvary-Schaefer and Falcone, 2003).

Finally, although intercurrent illnesses often alter sleep pattern, increases stress and sometimes make the patients reluctant to take their AEDs, fever may by itself cause seizures (Dubé et al., 2005). Febrile seizures rarely occur outside young childhood, but may persist in SCN1A-related epilepsies (Camfield and Camfield, 2015).

5.7 Methodological considerations

In addition to the methodological considerations discussed in papers I-III, this study does have some generally relevant methodological limitations. Only patients able to cooperate well completed the interview and the questionnaires with a risk of losing important patient groups including the intellectually disabled, patients with dementia, aphasia, or other severe comorbid medical conditions. This was done by careful clinical judgement, however, not without risk of selection bias. All patients were nevertheless included in the assessment of non-adherence. Fortunately, promising new methods to facilitate the inclusion of patients with intellectual disability in similar studies have recently been suggested (Illingworth et al., 2015).

The time to complete restoration after a seizure is hard to estimate with certainty in individual patients. The level of cognitive function does indeed vary, both habitually and postictally, and a more systematic approach with the use of a tool like the Mini Mental Status Examination (Folstein et al., 1975) could possibly have identified patients susceptible of giving inaccurate data.

Furthermore, questionnaires like ours tend to be associated with an increased number of false positives,as patients may want to seek an explanation for why the seizures occurred when they did. Patient awareness and knowledge of possible precipitants is important, as especially spontaneous seizures may have more severe vocational restrictions and consequences for driving. However, in a study with 37 selectable precipitants, only 53% of the sample reported

seizure precipitants (Nakken et al., 2005), in contrast to other studies with recognized precipitants in 62-91% of included patients (Frucht et al., 2000; Millett et al., 1997; Spatt et al., 1998; Spector et al., 2000). Whether the interview is done in proximity of a seizure or in a seizure free period might influence on the reporting of precipitants.

Unfortunately, complete data were not retrieved for all patients. However, the follow-up of 88-92% of included subjects is within the recommendation of more than 80% (Guyatt et al., 2011). In this regard, the data presented are assumed to be valid.

Another important issue is the prodromal phenomenon. It is defined as "a preictal subjective or objective preictal clinical alteration (e.g., ill-localized sensation or agitation) that heralds the onset of an epileptic seizure, but does not take part of it" (Blume et al., 2001). These sensations may be difficult to differentiate from a seizure precipitant for both patients and proxies. It may be associated with a range of unspecific symptoms, including stress, anxiety, irritability, nausea, poor sleep or depressed mood as a signal of an emerging seizure. It may last for hours or days and maybe even weeks, in contrast to the aura which usually is a shortlasting subjective ictal phenomenon that immediately precedes the seizure or occurs alone as a sensory seizure (Blume et al., 2001). Rarely, a more prolonged aura may take place (aura continua), as a form of focal status epilepticus (Proposal for revised clinical and electroencephalo-graphic classification of epileptic seizures 1981).

To date, the prodromal phenomenon *per se* has not convincingly been associated with abnormal electroencephalographic activity. However, in a Danish study, three of six patients had EEG changes corresponding to nonconvulsive status epilepticus during symptoms considered to represent a prodromal phase (Alving and Beniczky, 2013). One could only speculate whether some reported seizure precipitants in fact rather represent prodromes or prolonged auras. Nevertheless, a small study by Maiwald questions the predictive value of prodromes and the specificity of their occurrence in the preictal period (Maiwald et al., 2011). To make it even harder to decipher, the patients' ability to predict seizures could of course also be based on their knowledge of circumstances which increase the probability of a subsequent seizure, without being a prodrome. Last, but not least, a prodromal phase may promote other precipitants, for instance lack of sleep, and thereby initiate a vicious circle. There are obvious difficulties in distinguishing prodromes from life-style irregularities that

can be controlled by the patients themselves. In Paper III, we have been unable to control for this potential confounder.

Studies trying to identify various seizure triggers have predominantly been performed in outpatient clinics (Antebi and Bird, 1993; Ferlisi and Shorvon, 2014; Nakken et al., 2005; Spector et al., 2000; Wassenaar et al., 2014;) or in selected groups of patients (da Silva Sousa et al., 2005; Fang et al., 2008) partly with seizure remission. It is a strength that the present study was performed in patients with uncontrolled seizures and in close proximity of an acute seizure event. Obviously, the circumstances preceding a seizure are best remembered in the immediate period after a seizure when cognitive function is restored. Questionnaire studies in outpatients may to a higher degree be influenced by recall bias, myths and acquired knowledge of general aspects of epilepsy, which do not always relate to thepatients' own specific disorder. In interview studies, the patients may have an additional inclination to present themselves as responsible and reliable people, and might thus possibly have a tendency to ignore regrettable and self-inflicted situations that have led to seizure breakthrough in the past.

5.8 Suggestions for future research

We believe that future studies on seizure precipitating factors should focus on acute seizure events in uncontrolled epilepsy rather than questionnaires in routine outpatients who may have been seizure free for a long time.

Case reports on the seizure inducing effect of excessive caffeine intake in the form of energy drinks are not yet convincing due to the common occurrence of many other associated factors with potential contribution. Case series suggesting that these drinks alone may precipitate seizures are warranted.

More scientific attention should be given to the various causes of poor adherence. The clinical heterogeneity of poor medication behavior is vast. Barriers based on attitudes and perceptions: doubts about the need for AEDs, concerns about adverse effects and practical factors influencing medication taking have been emphasized recently (Chapman et al., 2014 and 2015; Pakpour et al., 2015). Accordingly, the management should focus on the individual

non-adherence pattern, tailoring the intervention to the patient profile (Blaschke et al., 2012; Eatock and Baker, 2007). The role of depression seems to be especially important to investigate further; in a recent study, adherence correlated with mood rather than with objective memory measures (McAuley et al., 2015). One could only speculate whether two different groups exist; one happy, careless party-related group and one unhappy, anxious group with psychosocial problems, lack of sleep and adherence resignation.

We have demonstrated that sleep loss alone may precipitate GTCs, but the role of sleep deprivation in order to facilitate the occurrence of focal non-motor seizures is less clear (Malow et al.2002; Malow, 2004) and should be further investigated.

Alcohol consumption in people with epilepsy varies a lot, as do the recommendations patients receive. How much alcohol is safe in people with active epilepsy? Follow-up studies after intervention on modifiable triggers like alcohol and sleep, with particular focus in idiopathic generalized epilepsy, are interesting areas for the further development of self-management epilepsy programs (Helmers et al., 2017).

6. Conclusions

The studies presented in this thesis emphasize the need for careful history taking to identify exogenous as well as endogenous seizure precipitants in order to enhance self-management support in seizure disorders.

Basic science investigations and anecdotal clinical reports suggest that caffeine might contribute to seizure generation, but our findings do not support the idea that increased dietary caffeine is a common seizure facilitator. Undue restrictions should be avoided.

Poor medication-taking behaviour is a common cause of breakthrough seizures, particularly in young adults with epilepsy. The need for adherence support should be considered for all individuals when uncontrolled seizures occur in spite of appropriately optimized AED regimens.

Sleep loss is an independent seizure trigger when other relevant seizure precipitants also are considered. The impact of alcohol on sleep and seizures is particularly difficult to sort out. Insights in these aspects may improve patient care.

The cascade of events leading to a seizure is complex. A practical strategy to prevent seizures should include the discussion of relevant precipitants with each individual patient, and to tailor interventions accordingly. Sufficient knowledge on seizure facilitation and appropriate communication with the patients are key elements in the comprehensive personalized management of epilepsy.

7. Epilogue

Some think a flap of a butterfly wing is enough to alter the course of the weather (Lorentz, 1963). Likewise, seizure precipitants often occur in combination forming multifaceted clinical circumstances that push the patient closer to a seizure, until finally the smallest factor not even thought of, is decisive. This is a fundamental and philosophical challenge when interpreting the results of the present thesis.

8. Erratum

In paper I, paragraph 3.2, 20 patients are reported lost to follow-up. Correctly, 12 patients were *lost to follow-up* and 8 patients *lost due to missing data* as illustrated in Figure 1, page 22.

9. References

Aird RB. The importance of seizure-inducing factors in the control of refractory forms of epilepsy. Epilepsia. 1983; 24:567-83.

Aird RB, Gordon NS. Some excitatory and inhibitory factors involved in the epileptic state. Brain Dev. 1993; 15:299-304. Review.

Alving J, Beniczky S. Epileptic prodromes: are they nonconvulsive status epilepticus? Seizure. 2013; 22:522-7.

Antebi D, Bird J. The facilitation and evocation of seizures. A questionnaire study of awareness and control. Br J Psychiatry. 1993; 162:759-64.

Aranda JV, Gorman W, Bergsteinsson H, Gunn T. Efficacy of caffeine in treatment of apnea in the low-birth-weight infant. J Pediatr. 1977; 90:467-472.

Bakken IJ, Revdal E, Nesvåg R, Brenner E, Knudsen GP, Surén P, Ghaderi S, Gunnes N, Magnus P, Reichborn-Kjennerud T, Camilla Stoltenberg, Trogstad LI, Håberg SE, Brodtkorb E. Substance use disorders and psychotic disorders in epilepsy: a population-based registry study. Epilepsy Res. 2014; 108:1435-43.

Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, Tomson T, Hauser WA. Recommendation for a definition of acute symptomatic seizure. Epilepsia. 2010; 51:671-5.

Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classifi cation and Terminology, 2005-2009. Epilepsia. 2010; 51:676–85.

Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: A summary of the Thirteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIII). Epilepsia. 2017 Jan 23.

Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002; 52:69-77.

Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annu Rev Pharmacol Toxicol. 2012; 52:275-301.

Blume WT, Lüders HO, Mizrahi E, Tassinari C, van Emde Boas W, Engel J Jr. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classifi cation and terminology. Epilepsia. 2001; 42:1212–18.

Boison D. Methylxanthines, seizures, and excitotoxicity. Handb Exp Pharmacol. 2011; 200:251–66.

Bonhila L, Li LM. Heavy coffee drinking and epilepsy. Seizure. 2004; 13:284-5.

Brodtkorb E, Michler RP, Gu W, Steinlein OK. Speech-induced aphasic seizures in epilepsy caused by LGI1 mutation. Epilepsia. 2005; 46:963-6.

Brodtkorb E, Samsonsen C, Sund JK, Bråthen G, Helde G, Reimers A. Treatment non-adherence in pseudo-refractory epilepsy. Epilepsy Res. 2016; 122:1-6.

Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, Laroche SM, Riviello JJ Jr, Shutter L, Sperling MR, Treiman DM, Vespa PM; Neurocritical Care Society Status Epilepticus Guideline Writing Committee.. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012; 17:3-23.

Bryant SG, Ereshefsky L. Determinants of compliance in epileptic outpatients. Drug Intell Clin Pharm. 1981; 15:572-7.

Bråthen G, Brodtkorb E, Helde G, Sand T, Bovim G. The diversity of seizures related to alcohol use. A study of consecutive patients. Eur J Neurol. 1999; 6:697-703.

Bråthen, Geir. The classification and clinical diagnosis of alcohol-related seizures. Tapir Akademisk Forlag; 2001.

Bråthen G, Ben-Menachem E, Brodtkorb E, Galvin R, Garcia-Monco JC, Halasz P, Hillbom M, Leone MA, Young AB. EFNS guideline on the diagnosis and management of alcohol-related seizures: report of an EFNS task force. Eur J Neurol. 2005 Aug; 12:575-81.

Burdette DE, Feldman RG. Factors that can exacerbate seizures. In S.R. Resor, H. Kutt (Eds.), The medical treatment of epilepsy, Marcel Dekker, New York; 1992, pp. 79–89.

Calabrò RS, Italiano D, Gervasi G, Bramanti P. Single tonic-clonic seizure after energy drink abuse. Epilepsy Behav. 2012; 23:384-5.

Camfield P, Camfield C. Febrile seizures and genetic epilepsy with febrile seizures plus (GEFS+). Epileptic Disord. 2015; 17:124-33.

Chapman SC, Horne R, Chater A, Hukins D, Smithson WH. Patients' perspectives on antiepileptic medication: relationships between beliefs about medicines and adherence among patients with epilepsy in UK primary care. Epilepsy Behav. 2014; 31:312-20.

Chapman SC, Horne R, Eade R, Balestrini S, Rush J, Sisodiya SM. Applying a perceptions and practicalities approach to understanding nonadherence to antiepileptic drugs. Epilepsia. 2015; 56:1398-407.

Chu NS. Caffeine- and aminophylline-induced seizures. Epilepsia. 1981; 22:85-94.

Cleary K, Levine DA, Hoffman RS. Adolescents and young adults presenting to the emergency department intoxicated from a caffeinated alcoholic beverage: a case series. Ann Emerg Med. 2012; 59:67-9.

Commission on Antiepileptic Drugs ILAE. Guidelines for therapeutic monitoring of antiepileptic drugs. Epilepsia. 1993; 34:585-7.

Cramer JA, Russell ML. Compliance in epilepsy. Strategies to enhance adherence to a medical regimen. Epilepsy Res Suppl. 1988; 1:163-75.

Cramer JA, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. Epilepsy Behav. 2002; 3:338-42.

Crespel A, Gelisse P, Reed RC, Ferlazzo E, Jerney J, Schmitz B, Genton P. Management of juvenile myoclonic epilepsy. Epilepsy Behav. 2013; 28 Suppl 1:S81-6.

Cutrufo C, Bortot L, Giachetti A, Manzini S. Differential effects of various xanthines on pentylenetetrazole-induced seizures in rats: an EEG and behavioural study. Eur J Pharmacol. 1992; 222:1-6.

Dahl J, Brorson LO, Melin L. Effects of a broad-spectrum behavioral medicine treatment program on children with refractory epileptic seizures: an 8-year follow-up. Epilepsia. 1992; 33:98-102.

da Silva Sousa P, Lin K, Garzon E, Sakamoto AC, Yacubian EM. Self-perception of factors that precipitate or inhibit seizures in juvenile myoclonic epilepsy. Seizure. 2005; 14:340-6.

Davis KL, Candrilli SD, Edin HM. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. Epilepsia. 2008; 49:446-54.

Dubé C, Vezzani A, Behrens M, Bartfai T, Baram TZ. Interleukin-1beta contributes to the generation of experimental febrile seizures. Ann Neurol. 2005; 57:152-5. Erratum in: Ann Neurol. 2005; 57:609.

Eatock J, Baker GA. Managing patient adherence and quality of life in epilepsy. Neuropsychiatr Dis Treat. 2007; 3:117-31.

Engel J Jr. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia. 2001; 42:796–803.

Ettinger A, Reed M, Cramer J. Depression and comorbidity in community-based patients with epilepsy or asthma. Neurology. 2004; 63:1008–14.

Ettinger AB, Manjunath R, Candrilli SD, et al. Prevalence and cost of nonadherence to antiepileptic drugs in elderly patients with epilepsy. Epilepsy Behav. 2009; 14:324-9.

Faingold CL, N'Gouemo P, Riaz A. Ethanol and neurotransmitter interactions--from molecular to integrative effects. Prog Neurobiol. 1998; 55:509-35.

Fang PC, Chen YJ, Lee IC. Seizure precipitants in children with intractable epilepsy. Brain Dev. 2008; 30:527-32.

Faught RE, Weiner JR, Guérin A, et al. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. Epilepsia. 2009; 50:501-9.

Faught E. Adherence to antiepilepsy drug therapy. Epilepsy Behav. 2012; 25:297-302.

Fenwick PB. Behavioural treatment of epilepsy. Postgrad Med J. 1990; 66:336-8. Review.

Ferlisi M, Shorvon S. Seizure precipitants (triggering factors) in patients with epilepsy. Epilepsy Behav. 2014; 33:101-5.

Ferre S, von Euler G, Johansson B, Fredholm BB, Fuxe K. Stimulation of high-affinity adenosine A2 receptors decreases the affinity of dopamine D2 receptors in rat striatal membranes. Proc Natl Acad Sci U S A. 1991; 88:7238-41.

Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, Engel J Jr. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia. 2005; 46:470-2.

Fisher RS, Harding G, Erba G, Barkley GL, Wilkins A; Epilepsy Foundation of America Working Group.. Photic- and pattern-induced seizures: a review for the Epilepsy Foundation of America Working Group. Epilepsia. 2005; 46:1426-41.

Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J Jr, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshé SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014; 55:475-82.

Foldvary-Schaefer N, Falcone T. Catamenial epilepsy: pathophysiology, diagnosis, and management. Neurology. 2003; 61:S2-15. Review.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975; 12:189-98.

Fountain NB, Kim JS, Lee SI. Sleep deprivation activates epileptiform discharges independent of the activating effects of sleep. J Clin Neurophysiol. 1998; 15:69-75.

Fredholm BB, Dunwiddie TV. How does adenosine inhibit transmitter release? Trends Pharmacol Sci. 1988; 9:130-4.

Frucht MM, Quigg M, Schwaner C, Fountain NB. Distribution of seizure precipitants among epilepsy syndromes. Epilepsia. 2000; 41:534-9.

Garnett WR. Antiepileptic drug treatment: outcomes and adherence. Pharmacotherapy. 2000; 20:191-199.

Gomes A, Das M, Vedasiromoni JR, Ganguly DK. Proconvulsive effect of tea

(Camellia sinensis) in mice. Phytother Res. 1999; 13:376-9.

Gunderson CH, Dunne PB, Feyer TL. Sleep deprivation seizures. Neurology. 1973; 23:678-86.

Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011; 64:407-15.

Haller CA, Meier KH, Olson KR. Seizures reported in association with use of dietary supplements. Clin Toxicol (Phila). 2005; 43:23-30.

Hao X, Goldberg D, Kelly K, et al. Uncontrolled epilepsy is not necessarily the same as drug-resistant epilepsy: differences between populations with newly diagnosed epilepsy and chronic epilepsy. Epilepsy Behav. 2013; 29:4-6.

Hayden M, Penna C, Buchanan N. Epilepsy: patient perceptions of their condition. Seizure. 1992; 1:191-7.

Heckman MA, Weil J, Gonzalez de Mejia E. Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. J Food Sci. 2010; 75:77-87.

Helde G, Brodtkorb E, Bråthen G, Bovim G. An easily performed group education programme for patients with uncontrolled epilepsy--a pilot study. Seizure. 2003; 12:497-501.

Helde G, Bovim G, Bråthen G, Brodtkorb E. A structured, nurse-led intervention program improves quality of life in patients with epilepsy: a randomized, controlled trial. Epilepsy Behav. 2005; 7:451-7.

Helmers SL, Kobau R, Sajatovic M, Jobst BC, Privitera M, Devinsky O, Labiner D, Escoffery C, Begley CE, Shegog R, Pandey D, Fraser RT, Johnson EK, Thompson

NJ, Horvath KJ; Centers for Disease Control and Prevention Managing Epilepsy Well Network.. Self-management in epilepsy: Why and how you should incorporate self-management in your practice. Epilepsy Behav. 2017 Feb 12. pii: S1525-5050(16)30651-5. doi: 10.1016/j.yebeh.2016.11.015. [Epub ahead of print]

Huskisson EC. Measurement of pain. Lancet. 1974; 2:1127-31.

Höppener RJ, Kuyer A, van der Lugt PJ. Epilepsy and alcohol: the influence of social alcohol intake on seizures and treatment in epilepsy. Epilepsia. 1983; 24:459-71.

Illingworth JL, Watson P, Xu S, Manford M, Ring H. A method for identifying associations between seizures and possible trigger events in adults with intellectual disability. Epilepsia. 2015; 56:1812-8.

Iyadurai SJ, Chung SS. New-onset seizures in adults: possible association with consumption of popular energy drinks. Epilepsy Behav. 2007; 10:504-8.

Jacobson KA, von Lubitz DK, Daly JW, Fredholm BB. Adenosine receptor ligands: differences with acute versus chronic treatment. Trends Pharmacol Sci. 1996; 17: 108–13.

Jarvie S, Espie CA, Brodie MJ. The development of a questionnaire to assess knowledge of epilepsy: 1--General knowledge of epilepsy. Seizure. 1993; 2:179-85.

Jesse S, Bråthen G, Ferrara M, Keindl M, Ben-Menachem E, Tanasescu R, Brodtkorb E, Hillbom M, Leone MA, Ludolph AC. Alcohol withdrawal syndrome: mechanisms, manifestations, and management. Acta Neurol Scand. 2017; 135:4-16.

Johannessen Landmark C, Johannessen SI, Tomson T. Host factors affecting antiepileptic drug delivery-pharmacokinetic variability. Adv Drug Deliv Rev. 2012; 64:896-910.

Kanner AM, Hesdorffer DC. Neuropsychiatric complications of epilepsy. Handb

Clin Neurol. 2012; 107:461-82. Review.

Kasteleijn-Nolst Trenité DG, Schmitz B, Janz D, Delgado-Escueta AV, Thomas P, Hirsch E, Lerche H, Camfield C, Baykan B, Feucht M, Martínez-Juárez IE, Duron RM, Medina MT, Rubboli G, Jerney J, Hermann B, Yacubian E, Koutroumanidis M, Stephani U, Salas-Puig J, Reed RC, Woermann F, Wandschneider B, Bureau M, Gambardella A, Koepp MJ, Gelisse P, Gurses C, Crespel A, Nguyen-Michel VH, Ferlazzo E, Grisar T, Helbig I, Koeleman BP, Striano P, Trimble M, Buono R, Cossette P, Represa A, Dravet C, Serafini A, Berglund IS, Sisodiya SM, Yamakawa K, Genton P. Consensus on diagnosis and management of JME: From founder's observations to current trends. Epilepsy Behav. 2013; 28 Suppl 1:S87-90.

Kaufman KR, Sachdeo RC. Caffeinated beverages and decreased seizure control. Seizure. 2003; 12:519-21.

Koepp MJ, Caciagli L, Pressler RM, Lehnertz K, Beniczky S. Reflex seizures, traits, and epilepsies: from physiology to pathology. Lancet Neurol. 2016; 15:92-105.

Kumlien E, Lundberg PO. Seizure risk associated with neuroactive drugs: data from the WHO adverse drug reactions database. Seizure. 2010; 19:69-73.

Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010; 51:1069-77.

Kyngäs H. Compliance with health regimens of adolescents with epilepsy. Seizure. 2000; 9:598-604.

Lawn N, Lieblich S, Lee J, Dunne J. Are seizures in the setting of sleep deprivation provoked? Epilepsy Behav. 2014; 33:122-5.

Leach JP, Mohanraj R, Borland W. Alcohol and drugs in epilepsy: pathophysiology, presentation, possibilities, and prevention. Epilepsia. 2012; 53 Suppl 4:48-57.

Lie IA, Hoggen I, Samsonsen C, Brodtkorb E. Treatment non-adherence as a trigger for status epilepticus: An observational, retrospective study based on therapeutic drug monitoring. Epilepsy Res. 2015; 113:28-33.

Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. Lancet. 2012; 380:1180-92.

Loiseau P. Seizure precipitants. In Engels J, Pedley TA. (Eds) Epilepsy. A comprehensive text book, Lippincott-Raven, Philadelphia; 1997, pp.93-7.

Lorenz EN. Deterministic nonperiodic flow. J. Atmos. Sci. 1963; 20: 130–141.

Maiwald T, Blumberg J, Timmer J, Schulze-Bonhage A. Are prodromes preictal events? A prospective PDA-based study. Epilepsy Behav. 2011; 21:184-8.

Malow BA, Passaro E, Milling C, Minecan DN, Levy K. Sleep deprivation does not affect seizure frequency during inpatient video-EEG monitoring. Neurology. 2002; 59:1371-4.

Malow BA. Sleep deprivation and epilepsy. Epilepsy Curr. 2004; 4:193-5.

Mattson, M.E (2013). Update on Emergency Department Visits Involving Energy Drinks: A Continuing Public Health Concern. The CBHSQ Report: January 10, 2013. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD.

McAuley JW, Passen N, Prusa C, Dixon J, Cotterman-Hart S, Shneker BF. An evaluation of the impact of memory and mood on antiepileptic drug adherence. Epilepsy Behav. 2015; 43:61-5.

McKee HR, Privitera MD. Stress as a seizure precipitant: Identification, associated factors, and treatment options. Seizure. 2017 Jan;44:21-26.

Méndez M, Radtke RA. Interactions between sleep and epilepsy. J Clin Neurophysiol. 2001; 18:106-27. Review.

Michelucci R, Gardella E, de Haan GJ, Bisulli F, Zaniboni A, Cantalupo G, Alberto Tassinari C, Tinuper P, Nobile C, Nichelli P, Kasteleijn-Nolst Trenité DG. Telephone-induced seizures: a new type of reflex epilepsy. Epilepsia. 2004; 45:280-3.

Millett CJ, Fish DR, Thompson PJ. A survey of epilepsy-patient perceptions of video-game material/electronic screens and other factors as seizure precipitants. Seizure. 1997; 6:457-9.

Mortelmans LJ, Van Loo M, De Cauwer HG, Merlevede K. Seizures and hyponatremia after excessive intake of diet coke. Eur J Emerg Med. 2008; 15:51.

Mørland, J. Alkohol i kroppen, Norwegian Directorate of Health; 2005. Accessed March 13th 2017: https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/455/Alkohol-i-kroppen-IS-1076-bokmal.pdf

Nakken KO. Physical exercise in outpatients with epilepsy. Epilepsia. 1999; 40:643-51.

Nakken KO, Solaas MH, Kjeldsen MJ, Friis ML, Pellock JM, Corey LA. Which seizure-precipitating factors do patients with epilepsy most frequently report? Epilepsy Behav. 2005; 6:85–9.

Nakken KO, Refsland G, Lillestølen KM, Solaas MH. Seizure-precipitating factors in epilepsy--what do patients report? Tidsskr Nor Laegeforen. 2005; 125:2172-4.

Nehlig A. Effects of coffee/caffeine on brain health and disease: What should I tell my patients? Pract Neurol. 2016; 16:89-95.

Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005; 353:487-97. Review.

Ottman R, Lipton RB, Ettinger AB, et al. Comorbidities of epilepsy: results from the Epilepsy Comorbidities and Health (EPIC) survey. Epilepsia. 2011; 52:308–15.

Pakpour AH, Gholami M, Esmaeili R, Naghibi SA, Updegraff JA, Molloy GJ, Dombrowski SU. A randomized controlled multimodal behavioral intervention trial for improving antiepileptic drug adherence. Epilepsy Behav. 2015; 52:133-42.

Panayiotopoulos CP. Reflex seizures and related epileptic syndromes. In Panayiotopoulos CP. A clinical guide to epileptic syndromes and their treatment, 2nd edn. London, Springer; 2010, pp.497–531.

Paschal AM, Hawley SR, St Romain T, et al. Measures of adherence to epilepsy treatment: review of present practices and recommendations for future directions. Epilepsia. 2008; 49:1115-22.

Pedersen SB, Petersen KA. Juvenile myoclonic epilepsy: clinical and EEG features. Acta Neurol Scand. 1998; 97:160-3.

Piccioli M, Vigevano F, Buttinelli C, Kasteleijn-Nolst Trenité DG. Do video games evoke specific types of epileptic seizures? Epilepsy Behav. 2005; 7:524-30.

Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1981; 22:489-501.

Röggla G, Moser B. Seizures in a night club. Lancet. 2007; 370:220.

Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. Addiction. 1993; 88:791-804.

Shiraishi H, Fujiwara T, Inoue Y, Yagi K. Photosensitivity in relation to epileptic syndromes: asurvey from an epilepsy center in Japan. Epilepsia. 2001; 42:393-7.

Shoja MM, Tubbs RS, Malekian A, Jafari Rouhi AH, Barzgar M, Oakes WJ. Video game epilepsy in the twentieth century: a review. Childs Nerv Syst. 2007; 23:265-7.

Singh R, Bhalla A, Lehl SS, Sachdev A. Video game epilepsy. Neurol India. 2001; 49:411-2.

Smithson WH, Hukins D, Colwell B, et al. Developing a method to identify medicines non-adherence in a community sample of adults with epilepsy. Epilepsy Behav. 2012; 24:49-53.

Spatt J, Langbauer G, Mamoli B. Subjective perception of seizure precipitants: results of a questionnaire study. Seizure. 1998; 7:391-5.

Specht U, Elsner H, May TW, Schimikowski B, Thorbecke R. Postictal serum levels of antiepileptic drugs for detection of compliance. Epilepsy Behav. 2003; 4:487-95.

Spector S, Cull C, Goldstein LH. Seizure precipitants and perceived self-control of seizures in adults with poorly-controlled epilepsy. Epilepsy Res. 2000; 38:207-16.

Stimmel GL, Dopheide JA. Psychotropic drug-induced reductions in seizure threshold. Incidence and consequences. CNS Drugs 1996; 5:37-50.

Sweileh WM, Ihbesheh MS, Jarar IS, et al. Self-reported medication adherence and treatment satisfaction in patients with epilepsy. Epilepsy Behav. 2011; 21:301-5.

Syvertsen MR, Thuve S, Stordrange BS, Brodtkorb E. Clinical heterogeneity of juvenile myoclonic epilepsy: follow-up after an interval of more than 20 years. Seizure. 2014; 23:344-8.

Syvertsen M, Nakken KO, Edland A, Hansen G, Hellum MK, Koht J. Prevalence and etiology of epilepsy in a Norwegian county-A population based study. Epilepsia. 2015; 56:699-706.

Tan J-H, Wilder-Smith E, Lim ECH, Ong BKC. Frequency of provocative factors in epileptic patients admitted for seizures: A prospective study in Singapore. Seizure. 2005; 14:464-9.

Tellez-Zenteno JF, Patten SB, Jette N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia. 2007; 48:2336–44.

Temkin NR, Davis GR. Stress as a risk factor for seizures among adults with epilepsy. Epilepsia. 1984; 25:450-6.

Thurman DJ, Beghi E, Begley CE, Berg AT, Buchhalter JR, Ding D, Hesdorffer DC, Hauser WA, Kazis L, Kobau R, Kroner B, Labiner D, Liow K, Logroscino G, Medina MT, Newton CR, Parko K, Paschal A, Preux PM, Sander JW, Selassie A, Theodore W, Tomson T, Wiebe S; ILAE Commission on Epidemiology.. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia. 2011; 52 Suppl 7:2-26.

Tomson T. Non-compliance and intractability of epilepsy. In Johannessen SI, Gram K, Sillanpää M, Tomson T. (Eds) Intractable epilepsy, Wrightson, Petersfield; 1995, pp.93-104.

Trabulo D, Marques S, Pedroso E. Caffeinated energy drink intoxication. Emerg Med J. 2011; 28:712-714.

Tsetsou S, Novy J, Rossetti AO. Recurrence of status epilepticus: prognostic role and outcome predictors. Epilepsia. 2015; 56:473-8.

Vedeld, L. Anfallsutløsende faktorer ved epilepsi. Student thesis. NTNU; 2005.

Wassenaar M, Kasteleijn-Nolst Trenité DG, de Haan GJ, Carpay JA, Leijten FS. Seizure precipitants in a community-based epilepsy cohort. J Neurol. 2014; 261:717-24.

Williams-Karnesky RL, Sandau US, Lusardi TA, et al. Epigenetic changes induced by adenosine augmentation therapy prevent epileptogenesis. J Clin Invest. 2013; 123:3552–3563.

World Health Organization. Adherence to long term therapies: evidence for action. Geneva: World Health Organization; 2003. Accessed March 13th 2017: http://www.who.int/chp/knowledge/publications/adherence_report/en/.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983; 67:361-70.

Zwillich CW, Sutton FD, Neff TA, Cohn WM, Matthay RA, Weinberger MM. Theophylline-induced seizures in adults. Correlation with serum concentrations. Ann Intern Med. 1975; 82:784-7.

10. Papers

Paper I

Paper II

Paper III

Paper I

Epilepsy & Behavior 28 (2013) 147–150

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Brief Communication

Is dietary caffeine involved in seizure precipitation?

Christian Samsonsen [a,*], Geir Bråthen [a,b], Arne Reimers [b,c], Grethe Helde [b], Eylert Brodtkorb [a,b]

[a] Department of Neurology and Clinical Neurophysiology, St. Olav's University Hospital, Trondheim, Norway
[b] Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway
[c] Department of Clinical Pharmacology, St. Olav's University Hospital, Trondheim, Norway

ARTICLE INFO

Article history:
Received 9 April 2013
Revised 3 May 2013
Accepted 4 May 2013
Available online 6 June 2013

Keywords:
Caffeine
Seizure
Epilepsy
Seizure precipitant

ABSTRACT

Caffeine acts as a central nervous stimulant by blocking A1 and A2A adenosine receptors. Its effect on seizures is complex. Animal studies and case reports indicate that acute caffeine exposure may induce seizures, whereas chronic exposure might have an opposite effect. Patients acutely hospitalized for seizures ($n = 174$) were asked for their consumption of caffeinated beverages 24 h prior to admission as well as their habitual caffeine intake. Twenty-four-hour caffeine consumption was also recorded in a later telephone interview on a seizure-free day ($n = 154$). Thus, the patients served as their own controls. Categorized data were analyzed using the Wilcoxon's signed-ranks test.

No difference was found between the intake of caffeine 24 h prior to the seizure and the habitual consumption ($p = 0.37$) or the consumption on a seizure-free day ($p = 0.13$).

Thus, caffeine does not appear to be a common seizure precipitant.

1. Introduction

Epilepsy is defined by recurrent seizures on a background of an enduring predisposition to seizures, presumed to be triggered by various precipitants, sometimes ill-defined and usually within physiological limits. Awareness of these factors is probably an underestimated part of the self-management of epilepsy [1].

Caffeine is the most commonly consumed central nervous system stimulant in Western society. Scandinavian countries top the worldwide list of caffeine consumption with around 400 mg of caffeine per person per day [2]. Caffeine has complex pharmacological actions. The main biological effects are mediated by blocking of the A1 and A2A adenosine receptors in the brain [3,4]. Adenosine is the final breakdown product of adenosine triphosphate (ATP). When the neuron is short of energy, adenosine is released from the postsynaptic cell and connects to receptors on the presynaptic membrane to slow down neuronal firing. Caffeine binds to the adenosine receptor but does not inhibit neurotransmitter release, and it therefore has an excitatory effect by allowing continued neuronal stimulation.

Animal studies indicate that caffeine may induce seizures [5–7]. Acute caffeine exposure has also been shown to diminish the seizure-protective effects of various antiepileptic drugs in electroshock- and pentylenetetrazole-induced convulsions in animal models [8–14]. Furthermore, several case reports suggest that excessive caffeine intake may precipitate seizures in some patients with epilepsy [15–23]. Caffeine-containing energy drinks have also been associated with new-onset seizures [19]. However, caffeine intake is so common that it may not be thought of in relation to seizures. In a large questionnaire study among people with epilepsy, caffeine consumption was not among the most frequently reported seizure precipitants, even though dietary factors were explicitly asked for [1].

The association between seizures and caffeine is complex. Acute and chronic exposure may have different effects [24,25]. In this study, we wanted to investigate the role of caffeine as a seizure precipitant in a clinical setting.

2. Methods

Unselected patients acutely hospitalized with epileptic seizures were included in this observational study. In patients considered to be able to cooperate, a semistructured interview including the pattern of caffeine consumption was performed. The patients were asked to estimate their caffeine intake during the last 24 h prior to the seizure, as well as their habitual 24 h caffeine consumption (Interview I). Interviews took place at a time when the patients were clinically considered to be cognitively restored after the seizure. A follow-up interview (Interview II) was performed at least 4 weeks later. The caffeine consumption was recorded on the same day of the week and at a time when no seizure had occurred within the last 24 h. The patients served as their own controls.

Beverages containing caffeine (coffee, tea, and colas) were recorded as standard units defined as one cup of coffee, two cups of tea, or three caffeinated soft drinks, according to their different caffeine contents [26].

* Corresponding author at: Department of Neurology and Clinical Neurophysiology, St. Olav's University Hospital, 7006 Trondheim, Norway. Fax: +47 72575774.
E-mail address: christian.samsonsen@stolav.no (C. Samsonsen).

1525-5050/$ – see front matter
http://dx.doi.org/10.1016/j.yebeh.2013.05.003

The caffeine intake was roughly categorized into four groups: (1) no caffeine, (2) low consumption (≤3 units), (3) moderate consumption (>3–≤6 units), and (4) high consumption (>6 units).

Seizures and epilepsies were categorized according to the revised 2010 classification of the International League Against Epilepsy [27].

Statistical analyses were performed using Wilcoxon's signed-ranks test.

The study was approved by the regional ethics committee, and all participants gave their informed written consent.

3. Results

3.1. Demographics and seizure characteristics

A total of 174 patients (mean age: 42.6 years, 57% males) with epileptic seizures were included in the study. Focal onset seizures were present in 102 patients, 62 had generalized seizures, and the seizure type could not be classified in 10.

Established epilepsy was present in 63 patients (36.2%), whereas new-onset epilepsy was diagnosed in 58 patients (33.3%). Genetic (idiopathic) generalized epilepsies were recognized in 22 patients (juvenile myoclonic epilepsy: 3, epilepsy with generalized tonic–clonic seizures only: 14, and various absence epilepsies: 5). Epilepsy with focal seizure onset was diagnosed in 89 patients, whereas the type of epilepsy could not be determined in 10 patients.

Twenty-one patients were considered to have alcohol-related seizures, whereas 32 had other sporadic or single seizures.

Of the 174 patients, 147 reported coffee as their main source of caffeine, whereas 17 reported soft drinks and 5 patients, exclusively tea. Some patients used a combination of caffeinated beverages.

3.2. Interviews

The median time from the seizure to Interview I was 23 h (range: 3–73 h). Of the 174 included patients, 154 were available for Interview II (median: 15 weeks after admission, range: 5–233 weeks). A total of 20 patients were lost to follow-up, ten of whom could not be interviewed a second time because of poor medical condition or death.

3.3. Caffeine consumption

Table 1 shows the reported caffeine consumption during the 24 h preceding the seizure and the estimated habitual daily intake (Interview I) as well as the consumption on a seizure-free day. Twenty-one patients had a high caffeine intake (>6 units) 24 h prior to the seizure. Twenty of them participated in Interview II. Nine of them also had a high intake (>6 units) at follow-up (Interview II), whereas 11 had a lower intake, and one reported no caffeine intake.

Table 2 shows the percentage distribution of the differences between the various 24-h caffeine consumptions: habitual consumption, prior to seizure (Interview I), and at follow-up on a seizure-free day (Interview II). It shows that 63% of the patients had kept their habitual caffeine intake during the 24 h prior the seizure, whereas 15% had a higher and 22% had a lower intake. Intake changes exceeding one category occurred in 8% only. One patient reported no habitual intake but had ingested more than six units 24 h prior to the seizure.

Table 1
Distribution of 24-h caffeine consumption in patients with an epileptic seizure.

	Interview I (n = 174)		Interview II (n = 154)
Caffeine consumption category	Prior to seizure, n (%)	Habitual, n (%)	Seizure-free day, n (%)
None	47 (27.0)	29 (16.7)	26 (16.9)
Low (≤3 units)	56 (32.2)	82 (47.1)	61 (39.6)
Moderate (>3–≤6 units)	50 (28.7)	41 (23.6)	43 (27.9)
High (>6 units)	21 (12.1)	22 (12.6)	24 (15.6)

Table 2
Changes in 24-h caffeine consumption.

Change in intake category	Habitual vs. prior to seizure (n = 174), n (%)	Follow-up vs. prior to seizure (n = 154), n (%)
Down three	2 (1.1)	6 (3.9)
Down two	4 (2.3)	6 (3.9)
Down one	32 (18.4)	35 (22.7)
Unchanged	110 (63.2)	72 (46.8)
Up one	18 (10.3)	28 (18.2)
Up two	7 (4)	6 (3.9)
Up three	1 (0.6)	1 (0.6)

Comparison of the caffeine consumption on the day of the seizure and on the follow-up day shows that 72 patients (47%) kept an unchanged intake; 16 of them were habitual nonconsumers both before and after the seizure. However, 56 patients reported use of caffeine in both situations; a higher intake prior to the seizure was reported by 23%, whereas 31% had a lower intake compared to follow-up.

The average consumption 24 h prior to the seizure was not higher than the reported average habitual consumption ($p = 0.37$) nor was it higher than the consumption on a seizure-free day ($p = 0.13$). The reported average habitual intake and the intake on a seizure-free day were similar ($p = 0.23$).

In the 121 patients diagnosed with epilepsy, the trend of less caffeine ingestion prior to the seizures was stronger compared to the habitual intake ($p = 0.073$). In the small subgroup with recognized genetic (idiopathic) epilepsies, it was even statistically significant ($p = 0.019$).

4. Discussion

In seizures perceived as spontaneous, trigger factors are vague or obscure. Various subthreshold factors may, in concert, lead to abnormal and hypersynchronous seizure activity in neuronal networks [28]. The role of caffeine has received little clinical attention in this context. We wished to investigate whether fluctuations in the consumption of caffeinated beverages might represent an overlooked seizure-precipitating factor. However, there was not even a trend towards increased intake prior to a seizure in this study, in spite of the fact that caffeine intake obviously may be associated with several other well-known seizure precipitants. Caffeine may cause impaired sleep and emotional tension. Conversely, stress, exhaustion, and fatigue may lead to increased caffeine intake. Caffeine is regularly used to restore alertness after lack of sleep. Alcohol consumption is also common in these settings.

Indeed, more patients (22%) had consumed less caffeine than habitually right before the seizure, whereas only 15% had increased their consumption. Even when asked on a seizure-free day after hospitalization, 31% of the patients reported higher caffeine consumption than on the day of the seizure, and only 23% reported a lower intake. One could speculate whether drowsiness resulting from reduced caffeine stimulation might contribute to seizure precipitation. However, only few patients had made substantial changes in their caffeine intake prior to the seizure. Surprisingly, in the subgroup of patients with genetic (idiopathic) epilepsies, the drop in caffeine intake prior to the seizures reached statistical significance. However, the number of patients was small, and the caffeine consumption may have been reduced by various other seizure-associated circumstances interfering with daily routines on the day of the attack. Anyhow, the findings corroborate that increased dietary caffeine intake is not a significant seizure precipitant in these patients.

Our results are not in conflict with previous studies showing that *acute* inhibition of adenosine receptors by caffeine may induce seizures, as *chronic* caffeine exposure has been suggested to have an

inverse effect. Long-term exposure to adenosine receptor antagonists may resemble the acute effects of adenosine receptor agonists. The mechanism behind this phenomenon is only partly understood. A decreased neuronal excitability caused by complex interactions leading to downregulation of adenosine receptors has been suggested [24,25]. Rats that received caffeine in their drinking water developed tolerance to the stimulatory effect of a challenge with caffeine. This tolerance was associated with altered striatal gene expression [29]. According to the theory of effect inversion, drops in caffeine levels could contribute to seizure generation by this mechanism in chronically caffeine-exposed individuals, as the clinical effects of tolerance rapidly abate within a few days after the discontinuation of caffeine [30]. In a recent survey on dietary risks for developing seizures or epilepsy, long-term caffeine intake did not represent a predisposing factor. In fact, high caffeine intake (≥400 mg/day) was rather associated with a mild trend towards a lower risk [31].

In our material, there was no difference in the proportion of patients without habitual caffeine intake who ingested caffeine prior to the seizure (four of 29 patients) compared to caffeine users who denied intake on the day of the seizure (22 of 145 patients). Unfortunately, in the published cases of seizures associated with high caffeine intake, habitual caffeine intake was only rarely reported [15–23]. Several of these patients were teenagers, who possibly might drink less coffee or tea on a daily basis than adults. These cases have, nevertheless, led some authors to suggest that people with epilepsy should avoid caffeinated beverages in general [15]. Our findings do not support these recommendations. A rise in daily dietary caffeine consumption does not seem to have a negative impact on seizure control. However, it is reasonable to suggest that extreme and acute caffeine intake should be avoided, particularly in caffeine-naïve individuals, and care should be taken to avoid sleep pattern disruption due to the stimulant effect. When counseling people with epilepsy on the use of caffeine, the balance between a positive effect on daytime vigilance and a negative effect on nighttime rest should be given attention.

There are some obvious limitations to this study. The recall of the exact caffeine ingestion in the preictal period might have been impaired by some degree of postictal obtundation. However, the interviews were postponed until the patients appeared cognitively restored by careful clinical judgment. Furthermore, we endeavored to control for this confounder by comparing the reported habitual consumption with the reported intake on the same day of the week at a later occasion when no seizure had occurred (Interview II).

Moreover, our categorization of consumption was rather rough, but a more detailed specification was not found to be relevant in this clinical situation. We mainly wished to detect the larger changes in caffeine intake. Also, the caffeine content of caffeinated beverages differs considerably, even from one cup of coffee to another [32], and most patients in this study appeared to stick to their established brand preferences. Coffee was the predominating caffeine source, and no patient used the recently introduced energy drinks. While it is true that the caffeine content might have differed considerably in the respective “units”, each patient served as his/her own control. It should be mentioned that variations in the type of caffeinated beverages may be less pronounced in Norway than in many other countries. In 1995 (no newer data available), more than 90% of the caffeine consumption in Norway was estimated to come from coffee [2].

Caffeine blood levels would certainly constitute a more exact method of assessing the immediate caffeine exposure. However, blood levels were not found to be meaningful in this study because of the short time to peak concentration and the short half-life of caffeine (peak caffeine plasma levels are reached within 30–75 min after ingestion, and the half-life is 4–5 h but may increase with high intake levels) [32]. Moreover, the time between the seizure and admission varied widely.

To our knowledge, this is the first systematic clinical study examining caffeine consumption as a potential seizure trigger. Our findings do not support the idea that increased dietary caffeine is a common contributor to the cascade of factors leading to a seizure.

Acknowledgment

This study was financially supported by a grant from UCB.

References

[1] Nakken KO, Solaas MH, Kjeldsen MJ, Friis ML, Pellock JM, Corey LA. Which seizure-precipitating factors do patients with epilepsy most frequently report? Epilepsy Behav 2005;6(1):85–9.
[2] Fredholm BB, Bättig K, Holmén J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol Rev 1999;51(1):83–133.
[3] Fredholm BB, Dunwiddie TV. How does adenosine inhibit transmitter release? Trends Pharmacol Sci 1988;9(4):130–4.
[4] Ferre S, von Euler G, Johansson B, Fredholm BB, Fuxe K. Stimulation of high-affinity adenosine A2 receptors decreases the affinity of dopamine D2 receptors in rat striatal membranes. Proc Natl Acad Sci USA 1991;88(16):7238–41.
[5] Chu NS. Caffeine- and aminophylline-induced seizures. Epilepsia 1981;22(1):85–94.
[6] Cutrufo C, Bortot L, Giachetti A, Manzini S. Differential effects of various xanthines on pentylenetetrazole-induced seizures in rats: an EEG and behavioural study. Eur J Pharmacol 1992;222(1):1–6.
[7] Gomes A, Das M, Vedasiromoni JR, Ganguly DK. Proconvulsive effect of tea (*Camellia sinensis*) in mice. Phytother Res 1999;13(5):376–9.
[8] Czuczwar SJ, Gasior M, Janusz W, Szczepanik B, Włodarczyk D, Kleinrok Z. Influence of different methylxanthines on the anticonvulsant action of common antiepileptic drugs in mice. Epilepsia 1990;31(3):318–23.
[9] Czuczwar SJ, Kleinrok Z. Modulation of the protective efficacy of common antiepileptic drugs by xanthine derivatives: implications for the clinical use of xanthines in epileptic patients. Pharmacol Res 1990;22(6):661–5.
[10] Gasior M, Borowicz K, Buszewicz G, Kleinrok Z, Czuczwar SJ. Anticonvulsant activity of phenobarbital and valproate against maximal electroshock in mice during chronic treatment with caffeine and caffeine discontinuation. Epilepsia 1996;37(3):262–8.
[11] Gasior M, Borowicz K, Kleinrok Z, Czuczwar SJ. Chronic caffeine and the anticonvulsant potency of antiepileptic drugs against maximal electroshock. Pharmacol Biochem Behav 1996;54(4):639–44.
[12] Luszczki JJ, Zuchora M, Sawicka KM, Kozińska J, Czuczwar SJ. Acute exposure to caffeine decreases the anticonvulsant action of ethosuximide, but not that of clonazepam, phenobarbital and valproate against pentetrazole-induced seizures in mice. Pharmacol Rep 2006;58(5):652–9.
[13] Chrościńska-Krawczyk M, Ratnaraj N, Patsalos PN, Czuczwar SJ. Effect of caffeine on the anticonvulsant effects of oxcarbazepine, lamotrigine and tiagabine in a mouse model of generalized tonic–clonic seizures. Pharmacol Rep 2009;61(5):819–26.
[14] Chrościńska-Krawczyk M, Jargiełło-Baszak M, Wałek M, Tylus B, Czuczwar SJ. Caffeine and the anticonvulsant potency of antiepileptic drugs: experimental and clinical data. Pharmacol Rep 2011;63(1):12–8.
[15] Kaufman KR, Sachdeo RC. Caffeinated beverages and decreased seizure control. Seizure 2003;12(7):519–21.
[16] Bonilha L, Li LM. Heavy coffee drinking and epilepsy. Seizure 2004;13(4):284–5.
[17] Haller CA, Meier KH, Olson KR. Seizures reported in association with use of dietary supplements. Clin Toxicol (Phila) 2005;43(1):23–30.
[18] Röggla G, Moser B. Seizures in a night club. Lancet 2007;370(9583):220.
[19] Iyadurai SJ, Chung SS. New-onset seizures in adults: possible association with consumption of popular energy drinks. Epilepsy Behav 2007;10(3):504–8.
[20] Mortelmans LJ, Van Loo M, De Cauwer HG, Merlevede K. Seizures and hyponatremia after excessive intake of diet coke. Eur J Emerg Med 2008;15(1):51.
[21] Trabulo D, Marques S, Pedroso E. Caffeinated energy drink intoxication. Emerg Med J 2011;28:712–4.
[22] Cleary K, Levine DA, Hoffman RS. Adolescents and young adults presenting to the emergency department intoxicated from a caffeinated alcoholic beverage: a case series. Ann Emerg Med 2012;59(1):67–9.
[23] Calabrò RS, Italiano D, Gervasi G, Bramanti P. Single tonic–clonic seizure after energy drink abuse. Epilepsy Behav 2012;23(3):384–5.
[24] Jacobson KA, von Lubitz DK, Daly JW, Fredholm BB. Adenosine receptor ligands: differences with acute versus chronic treatment. Trends Pharmacol Sci 1996;17(3):108–13.
[25] Boison D. Methylxanthines, seizures, and excitotoxicity. Handb Exp Pharmacol 2011;200:251–66.
[26] Heckman MA, Weil J, Gonzalez de Mejia E. Caffeine (1,3,7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. J Food Sci 2010;75(3):R77–87.
[27] Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010;51(4):676–85.
[28] Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005;46(4):470–2.

[29] Svenningsson P, Nomikos GG, Fredholm BB. The stimulatory action and the development of tolerance to caffeine is associated with alterations in gene expression in specific brain regions. J Neurosci 1999;19(10):4011–22.
[30] Benowitz NL, Jacob III P, Mayan H, Denaro C. Sympathomimetic effects of paraxanthine and caffeine in humans. Clin Pharmacol Ther 1995;58(6):684–91.
[31] Dworetzky BA, Bromfield EB, Townsend MK, Kang JH. A prospective study of smoking, caffeine, and alcohol as risk factors for seizures or epilepsy in young adult women: data from the Nurses' Health Study II. Epilepsia 2010;51(2):198–205.
[32] Mandel HG. Update on caffeine consumption, disposition and action. Food Chem Toxicol 2002;40(9):1231–4.

Paper II

BRIEF COMMUNICATION

Nonadherence to treatment causing acute hospitalizations in people with epilepsy: An observational, prospective study

***Christian Samsonsen, †‡Arne Reimers, *§Geir Bråthen, §Grethe Helde, and *§Eylert Brodtkorb**

Epilepsia, 55(11):e125–e128, 2014
doi: 10.1111/epi.12801

Christian Samsonsen is a neurologist at the Department of Neurology and Clinical Neurophysiology, St.Olav's University Hospital, Trondheim, Norway.

Summary

The aim was to assess the clinical relevance of antiepileptic drug (AED) nonadherence by means of therapeutic drug concentration monitoring (TDM). Two hundred eighty-two consecutive patients with epilepsy acutely admitted to hospital for seizures were included. Nonadherence was defined as having a serum concentration/dose ratio at admission of <75% of the patient's own control value (probable nonadherence: 50–75%; definite: <50%). Nonadherence was identified in 39% of patients (definite 24%; probable 15%). It was significantly more common in patients with generalized seizures compared to those with focal onset seizures, and in patients <30 years compared to older patients. When specifically asked, 44% of nonadherent patients claimed regular intake. Nonadherence is a major cause of seizure breakthrough in patients with epilepsy, particularly in young adults. Many patients seem to be unaware of missed drug intake. Prompt measurements of AED serum concentrations should be available as part of the emergency care for patients acutely hospitalized for seizures to permit this issue to be thoroughly addressed prior to discharge.

KEY WORDS: Adherence, Therapeutic drug monitoring, Seizure.

Missed antiepileptic drug (AED) intake persists as a major obstacle to optimal epilepsy care, but the extent of the problem has been difficult to assess.[1] Various methods have been used to study adherence to long-term drug therapies, including patient self-reports, pill counts, prescription refill rates, and electronic bottle tops.[1–4] Nevertheless, therapeutic drug concentration monitoring (TDM) stands out as the best indicator of adherence to AED treatment.[1,5] Although methodologic and interpretation problems as well as costs constitute disadvantages, TDM is objective, commonly used, and well understood by clinicians. However, rather few studies have used TDM to study nonadherence in patients with epilepsy, and they have been limited primarily to specific settings in selected materials.[6–8]

This study aimed to investigate the role of AED nonadherence as a precipitant of seizures by means of TDM and to explore the clinical characteristics of patients prone to this problem.

Methods

Consecutive patients (age >16) treated for epilepsy and acutely hospitalized for single or serial seizures were during 44 months included in this observational, prospective study at St. Olavs University Hospital, Trondheim, Norway.

On admission, blood was drawn from the patients for TDM of relevant AEDs. Time of last AED intake and time

Accepted August 15, 2014; Early View publication September 23, 2014.
*Department of Neurology and Clinical Neurophysiology, St. Olav's University Hospital, Trondheim, Norway; †Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway; ‡Department of Clinical Pharmacology, St. Olav's University Hospital, Trondheim, Norway; and §Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway

Address correspondence to Christian Samsonsen, Department of Neurology and Clinical Neurophysiology, St.Olav's University Hospital, N-7006 Trondheim, Norway. E-mail: christian.samsonsen@stolav.no

Wiley Periodicals, Inc.

for blood sampling, as well as concomitant medications were recorded. Concentration/dose (C/D) ratios were calculated. Each patient served as his or her own control. Steady-state, drug-fasting, control C/D ratios were obtained at scheduled outpatient appointments and controlled for comedication. The first postdischarge value was preferred (taken after at least five half-lives, steady state); if not available, the last routine value prior to admission was used. AED serum concentrations were determined by routine methods of the Department of Clinical Pharmacology, St. Olavs University Hospital, Trondheim. Valproate, carbamazepine, and phenytoin were analyzed by immunologic methods on a Roche Cobas Integra 400 autoanalyzer (Roche Diagnostics Norway AS, Oslo, Norway). The remaining AEDs were analyzed on an Agilent MSD 1100 LC-MS system (Agilent, Palo Alto, CA, U.S.A.).

Nonadherence was defined as probable when the C/D ratio at admission was 50–75% of the control C/D ratio, and as definite when it was <50%. Patients using multiple AEDs were assessed according to the drug with the lowest C/D ratio. The medical records were reviewed for information on the patients' own history of recent adherence.

Fisher's exact test was used for statistical analysis. The study was approved by the Regional Committee for Medical and Health Research Ethics.

Results

A total of 306 admissions of 225 patients (mean age 49.5 years, range 16–91; 62% male) were available for recruitment (Fig. 1). Demographic details and seizure characteristics are shown in Table 1. An applicable control C/D ratio after discharge was available in 229 cases. In a further 53, a value prior to admission was used, resulting in a total of 282 comparable cases. The remaining 24 patients were excluded due to missing control values. Multiple admissions due to nonadherence (C/D ratio <75% of control) occurred in nine of the patients (twice in seven, three times in one, and six times in one). A total of 14 different AEDs were used in the 282 comparable cases. Monotherapy was used in 149 admissions and polytherapy in 133 (two AEDs in 84, three in 37, and four in 12).

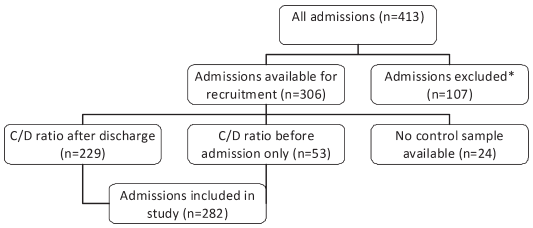


Figure 1.
Overview of seizure admissions in patients using antiepileptic drugs. *Serum concentrations not available/sampling time unknown (n = 93); nonepileptic seizures (n = 14).

Nonadherence was revealed in 39% of all admissions, definite in 24% and probable in 15% (Table 1).

Almost 37% of admissions in patients <30 years were definitely nonadherent, compared to 27% aged 30–60, and 10% in patients >60. The differences between the age groups were significant, and even highly significant for the youngest patients compared to the oldest. In addition, nonadherence was significantly more prevalent in admissions of patients with generalized seizures compared to those with focal-onset seizures (Table 1).

There was no difference in nonadherence when comparing gender, patients living alone to those living with companions, or patients on monotherapy to those on polytherapy, but it was less common in association with intellectual disability (Table 1). Among the most commonly used AEDs (valproate, carbamazepine, lamotrigine, and levetiracetam), nonadherence values were most frequently found for levetiracetam. No differences were found when comparing the other AEDs (data not shown).

Unfortunately, the history of recent drug adherence was not addressed in the medical records of all patients. However, 40 patients reported missed intake, whereas 66 denied it. TDM confirmed nonadherence in 68% reporting it and in 44% refuting it. In the remaining 176, current drug intake was uncertain or not specifically commented upon.

Discussion

This study is the first to demonstrate the extent of nonadherence by means of TDM in consecutive patients admitted to hospital for acute seizures. Nearly 40% had C/D ratios that were consistent with missed AED intake. A previous study using TDM demonstrated nonadherence in a slightly higher proportion of young adults who themselves requested postictal blood sampling in a special setting when attending a rehabilitation program.[6] Among long-term therapies, epilepsy treatment is associated with several unique aspects.[3] When in remission, patients may question the need for persistent treatment, whereas uncontrolled seizures may induce hopelessness and resignation. On the other hand, many people with epilepsy may have a particularly strong incentive to comply with prophylactic therapy, as treatment failure may have dramatic consequences, including driving and vocational restrictions.

Our study confirms young adult age as an important risk factor for nonadherence.[9] Coping difficulties, immature attitudes, and irregular lifestyle with use of alcohol may be related factors that need clinical attention.

This study also demonstrated that nonadherence was significantly more prevalent among admissions of patients with generalized epilepsies compared to those with focal epilepsies. Similar results were obtained by a recent study where children with generalized epilepsy were more likely

Table 1. Treatment adherence in 282 seizure admissions

	Total n (%)	Definite nonadherence (<50%) n (%)	Probable nonadherence (50–75%) n (%)	Adequate adherence (>75%) n (%)	p-Value
Demographics					
All	282 (100)	67 (24)	42 (15)	173 (61)	
Male	174 (62)	43 (25)	25 (14)	106 (61)	n.s
Female	108 (38)	24 (22)	17 (16)	67 (62)	
Age <30 years	46 (16)	17 (37)	4 (9)	25 (54)	0.004
Age 30–60 years	157 (56)	42 (27)	22 (14)	93 (59)	0.001[a]
Age >60 years	79 (28)	8 (10)	16 (20)	55 (70)	
Living alone	59 (21)	17 (29)	8 (14)	34 (58)	n.s
Living with companions	223 (79)	50 (22)	34 (15)	139 (62)	
Intellectual disability	50 (18)	6 (12)	11 (22)	33 (66)	0.048
No intellectual disability	232 (82)	61 (26)	31 (13)	140 (60)	
Seizure characteristics[b]					
Generalized[c]	30 (11)	13 (43)	4 (13)	13 (43)	0.029[d]
Focal	241 (85)	50 (21)	38 (16)	153 (63)	
Unclassified	11 (4)	4 (36)	0 (0)	7 (64)	
AED treatment					
Monotherapy	149 (53)	33 (22)	25 (17)	91 (61)	n.s
Polytherapy	133 (47)	34 (26)	17 (13)	82 (62)	

n.s., non significant.
[a]Comparing age <30 to age >60.
[b]Single convulsive seizures 256, convulsive status epilepticus 5, nonconvulsive seizures 21.
[c]Juvenile myoclonic epilepsy, 7; epilepsy with generalized tonic–clonic seizures only, 18; various absence epilepsies, 5.
[d]Comparing generalized to focal seizures.

to be classified as nonadherent than those with focal epilepsy.[8] Patients with generalized epilepsy might be more vulnerable to the effect of nonadherence. As these patients are usually well controlled, seizure breakthrough may more commonly result in hospitalization. Although nonadherence was less common in patients with intellectual disability and supervised drug ingestion, it was also identified as a considerable problem in this group.

Although monotherapy has been associated with a higher degree of adherence,[6,10–12] we found no difference compared to polytherapy. Easy-to-follow medication regimens and few adverse effects are considered important factors for good adherence.[3] On the other hand, patients taking polytherapy more frequently have uncontrolled epilepsy, and may therefore have more focus on following strict medication routines. They are also more likely to be seen regularly at outpatient clinics where concerns can be dealt with. The shorter plasma half-life of levetiracetam was probably causing this drug to be more frequently associated with nonadherence than other commonly used AEDs.

A strength of this study is that all patients hospitalized for epileptic seizures in the present catchment area are admitted to one single neurologic department affiliated with one single pharmacologic laboratory. It is common practice in Norway that all patients treated for epilepsy are followed by trough, steady-state TDM of all AEDs available for analysis. Furthermore, all patients with epilepsy admitted for seizure breakthrough to our hospital routinely have immediate blood sampling for TDM in the emergency department. Nevertheless, an important limitation to the study is that these procedures sometimes may fail. Conceivably, patients suspected of nonadherence could be more likely to have had TDM than others.

Overconsumption of AEDs as a form of nonadherence has also recently received attention.[7] Along with the occurrence of so-called "white-coat adherence" prior to scheduled visits,[13] this phenomenon may represent limitations to the validity of the control TDM value. However, the compatibility between dose and serum concentration had been evaluated by a clinical pharmacologist for all analyses.

The reasons for nonadherence are multiple and include costs, poor knowledge, forgetfulness, and side effects[3]; these factors should be discussed with the patients. In a global perspective, we believe that the extent of this problem is even larger than presented here. In Norway, epilepsy is generally treated at a specialist level, expenses for epilepsy treatment are reimbursed, and education and information to people with chronic disorders are warranted by legislation. When specifically asked for recent treatment adherence, >40% of obviously nonadherent patients claimed regular drug intake. Many seem to be unaware of missed doses, indicating the need for pill dispensers and reminding/educational interventions,[14] as well as the value of routine TDM at admission of patients referred for acute seizures. Rapid identification of nonadherence is essential. Dose increase on false premises will certainly not improve adherence.

Conclusion

Nonadherence is a common cause of breakthrough seizures in patients with epilepsy, particularly in young adults. Prompt measurement of AED serum concentrations should be available as part of the emergency care for patients acutely hospitalized for seizures. The usefulness of this approach has been demonstrated. It permits nonadherence to be disclosed and properly addressed prior to discharge. Undue dose increase should be avoided. A clear understanding of why a seizure has occurred is essential for improving future seizure control. A persistent focus on the importance of adequate adherence, including appropriate information to the patients, is an essential part of the comprehensive management of epilepsy.

Acknowledgment

This study was supported by a grant from UCB.

Disclosure or Conflicts of Interest

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Christian Samsonsen, Geir Bråthen, and Eylert Brodtkorb have received honoraria and/or financial support for attending conferences from GlaxoSmithKline, UCB, and Eisai. Arne Reimers has received speaker's honoraria from GlaxoSmithKline and UCB. Grethe Helde has no disclosures.

References

1. World Health Organization. *Adherence to long term therapies: evidence for action*. Geneva: World Health Organization; 2003. Available at: http://www.who.int/chp/knowledge/publications/adherence_report/en/. Accessed August 8, 2014.
2. Paschal AM, Hawley SR, St Romain T, et al. Measures of adherence to epilepsy treatment: review of present practices and recommendations for future directions. *Epilepsia* 2008;49:1115–1122.
3. Faught E. Adherence to antiepilepsy drug therapy. *Epilepsy Behav* 2012;25:297–302.
4. Smithson WH, Hukins D, Colwell B, et al. Developing a method to identify medicines non-adherence in a community sample of adults with epilepsy. *Epilepsy Behav* 2012;24:49–53.
5. Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs–best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia* 2008;49:1239–1276.
6. Specht U, Elsner H, May TW, et al. Postictal serum levels of antiepileptic drugs for detection of noncompliance. *Epilepsy Behav* 2003;4:487–495.
7. Carpentier N, Jonas J, Frismand S, et al. Direct evidence of nonadherence to antiepileptic medication in refractory focal epilepsy. *Epilepsia* 2013;54:20–23.
8. Shah NM, Hawwa AF, Millership JS, et al. Adherence to antiepileptic medicines in children: a multiple-methods assessment involving dried blood spot sampling. *Epilepsia* 2013;54:1020–1027.
9. Buck D, Jacoby A, Baker GA, et al. Factors influencing compliance with antiepileptic drug regimens. *Seizure* 1997;6:87–93.
10. Bryant SG, Ereshefsky L. Determinants of compliance in epileptic outpatients. *Drug Intell Clin Pharm* 1981;15:572–577.
11. Cramer JA, Glassman M, Rienzi V. The relationship between poor medication compliance and seizures. *Epilepsy Behav* 2002;3:338–342.
12. Sweileh WM, Ihbesheh MS, Jarar IS, et al. Self-reported medication adherence and treatment satisfaction in patients with epilepsy. *Epilepsy Behav* 2011;21:301–305.
13. Modi AC, Ingerski LM, Rausch JR, et al. White coat adherence over the first year of therapy in pediatric epilepsy. *J Pediatr* 2012;161:695–699.
14. Li J, Si Y, Hu J, et al. Enhancing medical compliance of patients with convulsive epilepsy in rural community: a randomized intervention trial. *Epilepsia* 2013;54:1988–1996.

Paper III

Epilepsy Research 127 (2016) 260–266

Contents lists available at www.sciencedirect.com

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

The impact of sleep loss on the facilitation of seizures: A prospective case-crossover study

Christian Samsonsen[a,b,*], Trond Sand[a,b], Geir Bråthen[a,b], Grethe Helde[b], Eylert Brodtkorb[a,b]

[a] Department of Neurology and Clinical Neurophysiology, St. Olav's University Hospital, Trondheim, Norway
[b] Department of Neuroscience, Faculty of Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

ARTICLE INFO

Article history:
Received 24 June 2016
Received in revised form 2 September 2016
Accepted 15 September 2016
Available online 16 September 2016

Keywords:
Sleep
Seizures
Alcohol
Seizure precipitants
Epilepsy
Non-adherence
Antiepileptic drugs

ABSTRACT

Purpose: The relationship between sleep and seizures is intricate. The aim of this study was to assess whether sleep loss is an independent seizure precipitant in a clinical setting.
Methods: In this prospective, observational cross-over study, 179 consecutive hospital admissions for epileptic seizures were included. A semi-structured interview regarding several seizure precipitants was performed. The sleep pattern prior to the seizure, as well as alcohol, caffeine and drug use, were recorded. The interview was repeated by telephone covering the same weekday at a time when there had been no recent seizure. The Hospital Anxiety and Depression Scale (HADS) and a visual analogue scale for perceived stress were applied at admission. Student's *t*-test, Fisher exact test and ANOVA were used for statistical analyses.
Results: Complete data for analysis were retrieved in 144 patients. The sleep-time during the 24 h prior to the seizure was lower (7.3 h) compared to follow-up (8.3 h; $p < 0.0005$). Caffeine consumption and use of relevant non antiepileptic drugs (AED) were not different. HADS and stress scores at admission did not correlate with sleep-time difference. In ANOVA, controlled for alcohol consumption and AED use, the sleep-time difference remained significant ($p = 0.008$). The interaction with alcohol intake was high, but the sleep-time difference remained highly significant also for the non- and low-consumption (≤2 units per day) subgroup (n = 121, 7.50 h vs 8.42 h, $p = 0.001$).
Conclusion: Epileptic seizures are often precipitated by a combination of various clinical factors, but sleep loss stands out as an independent seizure trigger.

1. Introduction

The interaction between seizures and sleep is complex and reciprocal (Bazil, 2000; Ismayilova et al., 2015; Matos et al., 2010; Nobili et al., 2014). Patients with epilepsy may be prone to both daytime sleepiness and insomnia, as anti-epileptic drugs (AED), sleep-related epileptiform EEG discharges and anxiety may influence sleep structure (Bazil, 2003, 2000; Frucht et al., 2000; Legros and Bazil, 2003; Manni and Terzaghi, 2010; Méndez and Radtke, 2001; Quigg et al., 2016; Vendrame et al., 2013). Up to one third of patients with epilepsy self-report lack of sleep as a seizure-provoking factor (Frucht et al., 2000). Accordingly, several studies suggest sleep deprivation as a seizure trigger (Aird, 1983; Antebi and Bird, 1993; da Silva Sousa et al., 2005; Ferlisi and Shorvon, 2014; Frucht et al., 2000; Gunderson et al., 1973; Lawn et al., 2014; Méndez and Radtke, 2001; Nakken et al., 2005; Spector et al., 2000; Tan et al., 2005; Wassenaar et al., 2014). A study combining transcranial magnetic stimulation and EEG suggested that the excitability of the human frontal cortex progressively increased with time awake and decreased after sleep recovery (Huber et al., 2013). Nevertheless, the clinical evidence for the effect of prolonged wakefulness on the seizure threshold is controversial. In one study, sleep deprivation alone did not affect seizure frequency during inpatient video-EEG monitoring (Malow et al., 2002). It has been argued that lack of sleep rarely occurs in isolation, but is usually associated with a range of confounding factors, such as alcohol, drugs, caffeine and emotional stress (Cobabe et al., 2015; Malow, 2004). The interaction between these various factors has been poorly investigated.

* Corresponding author at: Department of Neurology and Clinical Neurophysiology, St. Olav's University Hospital, 7006 Trondheim, Norway.
E-mail address: christian.samsonsen@stolav.no (C. Samsonsen).

http://dx.doi.org/10.1016/j.eplepsyres.2016.09.014
0920-1211/

In particular, the relationship between seizures, sleep and alcohol is a complicated and much-debated issue (Ebrahim et al., 2015, 2013; Pressman et al., 2015). Seizures and sleep disturbances are common during phases of active drinking and abstinence among individuals with alcohol-use disorders, while the situation is different after occasional alcohol intake because alcohol is a frequently used tranquilizer and sleep inducer with probable effects upon the seizure threshold in patients and susceptible individuals. Hence, it is important to eliminate bias created by potential confounders like alcohol when the relation between sleep loss and seizures are studied.

The aim of this study was accordingly to disentangle the sleep-related circumstances that may facilitate the generation of an epileptic seizure. Specifically, we wished to assess whether lack of sleep is an independent seizure-provoking factor in a clinical setting.

2. Methods

Unselected patients acutely hospitalized with epileptic seizures at St. Olav's University Hospital, Trondheim, Norway, were included in this prospective, observational case-crossover study. In patients able to cooperate, a semi-structured interview took place at a time when the patients were considered to be cognitively restored after the seizure. Total sleep-time during the last 24 h prior to the seizure was obtained by the interviewer in a sleep diary with half an hour as the lowest unit.

Alcohol use was assessed by the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993) and the recording of daily alcohol unit consumption during the five days prior to the seizure day. 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).

Drugs ingested during the last week were recorded to identify agents which might influence the seizure threshold. Caffeine consumption during the last 24 h prior to the seizure was also reported in units and categorized (0–3) as no consumption, low ($\leq$3 units), moderate (>3-$\leq$ 6 units) and high (>6 units) (Samsonsen et al., 2013).

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. The patients were also asked to score the perceived role of stress as a seizure precipitant for the present seizure on a visual analogue scale (VAS).

All patients with epilepsy included in the study either used or started with AEDs. In patients using AEDs at admission, serum concentrations were drawn in the emergency room and compared with drug-fasting steady state controls. Definite non-adherence was defined as a concentration/dose ratio on admission of 50% or lower compared to the control ratio (Samsonsen et al., 2014).

A follow-up interview was performed by telephone at least four weeks later at a time when there had been no seizure for >3 days. The following elements of the admission interview were repeated: a sleep record, alcohol consumption (five preceding days), as well as the history of medications used during the last week and the caffeine consumption during the last 24 h. The follow-up interview covered the same weekdays as the admission interview. In patients with repeated admissions, only the first admission was used in the statistical analysis.

Seizure-related sleep deprivation was defined as total sleep-time <50% during the last 24 h prior to admission compared to follow-up. Seizures and epilepsies were categorized according to current classifications by the International League Against Epilepsy (ILAE) (Berg et al., 2010; Thurman et al., 2011). Focal onset seizures were defined as seizures with localized clinical onset and/or focal findings in brain imaging and EEG. Tonic-clonic seizures were considered generalized when occurring in the context of generalized epilepsy syndromes and/or associated with generalized epileptiform EEG discharges, or if EEG and imaging was normal and no focal onset was presented by history.

Statistical analyses were performed using SPSS version 22, and the significance of observed crude differences determined using paired Student's *t*-test. Subgroup differences were assessed with a two-group Student's *t*-test. Categorical 2×2 data were assessed with Fisher exact test or paired McNemar's test for symmetry. Pearson correlation was used to explore associations between main outcome variables and background variables like anxiety and depression scores. In addition, a supplementary repeated measures ANOVA model was used to control for the effects of AED and alcohol consumption change. The dependent variable was total sleep-time during the 24 h preceding the seizure and the paired control sleep-time recorded similarly from the telephone interview data, i.e. for the 24 h prior to the same point in time. Since the alcohol unit variable distribution summarized across the last five days (x = units) was predictably skewed, the $(x+b)\hat{y}$ power transformation was applied before the difference variable (alcohol consumption before attack minus consumption before interview) was calculated in order to achieve a symmetrical near-Gaussian distribution ($y = -4, b = 1$), and subsequently entered as a covariate in the ANOVA-model.

Regarding the first categorical variable, AED change, patients with AED treatment onset after the present seizure admission were scored as "1", the others as "0".

A p value <0.05 was considered statistically significant.

The study was approved by the regional ethics committee, and all participants gave their informed written consent.

3. Results

3.1. Recruitment, demographics and non-AED medications

Interviews were performed in 179 consecutive admissions of a total of 169 patients. The number of admissions excluded or lost to follow-up is shown in Fig. 1. A follow-up interview was performed in 152 patients, but due to insufficient sleep data, only 144 admissions were left for analysis. Demographic and clinical data are reported in Table 1.

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. In addition, the use of hypnotic drugs (predominantly alimemazine and zopiclone) is similar at admission and follow-up (Table 1).

3.2. Seizure and epilepsy characteristics

The distribution of seizure types is shown in Table 1. Of the 144 patients, 99 had epilepsy; focal onset was present in 70 of the 99 with epilepsy. Previously established epilepsy was present in forty-five, whereas 54 were diagnosed during hospitalization. Genetic (idiopathic) generalized epilepsies were recognized in 29 (juvenile myoclonic epilepsy, 3; epilepsy with generalized tonic-clonic seizures (GTCs) only, 22; various absence epilepsies, 4). In the 45 patients not diagnosed with epilepsy, alcohol withdrawal seizures were presumed in 14 patients; 31 had GTCs of undetermined cause.

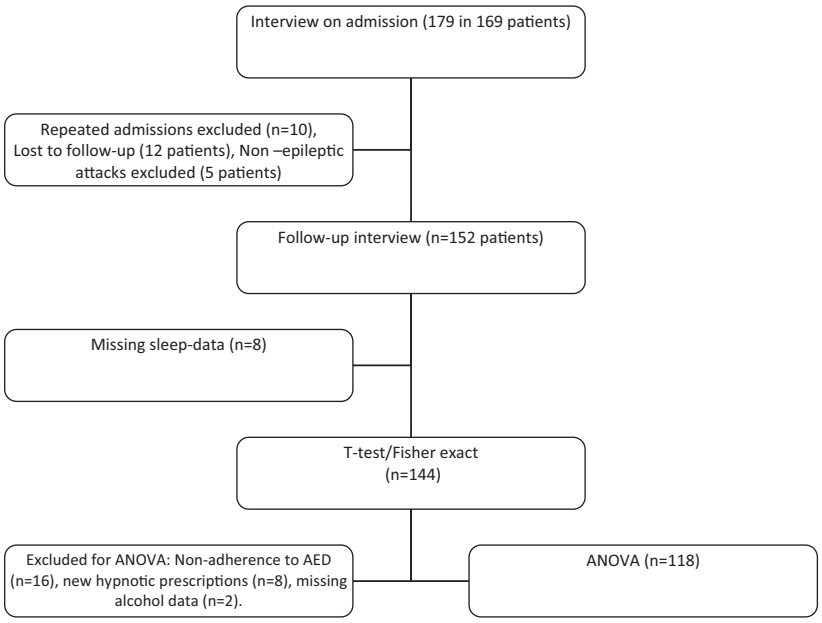


Fig. 1. Summary of patient recruitment.

Table 1
Demographics, seizure types and questionnaire scores obtained at admission; mean (SD) or percentage (n = 144[a]).

Age	40.4 (16.8)
Males [n (%)]	85 (59%)
Focal seizures [n (%)]	82 (57%)
Generalized seizures [n (%)]	62 (43%)
AUDIT score, n = 137	6.2 (6.2)
HADS anxiety score (0–21), n = 139	7.0 (4.2)
HADS depression score (0–21), n = 139	3.9 (3.6)
Perceived stress prior to seizure (VAS 0–100), n = 128	41.4 (34.0)

AUDIT, Alcohol use identification test; HADS, Hospital anxiety and depression scale; VAS, visual analogue scale.
[a] Complete data not available for all patients.

Table 2
Sleep, drug treatments, coffee and alcohol consumptions before seizure and follow-up in all patients (n = 144[a]).

	Before seizure	Before follow-up	p-value[**]
Sleep-time last 24 h, mean (SD)	7.3 (2.8)	8.3 (2.0)	<0.0005
AED users, n (%)	45 (31)	99(69)	<0.0005
Hypnotic users, n (%)	19 (13)	12(8)	0.16
Coffee (categories), mean (SD)	1.3 (1.0)	1.5 (1.0)	0.06
Alcohol units last 5 days (n=140), mean (SD)	5.2 (11.5)	4.4 (12.8)	0.47

AED, antiepileptic drug.
[a] Complete data not available for all patients.
[**] p-value Paired Student's *t*-test or McNemar's symmetry chi-square.

3.3. Sleep duration

Average sleep-time during the last 24 h prior to the seizure was 7.3 h (range 0–14.5 h, 95% CI 6.82–7.74). Prior to the follow-up interview, average sleep duration was significantly longer, 8.3 h (range 1.5–17.5 h, 95% CI 8.02–8.67) (Table 2). Six patients reported no sleep during the last 24 h preceding the seizure, none at follow-up. Prior to the seizure 19 patients (13.2%) slept ≤ 4 h, only two (1.4%) at follow-up (1.5 and 3.5 h) (p = 0.0001).

Sleep duration was not significantly different in generalized and focal onset seizures either prior to admission (p = 0.08) or at follow-up (p = 0.55).

Significant correlations between sleep-time differences between seizure and follow-up, and HAD-scores (depression or anxiety) and perceived stress were not found.

In patients with epilepsy, there were also no differences between genetic generalized epilepsies (n = 29) compared to those with focal epilepsies (n = 70) regarding sleep 24 h prior to the seizure (7.22 h (SD 2.99) vs 7.74 h (SD 2.52), p = 0.39) or HAD scores (10.7 (SD 6.29) vs 9.54 (SD = 5.98), p = 0.39).

3.4. Seizure-related sleep deprivation

Table 3 shows the relationship between sleep deprivation (sleep-time prior to seizure <50% compared to follow-up) and clinical characteristics. Sleep-deprived patients were younger (mean 30.4 years) than those without (mean 42.1 years, p = 0.004). Generalized seizures tended to be more common than focal seizures in sleep deprived patients p = 0.05). The difference was not significant (p = 0.29) when sleep-deprived patients with evident genetic generalized epilepsy syndromes (5 of 29) were compared to those diagnosed with focal epilepsy (6 of 70).

When comparing patients with sleep deprivation to those without, there were no significant differences for anxiety, depression or perceived stress.

3.5. Alcohol and sleep habits

Total alcohol consumption for patients with alcohol data available (n = 140) during the last five days prior to the seizure day did not differ significantly compared to follow-up (5.2 vs. 4.4

Table 3
Seizure-related sleep deprivation and clinical characteristics (n = 144[a]).

	No sleep deprivation, n (%)	Sleep deprivation, n (%)	p
All	124 (86.1)	20 (13.9)	
Gender			
Males	73 (85.9)	12 (14.1)	
Females	51 (86.4)	8 (13.6)	0.92
Age			
<30	36 (73.5)	13 (26.5)	
30–60	70 (90.9)	7 (9.1)	
>60	18 (100)	0 (0)	0.004
Seizures			
Focal	75 (91.5)	7 (8.5)	
Generalized	49 (79.0)	13 (21.0)	0.050
Epilepsy			
Not diagnosed	36 (80)	9 (20)	
Diagnosed	88 (88.9)	11 (11.1)	0.19
Alcohol use			
AUDIT scores, n = 137, mean(SD)	5.26 (4.93)	11.35 (9.71)	0.012
Units[b], n = 140, mean(SD)	0.83 (2.17)	2.32 (2.67)	0.022
Mental symptoms			
HADS Anxiety, n = 139, mean(SD)	6.86 (4.20)	7.95 (3.97)	0.28
HADS Depression, n = 139, mean(SD)	3.73 (3.61)	5.30 (3.25)	0.07
Perceived Stress (VAS), n = 128, mean(SD)	40.2 (33.9)	48.2 (34.1)	0.33

AUDIT, Alcohol use identification test; HADS, Hospital anxiety and depression scale; VAS, visual analogue scale.
[a] All data not available for all patients.
[b] Average daily alcohol intake in standard units the last five days, prior to the seizure day.

units, p = 0.47). The difference was also not significant when non-consumers were excluded (9.2 to 6.4 units, p = 0.15) nor in those consuming an average of >2 units daily prior to the seizure (25.2 vs. 17.9 units p = 0.38).

However, patients with sleep deprivation consumed more alcohol during the last five days prior to the seizure day, compared to other patients (mean 11.6 units vs 4.2 units, p = 0.027). Also, the sleep-deprived patients had higher AUDIT scores at admission (Table 3).

Table 4 shows the association between alcohol consumption and sleep habits in the 140 patients with complete alcohol data. Sleep duration was significantly shorter prior to the seizure compared to follow-up for both high consumers (p = 0.008) and low-and non-consumers combined (mean 7.5 h vs 8.4 h, p = 0.001). However, for non-consumers alone, the difference was not significant. Nevertheless, the 49 patients with epilepsy among non-consumers (80%), slept significantly less prior to the seizure (7.9 h) compared to follow-up (8.9 h, p = 0.029).

3.6. ANOVA model

Twenty-six patients were excluded for ANOVA; 16 due to probable seizure precipitation by non-adherence, eight due to new prescriptions of hypnotic drugs and two due to missing alcohol data (Fig. 1). Alcohol consumption was reduced, while AED-use was increased due to treatment onset in patients diagnosed with epilepsy after admission. Hence, these variables were included in the ANOVA. Caffeine consumption did not change from seizure to follow-up and was not included in the ANOVA.

In the 118 patients available for this analysis, the within-subject sleep-time difference (shorter sleep-time before the attack) remained significant (F = 7.89, df1, p = 0.010) after controlling for the effects of alcohol and onset of AED treatment in the model (Table 5).

However, the interaction between sleep and alcohol use was significant (Table 5), reflecting the association between alcohol consumption and less sleep preceding the seizure (Fig. 2). Patients with the shortest sleep-times tended to have a larger difference in alcohol consumption, i.e. lower alcohol consumption reported at the follow-up, while no significant correlation was found with sleep-time prior to the follow-up interview (Fig. 2). When the subgroup with an average alcohol consumption ≥2 units/day was removed, this interaction between sleep and alcohol was no longer significant (ANOVA F = 3.27, p = 0.07).

4. Discussion

4.1. Sleep loss and seizure facilitation

The present study elucidates the role of sleep loss as a seizure precipitant in a clinical setting by using patients admitted to hospital for seizures as their own controls. The entire spectrum of seizures was included as the border between spontaneous and provoked seizures often is blurred. Because reduced sleep rarely occurs alone, but rather in combination with a range of other potential seizure-promoting circumstances, it is difficult to sort out its independent effect. Nevertheless, our findings suggest that sleep loss is a seizure trigger by itself because we have controlled for other factors influencing the propensity to develop seizures, such as alcohol intake and treatment related factors in patients with established epilepsy, including non-adherence to AEDs. Furthermore, we considered confounders influencing sleep, such as sleep-inducing drugs and the effect of caffeine. Caffeine was left out from the analysis as the dietary intake was unchanged between admission and follow-up, and had been found not to influence seizure occurrence

Table 4
Alcohol and sleep habits (n = 140[a]).

	Clinical characteristics			Alcohol			Hours of sleep (SD)			
	n	Males, n (%)	Established epilepsy, n (%)	Day before seizure, units (SD)	Average last 5 days, units (SD)	AUDIT[b]	Sleep last 24 h before seizure	Sleep last 24 h at control	Sleep difference	p
All patients	140	82 (58.6)	97 (69.3)	1.20 (3.14)	1.04 (2.30)	6.16 (6.27)	7.21 (2.80)	8.38 (1.95)	1.17 (3.26)	<0.0005
High consumers(>2 units daily on average)	19	10 (52.6)	6 (31.6)	4.53 (6.31)	5.03 (4.39)	15.6 (9.2)	5.37 (3.35)	8.13 (2.29)	2.76 (4.04)	0.008
Low consumers (>0–2 units daily)	60	34 (56.7)	42 (70)	1.38 (2.45)	0.84 (0.54)	5.65 (3.22)	7.09 (2.72)	8.18 (1.84)	1.08 (3.07)	0.008
Non consumers (0 units daily)	61	38 (62.3)	49 (80.3)	0 (0)	0 (0)	3.57 (4.29)	7.90 (2.45)	8.66 (1.94)	0.76 (3.08)	0.058

[a] Patients with complete alcohol consumption data.
[b] AUDIT, alcohol use identification test (recorded at admission), n = 134.

Fig. 2. Scatterplots of the correlation between alcohol unit difference (transformed alcohol units 5 days prior to seizure minus follow-up) and total 24 h sleep time. The regression line to the left shows that subjects with positive alcohol unit difference-values had the shortest sleep-times prior to the seizure ($r = -0.25$, $p = 0.007$). To the right, alcohol unit difference and sleep at follow up ($r = 0.02$, $p = 0.84$).

in a previous study (Samsonsen et al., 2013). Thus, we selected alcohol consumption and AED treatment for the ANOVA model along with sleep duration.

Both reduced sleep and alcohol consumption remained as significant seizure triggers. These two factors are often clinically associated. Nevertheless, since the sleep-time difference still was highly significant, even among those with low alcohol consumption, our findings suggest that their effects are partly independent. To what extent anxiety, depression and perceived stress by themselves contribute to the occurrence of seizures is hard to decipher, but these factors were not convincingly correlated with sleep duration in this study.

The notion that sleep loss may have a specific effect on neuronal excitability is in line with a range of previous clinical and EEG studies (Aird, 1983; Antebi and Bird, 1993; Badawy et al., 2006; da Silva Sousa et al., 2005; Ferlisi and Shorvon, 2014; Frucht et al., 2000; Gunderson et al., 1973; Huber et al., 2013; Lawn et al., 2014; Méndez and Radtke, 2001; Nakken et al., 2005; Spector et al., 2000; Tan et al., 2005; Wassenaar et al., 2014). Sleep deprivation facilitates interictal epileptiform discharges, not only during non-REM sleep, but also during wakefulness (Malow, 2004). One classic clinical study from 1973 investigated the occurrence of seizures in North-American soldiers returning from overseas. Seizures occurred in 40 returnees, significantly more common in sleep-deprived individuals. Enrolled subjects were considered non-alcoholic, but the majority had still ingested alcohol the night before (Gunderson et al., 1973). Moreover, studies in patients with epilepsy and chronic sleep loss due to obstructive sleep apnea have shown a reduced seizure frequency after treatment of the sleep disorder (Vendrame et al., 2011).

The subgroup with overt sleep deprivation (>50% sleep loss compared to follow up) comprised 14% among the present patients. Unsurprisingly, young age predominated in this group, and heavy alcohol consumption was more common, whereas anxiety, depression and stress were not significant features (Table 3). Irregular lifestyle is common in adolescents, and compliance with recommended behaviour is often poor in young people with epilepsy (Kyngäs, 2000). In patients with sleep deprivation there was also a trend towards more generalized seizures compared to focal seizures, whereas the difference between genetic generalized epilepsy syndromes and focal epilepsies did not reach significance, conceivably due to the present sample size. A study using transcranial magnetic stimulation demonstrated an increased neuronal excitability after sleep deprivation in new onset epilepsy which was more prominent in generalized than in focal epilepsy (Badawy et al., 2006). Likewise, a different response to sleep deprivation in idiopathic (genetic) generalized and focal epilepsy is also supported by EEG findings (Renzel et al., 2016).

However, one controlled clinical study questioned the seizure-inducing effect of sleep deprivation alone. In drug resistant surgical candidates undergoing long-term EEG-monitoring, seizure frequency did not differ between sleep-deprived and normal sleep groups (Malow et al., 2002), leaving this question open. However, the situation may be different in these highly treatment refractory patients with frequent spontaneous focal seizures compared to patients with occasional, predominantly GTCs acutely admitted to hospital. In such patients, the effect of sleep deprivation and alcohol is frequently associated, partly as an acute party effect and partly in the context of chronic abuse.

Table 5
Repeated measures ANOVA (n = 118). Dependent variable is the total sleep-time 24 h before seizure and the corresponding follow-up sleep-time, respectively. Within-subject sleep-times were controlled for AED onset and difference in alcohol consumption from seizure to follow-up.

	F(df = 1)	p
Between subjects		
AED-difference	0.56	0.46
Alc.unit-difference	3.19	0.08
Error mean square (df 115) = 5.54		
Within subjects		
Day	6.89	0.010
Day*AED-difference	0.71	0.40
Day*Alc.unit-difference	6.04	0.015
Error mean square (df 115) = 4.49		

Day: Factor reflecting total sleep-time-change (from 24 h before seizure to the corresponding 24 h follow-up); AED-difference: Onset of AEDs after admission. Patients with AED non-adherence (n = 16), new hypnotic prescriptions (n = 8) and those with missing alcohol data (n = 2) were excluded, leaving 118 patients for ANOVA.
Alc.unit-difference entered as covariate: Transformed difference between units five days before admission and follow-up (seizure and interview-days excluded).

4.2. Sleep and alcohol

Insomnia is a core symptom of the alcohol withdrawal syndrome along with other signs of glutamate-mediated central nervous excitation, including autonomic symptoms of sympathetic overactivity, restlessness, anxiety as well as seizures (Jesse et al., 2016). A single occasional alcohol dose causes a reduction of sleep onset latency, a more consolidated first half of sleep, but an increase in sleep disruption during the second half. The effects on REM-sleep in the first half of sleep appear to be dose-related with low to moderate doses showing no clear trend, whereas at high doses REM sleep reduction is significant along with increased slow wave sleep (Ebrahim et al., 2013).

In the present study, high alcohol consumers had a 2.8 h shorter mean duration of sleep prior to the seizure compared to follow up (Table 4), a finding which may have been influenced by dependence and withdrawal. In the combined group of low/non-consumers with presumed little or no alcohol effect on sleep architecture, sleep difference was less, but still strongly significant, supporting the view that reduced sleep alone might increase the propensity to seizures in the absence of an abusive drinking pattern.

The controlled ANOVA analysis disclosed a significant interaction between day and alcohol unit change on sleep-time, reflecting that patients with a high consumption before the attack had the shortest sleep-times (Table 5). However, when removing the subgroup with an average alcohol consumption $\geq$2 units/day in the ANOVA, this interaction was no longer significant, also supporting the notion that sleep loss and alcohol consumption are both independent risk factors for seizures.

Nevertheless, these effects are clinically and mechanistically intertwined and difficult to separate, particularly in high-consumers with binge drinking and/or chronic abuse. The mechanism behind the alcohol withdrawal seizure might also be strongly linked to sleeplessness, pointing to the importance of the therapeutic effect of sleep induction in the alcohol withdrawal syndrome (Jesse et al., 2016). Moreover, the notion that sleep loss by itself can facilitate the development of seizures is supported by a previous study on the weekday distribution of seizures in relation to alcohol consumption. More seizures occurred on Mondays compared to Saturdays. However, the group of patients without harmful drinking (AUDIT $\leq$8), of which binge drinking occurred in only 5%, caused this difference. Thus, it was concluded that the increased number of seizures during the first days of the week was mainly due to weekend-related factors other than alcohol use (Bråthen et al., 2000). Moreover, even in the present subgroup of non-consumers with established epilepsy, the sleep-time difference between admission and follow-up was significant.

4.3. Strengths and limitations

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. It is acknowledged that sleep-time and quality of sleep are hard to measure by means of a simple questionnaire.

4.4. Conclusion

This study is the first to provide scientific evidence for the notion that sleep loss is an independent seizure trigger when other relevant seizure precipitants also are considered. The complex impact of alcohol on sleep and seizures is particularly difficult to decipher. Alcohol and late nights are linked in the party setting, whereas alcohol abuse and withdrawal disrupt sleep. When seizures occur after sleep loss, the role of alcohol should be explored. Improved understanding and awareness of the intricate role of sleep in the cascade of events that leads to a seizure can improve patient care.

Disclosure of conflicts of interest

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Christian Samsonsen, Geir Bråthen and Eylert Brodtkorb have received honoraria and/or financial support for attending conferences from GlaxoSmithKline, UCB and Eisai. Trond Sand and Grethe Helde have no disclosures.

References

Aird, R.B., 1983. The importance of seizure-inducing factors in the control of refractory forms of epilepsy. Epilepsia 24, 567–583.

Antebi, D., Bird, J., 1993. The facilitation and evocation of seizures. A questionnaire study of awareness and control. Br. J. Psychiatry 162, 759–764.

Badawy, R.A., Curatolo, J.M., Newton, M., Berkovic, S.F., Macdonell, R.A., 2006. Sleep deprivation increases cortical excitability in epilepsy: syndrome-specific effects. Neurology 67, 1018–1022.

Bazil, C.W., 2000. Sleep and epilepsy. Curr. Opin. Neurol. 13, 171–175.

Bazil, C.W., 2003. Epilepsy and sleep disturbance. Epilepsy Behav. 4 (Suppl. 2), 39–45.

Berg, A.T., Berkovic, S.F., Brodie, M.J., Buchhalter, J., Cross, J.H., van Emde Boas, W., Engel, J., French, J., Glauser, T.A., Mathern, G.W., Moshé, S.L., Nordli, D., Plouin, P., Scheffer, I.E., 2010. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE commission on classification and terminology, 2005–2009. Epilepsia 51, 676–685.

Bråthen, G., Brodtkorb, E., Sand, T., Helde, G., Bovim, G., 2000. Weekday distribution of alcohol consumption in Norway: influence on the occurrence of epileptic seizures and stroke? Eur. J. Neurol. 7, 413–421.

Cobabe, M.M., Sessler, D.I., Nowacki, A.S., O'Rourke, C., Andrews, N., Foldvary-Schaefer, N., 2015. Impact of sleep duration on seizure frequency in adults with epilepsy: a sleep diary study. Epilepsy Behav. 43, 143–148.

da Silva Sousa, P., Lin, K., Garzon, E., Sakamoto, A.C., Yacubian, E.M., 2005. Self-perception of factors that precipitate or inhibit seizures in juvenile myoclonic epilepsy. Seizure 14, 340–346.

Ebrahim, I.O., Shapiro, C.M., Williams, A.J., Fenwick, P.B., 2013. Alcohol and sleep I: effects on normal sleep. Alcohol. Clin. Exp. Res. 37, 539–549.

Ebrahim, I., Fenwick, P., Williams, A.J., Shapiro, C., 2015. Alcohol and sleep review: sound statistics and valid conclusions. Alcohol. Clin. Exp. Res. 39, 944–946.

Ferlisi, M., Shorvon, S., 2014. Seizure precipitants (triggering factors) in patients with epilepsy. Epilepsy Behav. 33, 101–105.

Frucht, M.M., Quigg, M., Schwaner, C., Fountain, N.B., 2000. Distribution of seizure precipitants among epilepsy syndromes. Epilepsia 41, 1534–1539.

Gunderson, C.H., Dunne, P.B., Feyer, T.L., 1973. Sleep deprivation seizures. Neurology 23, 678–686.

Huber, R., Mäki, H., Rosanova, M., Casarotto, S., Canali, P., Casali, A.G., Tononi, G., Massimini, M., 2013. Human cortical excitability increases with time awake. Cereb. Cortex 23, 332–338.

Ismayilova, V., Demir, A.U., Tezer, F.I., 2015. Subjective sleep disturbance in epilepsy patients at an outpatient clinic: a questionnaire-based study on prevalence. Epilepsy Res. 115, 119–125.

Jesse, S., Bråthen, G., Ferrara, M., Keindl, M., Ben-Menachem, E., Tanasescu, R., Brodtkorb, E., Hillbom, M., Leone, M.A., Ludolph, A.C., 2016. Alcohol withdrawal syndrome: mechanisms, manifestations, and management. Acta Neurol. Scand. 00, 1–13.

Kyngäs, H., 2000. Compliance with health regimens of adolescents with epilepsy. Seizure 9, 598–604.

Lawn, N., Lieblich, S., Lee, J., Dunne, J., 2014. Are seizures in the setting of sleep deprivation provoked? Epilepsy Behav. 33, 122–125.

Legros, B., Bazil, C.W., 2003. Effects of antiepileptic drugs on sleep architecture: a pilot study. Sleep Med. 4, 51–55.

Méndez, M., Radtke, R.A., 2001. Interactions between sleep and epilepsy. J. Clin. Neurophysiol. 18, 106–127.

Mørland, J., 2005. Alkohol i kroppen. Norwegian Directorate of Health, https://helsedirektoratet.no/Lists/Publikasjoner/Attachments/455/Alkohol-i-kroppen-IS-1076-bokmal.pdf (accessed 5.05.16).

Malow, B.A., Passaro, E., Milling, C., Minecan, D.N., Levy, K., 2002. Sleep deprivation does not affect seizure frequency during inpatient video-EEG monitoring. Neurology 59, 1371–1374.

Malow, B.A., 2004. Sleep deprivation and epilepsy. Epilepsy Curr. 4, 193–195.

Manni, R., Terzaghi, M., 2010. Comorbidity between epilepsy and sleep disorders. Epilepsy Res. 90, 171–177.

Matos, G., Andersen, M.L., do Valle, A.C., Tufik, S., 2010. The relationship between sleep and epilepsy: evidence from clinical trials and animal models. J. Neurol. Sci. 295, 1–7.
Nakken, K.O., Solaas, M.H., Kjeldsen, M.J., Friis, M.L., Pellock, J.M., Corey, L.A., 2005. Which seizure-precipitating factors do patients with epilepsy most frequently report? Epilepsy Behav. 6, 85–89.
Nobili, L., Proserpio, P., Combi, R., Provini, F., Plazzi, G., Bisulli, F., Tassi, L., Tinuper, P., 2014. Nocturnal frontal lobe epilepsy. Curr. Neurol. Neurosci. Rep. 14, 424.
Pressman, M.R., Grunstein, R.R., Mahowald, M.W., Schenck, C.H., Montplaisir, J.Y., Bornemann, M.C., Zadra, A., Buchanan, P.R., 2015. Alcohol and sleep review: flawed design methods, and statistics cannot support conclusions. Alcohol. Clin. Exp. Res. 39, 941–943.
Quigg, M., Gharai, S., Ruland, J., Schroeder, C., Hodges, M., Ingersoll, K.S., Thorndike, F.P., Yan, G., Ritterband, L.M., 2016. Insomnia in epilepsy is associated with continuing seizures and worse quality of life. Epilepsy Res. 122, 91–96.
Renzel, R., Baumann, C.R., Poryazova, R., 2016. EEG after sleep deprivation is a sensitive tool in the first diagnosis of idiopathic generalized but not focal epilepsy. Clin. Neurophysiol. 127, 209–213.
Samsonsen, C., Bråthen, G., Reimers, A., Helde, G., Brodtkorb, E., 2013. Is dietary caffeine involved in seizure precipitation? Epilepsy Behav. 28, 147–150.
Samsonsen, C., Reimers, A., Bråthen, G., Helde, G., Brodtkorb, E., 2014. Nonadherence to treatment causing acute hospitalizations in people with epilepsy: an observational, prospective study. Epilepsia 55, 125–128.
Saunders, J.B., Aasland, O.G., Babor, T.F., de la Fuente, J.R., Grant, M., 1993. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption—II. Addiction 88, 791–804.
Spector, S., Cull, C., Goldstein, L.H., 2000. Seizure precipitants and perceived self-control of seizures in adults with poorly-controlled epilepsy. Epilepsy Res. 38, 207–216.
Tan, J.H., Wilder-Smith, E., Lim, E.C., Ong, B.K., 2005. Frequency of provocative factors in epileptic patients admitted for seizures: a prospective study in Singapore. Seizure 14, 464–469.
Thurman, D.J., Beghi, E., Begley, C.E., Berg, A.T., Buchhalter, J.R., Ding, D., Hesdorffer, D.C., Hauser, W.A., Kazis, L., Kobau, R., Kroner, B., Labiner, D., Liow, K., Logroscino, G., Medina, M.T., Newton, C.R., Parko, K., Paschal, A., Preux, P.M., Sander, J.W., Selassie, A., Theodore, W., Tomson, T., Wiebe, S., 2011. ILAE commission on epidemiology. Standards for epidemiologic studies and surveillance of epilepsy. Epilepsia 52 (Suppl. 7), 2–26.
Vendrame, M., Auerbach, S., Loddenkemper, T., Kothare, S., Montouris, G., 2011. Effect of continuous positive airway pressure treatment on seizure control in patients with obstructive sleep apnea and epilepsy. Epilepsia 52, 168–171.
Vendrame, M., Yang, B., Jackson, S., Auerbach, S.H., 2013. Insomnia and epilepsy: a questionnaire-based study. J. Clin. Sleep Med. 9, 141–146.
Wassenaar, M., Kasteleijn-Nolst Trenité, D.G., de Haan, G.J., Carpay, J.A., Leijten, F.S., 2014. Seizure precipitants in a community-based epilepsy cohort. J. Neurol. 261, 717–724.
Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67, 361–370.