The patients' perspective on epilepsy – challenges, sexual problems, provision of information and adherence to treatment

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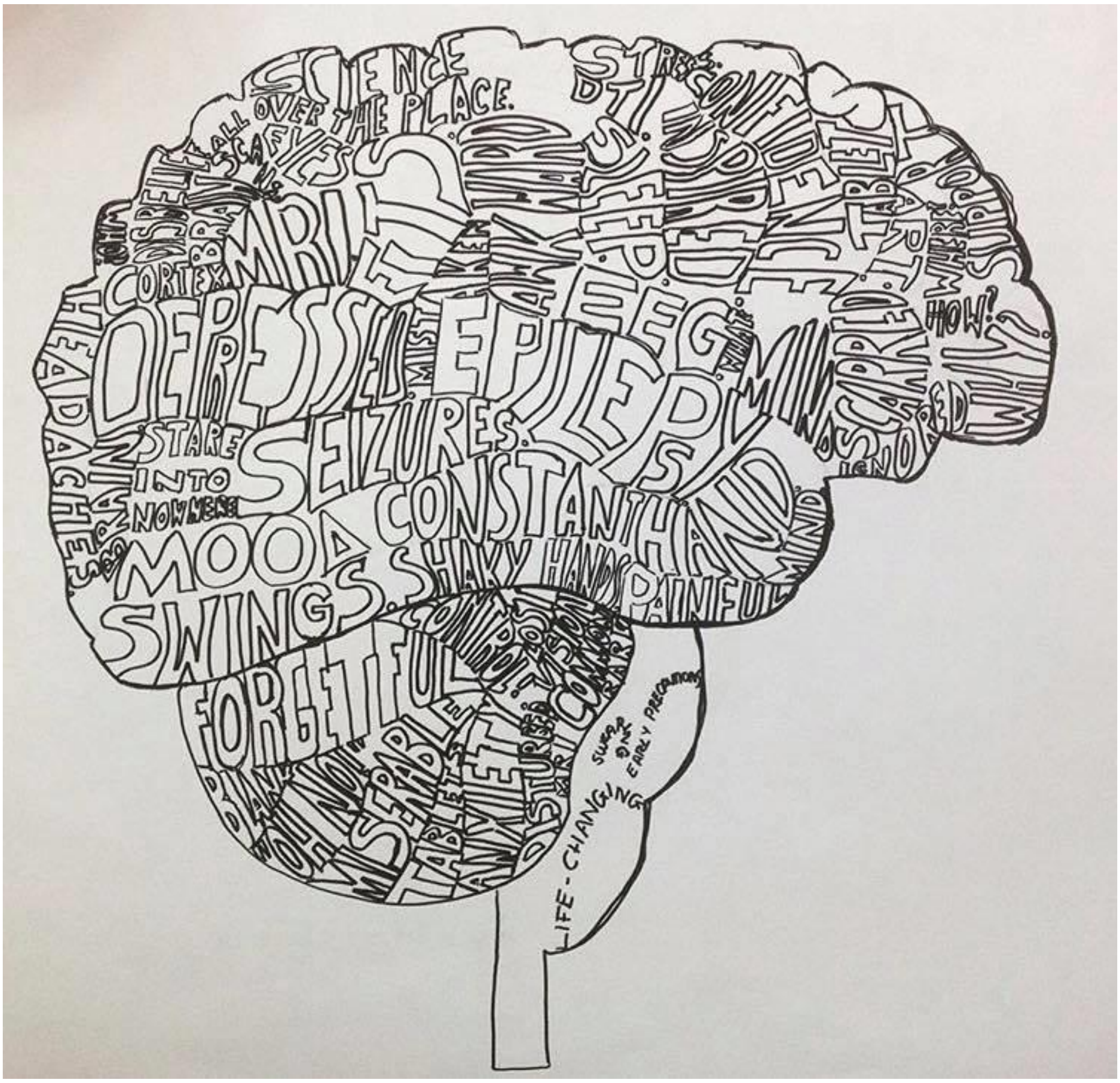
Preface

The following work was initiated by the doctoral candidate in cooperation with Morten Lossius, Cecilie Johannessen Landmark, Bente Træen, and Karl Otto Nakken. The research questions were posed, and the questionnaires and their implementation were organized by the doctoral candidate.

Many of the people with epilepsy whom I met during my clinical work reported problems in daily life that were not necessarily related directly to seizures. Their accounts gave me the incentive for starting this work.

The artwork “Epilepsy in typography” by artist James Bletsoe summarizes all these experiences. James is a 22-years-old Welsh art student, currently studying in Cardiff. He bases his artwork mostly on his epilepsy and his experiences with epilepsy. His work has also gained him considerable recognition and, in 2016, he won a Young Epilepsy “Inspirational Bright Star Award”. I am grateful to James for his permission to use his artwork in this thesis.



"Epilepsy in typography" reproduced with permission of the artist, James Bletsoe

Acknowledgements

The present work was carried out at the National Centre for Epilepsy, Oslo University Hospital, starting in 2006 and continuing until the end of 2019. Parts of the work were conducted in cooperation with the Department for Neurology at Lillehammer Hospital, the Department for Psychology at Oslo University, and the Norwegian Epilepsy Association. The research was carried out during or parallel to my clinical work, with additional financial support from the National Centre for Epilepsy and the Norwegian Epilepsy Association.

First, I want to thank everyone with epilepsy who participated in these studies. By using their time completing questionnaires, they thereby made this work possible.

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Abbreviations

AEP	Adverse events profile
BDI	Becks depression inventory
CI	Confidence interval
DSM	Diagnostic and statistical manual of mental disorders
IBE	International bureau for epilepsy
ICD	International statistical classification of diseases and related health problems
ILAE	International league against epilepsy
NDDI-E	Neurological disorders depression inventory for epilepsy
OR	Odds ratio
SHBG	Sex hormone-binding globulin
SSRI	Selective serotonin reuptake inhibitor
SUDEP	Sudden unexpected death in epilepsy
WHO	World health organization

List of publications

This thesis is based on the following original articles:

I. Henning O, Landmark CJ, Henning D, Nakken KO, Lossius MI. Challenges in epilepsy - the perspective of Norwegian epilepsy patients. Acta Neurologica Scandinavica 2019;140:40-47.
II. Henning OJ, Nakken KO, Træen B, Mowinckel P, Lossius M. Sexual problems in people with refractory epilepsy. Epilepsy & Behavior 2016;61:174-179.
III. Henning OJ, Landmark CJ, Træen B, Svendsen T, Farmen A, Nakken KO, Lossius MI. Sexual function in people with epilepsy: similarities and differences with the general population. Epilepsia 2019; 60(9):1984-1992.
IV. Henning O, Alfstad KA, Nakken KO, Lossius MI. A call for better information about epilepsy: The patients' perspective - an online survey. Seizure 2019;69:173-179.
V. Henning O, Nakken KO, Lossius MI. People with epilepsy and their relatives want more information about risks of injuries and premature death. Epilepsy & Behavior 2018;82:6-10.
VI. Henning O, Landmark CJ, Nakken KO, Lossius MI. Non-adherence to treatment regimens in epilepsy from the patient's perspective and predisposing factors: differences between intentional and unintentional lack of adherence. Epilepsia 2019;60(5):e58-e62.
VII. Henning OJ, Lossius MI, Lima M, Mevåg M, Villagran A, Nakken KO, Landmark CJ. Refractory epilepsy and non-adherence to drug treatment. Epilepsia Open 2019;https://doi.org/10.1002/epi4.12367

Summary

Epilepsy is a brain disease that is characterized by abnormal neuronal activity causing epileptic seizures, i.e., convulsions or unusual behaviour, sensations, and sometimes loss of awareness. It carries neurological, cognitive, psychological, and social consequences that can impose significant burdens on those affected and their families. Even in seizure-free patients, epilepsy may have an adverse impact on daily activities and feeling of well-being. In order to achieve modern, comprehensive, patient-centred care, we need to know where we encounter the major challenges or obstacles in this pursuit.

Our aim was to evaluate the patients' perspective on different epilepsy-related issues. In particular, we wanted to evaluate the patients' experiences of different epilepsy-related challenges, and explore the prevalence and types of sexual problems, sexual behaviour, and extent of satisfaction with sex life in different groups of patients with epilepsy in comparison with representative samples from the general population. We also wanted to investigate how patients with epilepsy perceive how well they have been informed about different epilepsy-related issues and determine whether the degree of information corresponds with the wishes of patients and caregivers. Finally, we wanted to assess self-rated intentional and unintentional non-adherence to anti-seizure medication in people with either refractory or better-controlled epilepsy.

One of the surveys was an online questionnaire, developed and made available as a pop-up for all those visiting the Norwegian Epilepsy Association's homepage. Another survey used questionnaires that were to be completed by patients and their physicians at the National Centre for Epilepsy in Norway, and compared the results with corresponding data regarding sexual problems from a representative sample of the general population. During the third and final survey, patients at the National Centre for Epilepsy in Norway and patients at a second-line neurology specialist service completed an anonymous questionnaire. Results regarding sexual problems were compared with a new representative sample from the Norwegian general population.

Our results show that even patients with well-controlled epilepsy reported different epilepsy-related challenges, such as cognitive, medical, and psychosocial problems, and physical limitations. Among the risk factors we found were feeling depressed, use of polytherapy, not being seizure free, and female gender.

Despite sexual problems being more frequent among people with epilepsy, they seemed less concerned by this situation than would members of the general population. Quality of life and symptoms of depression were identified as risk factors for sexual problems.

The degree to which patients with epilepsy have been informed about different epilepsy-related issues varies considerably, as did the perceived quality of the information provided. Different factors, among them gender, age, and seizure control, were identified as influencing provision of information. Nearly all patients or caregivers wished to be informed about the risk for premature death related to epilepsy, but only about one third of patients or caregivers reported having received information on this serious possibility.

In a sample with more well-controlled epilepsy, about 30% reported intentional non-adherence to treatment and 40% reported unintentional non-adherence. Among identifiable risk factors were feeling depressed, having memory problems, being young, being male, and having experienced stigmatization. Among patients with refractory epilepsy, non-adherence, either intentional or unintentional, was about 20% lower.

Chapter 1: Introduction and Background

1.1. Introduction

Epilepsy is a brain disease that is characterized by abnormal neuronal activity causing epileptic seizures, i.e., convulsions or unusual behaviour, sensations, and sometimes loss of awareness [1]. Epilepsy may be associated with neurological, cognitive, psychological, and social consequences, all of which can impose significant burdens on those affected and their families [1; 2]. Epilepsy is associated with a significantly increased risk of premature death compared with the general population [3-5], and roughly half of the patient population has coexisting physical or psychiatric comorbidities [2; 6; 7].

In this setting, care that is tailored to the individual patient and that may increase patient empowerment, as well as symptom reduction, has gained increased attention during recent years [8-10]. Important factors in this model are the patients' own perspectives on the challenges related to epilepsy [11-13]. The degree to which patients themselves feel that they have been satisfactorily informed about different aspects of the disease, such as the diagnosis and treatment options, and the importance of being adherent to the treatment, are important in this context [14].

In our studies, we have tried to explore the patients' perspectives on challenges in living with epilepsy. We particularly investigated the patients' perceptions on how to cope with epilepsy in daily life, e.g., sexual function, adherence to treatment, and the quality of information received from healthcare providers.

1.2. Patient-centred care

In the 1940s, the American psychologist Carl R. Rogers developed the concept of client-centred therapy [15], later promoted as patient-centred medicine [16]. Today, patient-centred care is widely acknowledged as a core value in family medicine [17] . It has been associated with various positive outcomes, including improvements in: physician satisfaction, consultation time, patients’ emotional state, and medication adherence. Patient-centred care may increase patient satisfaction and empowerment, as well as reducing symptom severity, improving use of healthcare resources and decreasing healthcare costs [18; 19] .

Definitions of patient-centred care often differ. Stewart proposed a definition of patient-centred being care that “(a) explores the patients' main reason for the visit, concerns, and need for information; (b) seeks an integrated understanding of the patients' world - that is, their whole person, emotional needs, and life issues; (c) finds common ground on what the problem is and mutually agrees on management; (d) enhances prevention and health promotion; and (e) enhances the continuing relationship between the patient and the doctor.” [10]

Person-centred care has also been discussed recently; the borders between these two concepts are vague and there is considerable overlap [8]. In a model of the various aspects of the doctor-patient relationship in patient-centred care, the following dimensions were identified: biopsychosocial perspective, patient-as-person, sharing power and responsibility, therapeutic alliance, and doctor-as-person [9] . Important common factors in this model, and that can be transferred to epilepsy care, are the patients’ perspective and perception, both of comorbidity and challenges related to a life with epilepsy (biopsychosocial perspective), the degree to which the patients feels informed about different aspects of the disease, like diagnosis, treatment options, and challenges (sharing power and responsibility), and the degree to which the patient has the opportunity to be part of the treatment decisions (therapeutic alliance) [13; 20].

In order to achieve the goal of a modern, comprehensive, patient-centred care, we need to know where we encounter the major challenges or obstacles in this pursuit. It has been shown that patients are least satisfied with the communication abilities, actual skills, and knowledge of care givers[14]. The data whether patients with epilepsy feel that they are included in sharing of information or respected as a part of a therapeutically alliance are sparse, and often patients do not feel as included as they wish to be [20; 21]; we therefore asked Norwegian epilepsy patients about this in our online study.

1.3. What is epilepsy?

Epilepsy is a neurological disease with repeated spontaneous epileptic seizures and has been clinically defined, in an official report by the International League Against Epilepsy (ILAE), by any of the following conditions: (a) at least two unprovoked (or reflex) seizures occurring >24 h apart; (b) 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; (c) diagnosis of an epilepsy syndrome[22].

At least one seizure is required to set the diagnosis of epilepsy. Epileptic seizures can present in a broad variation of behavioural, motor, or cognitive patterns. The classification of the epilepsies was revised in 2017[23] (Figure 1).

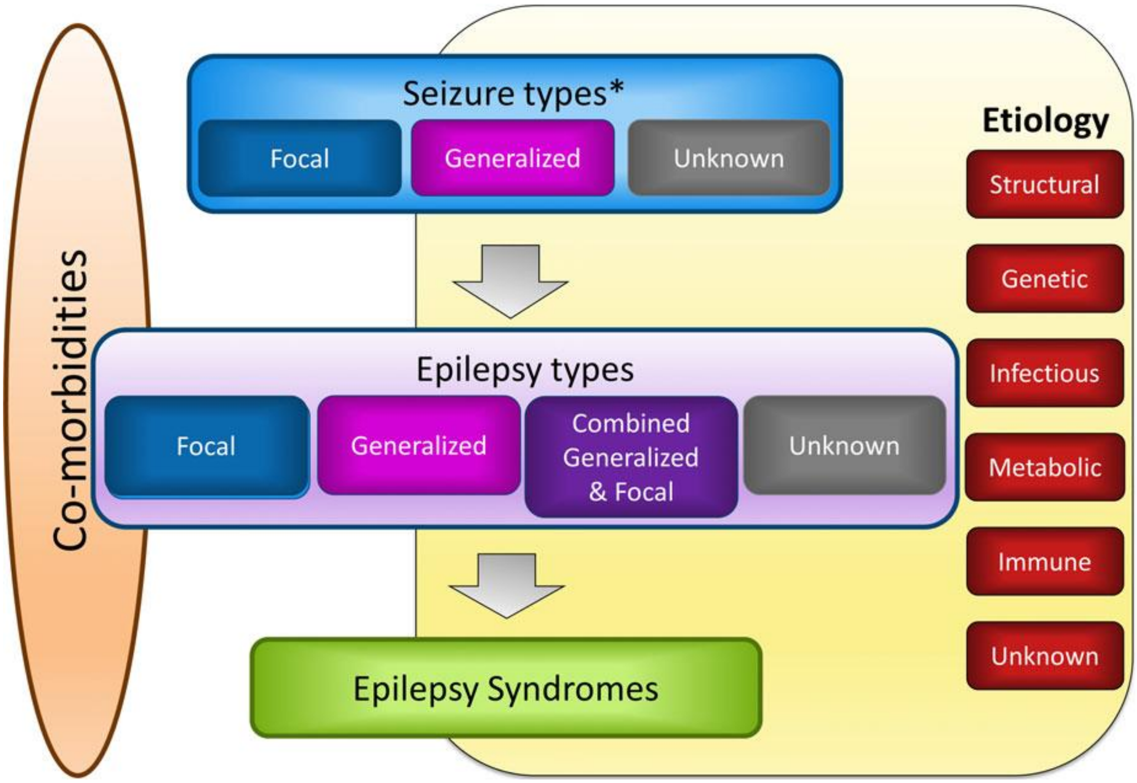

Figure 1. Framework for classification of the epilepsies (with permission of the ILAE) [23].

The classification has three levels, starting with seizure type according to the 2017 ILAE Seizure Classification [24]. Diagnosis of seizure type is followed by diagnosis of epilepsy type, including focal epilepsy, generalized epilepsy, and combined generalized and focal epilepsy, and also epilepsy of unknown type. On the third level are the epilepsy syndromes, if known. Epilepsy aetiology is incorporated along each step, as is comorbidity, if present [23].

In a joint proposal by the ILAE and the International Bureau for Epilepsy (IBE), epilepsy was defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition [25]. With the current treatment armamentarium, up to 70% of the patients become seizure free [26; 27]. The remaining proportion is characterized as refractory, which means that they are difficult to treat.

Of Norway's population, i.e., 5.3 million inhabitants, about 0.65% suffer from epilepsy [28] . This is in line with systematic reviews and meta-analyses of prevalence studies from high-income countries, where pooled data showed an overall lifetime prevalence of epilepsy of 5.18 per 1000, and a point prevalence of active epilepsy of 5.49 per 1,000 persons [29] .

The risk of death from various causes in people with epilepsy is up to three times higher than in the general population [5]. In selected groups of patients, this risk can be much higher; having three or more tonic-clonic seizures per year is associated with a 15-fold increase in sudden unexpected death in epilepsy (SUDEP) risk [30]. Among deaths attributable to epilepsy or seizures, important immediate causes include SUDEP, status epilepticus, seizure-related injuries, and suicide [4]. In people with epilepsy, the rate of SUDEP is 1.2 per 1000 person-years (95% CI: 0.9–1.5) [3]. Major risk factors for SUDEP are the presence and frequency of generalized tonic-clonic seizures, nocturnal seizures, and lack of seizure freedom [31].

However, with correct diagnosis and treatment, the overall prognosis with regards to seizure freedom is favourable in the majority of individuals; up to 70% of patients achieve prolonged seizure remission [1].

1.4. Challenges associated with epilepsy

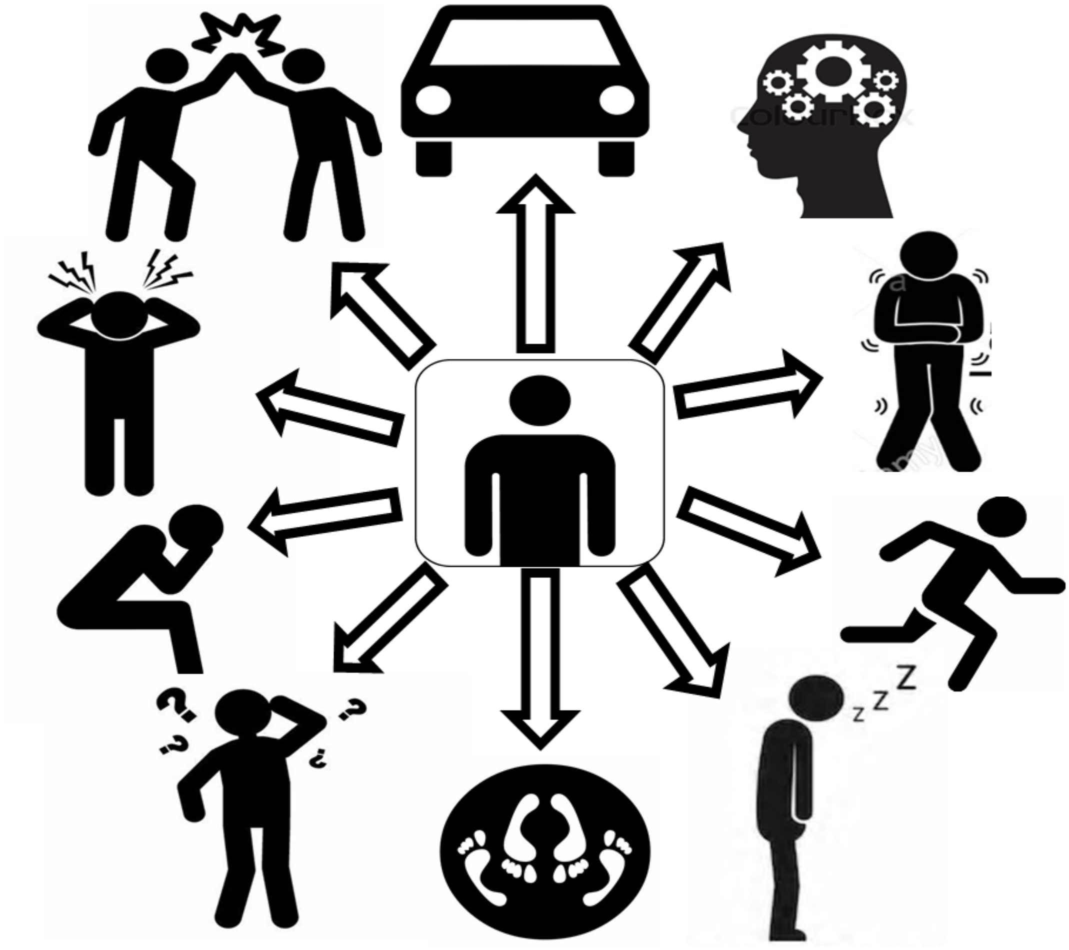

Figure 2. Different challenges faced by people with epilepsy.

Even in seizure-free patients, epilepsy may have an adverse impact on daily activities and feelings of wellbeing; see figure 2. This is reflected in the definition of epilepsy proposed by ILAE in 2005 [22]. By including the consequences of the disease in the definition, ILAE emphasized that the consequences of epilepsy encompass far more than recurrent seizures [22]. Due to the lack of predictability of epileptic seizures, many patients have a constant fear of having a new seizure, even when they have been seizure free for a long time [11].

Moreover, some patients may experience chronic adverse effects from the drugs or other treatment. For others, the disease may be an obstacle to education, work, driving, establishing a family, and developing and maintaining social relationships. In addition, epilepsy is still a disease associated with discrimination and stigmatization, which may adversely affect an individual's self-esteem and self-image [11; 32-34]. Fear of having a seizure, fear of dying during a seizure, fear of being disqualified from driving, fear of long-term side effects of the drugs, including cognitive problems, and fear of being stigmatized, are major concerns in many of these patients [11; 12; 34-38].

1.5. Comorbidities associated with epilepsy

Comorbidity is a term used when a condition or disease occurs during the course of an index disease (e.g., epilepsy). It has been estimated that about 50% of adults with active epilepsy have at least one comorbid medical disorder [2]. As these comorbidities can affect quality of life and the epilepsy prognosis (for example, psychiatric disorders [39-41]), it is important both to detect comorbidities and to treat them as a part of comprehensive epilepsy care.

1.5.1. Psychiatric comorbidities

Epilepsy is associated with an increased prevalence of psychiatric disorders. Large population-based studies clearly show increased rates of major depressive disorders, mood disorders, anxiety disorder, suicidal ideation, and any mental disorder in persons with epilepsy [6; 7].

Depression is one of the most prevalent psychiatric comorbidities in epilepsy and has been identified as a serious comorbidity in persons with epilepsy [6; 7]. It is associated with a reduced quality of life [41], a less favourable prognosis [39; 42], more frequent reports of adverse events related to anti-seizure drugs [43], reduced adherence to treatment [44], and increased mortality [45]. A meta-analysis of population-based studies revealed a pooled prevalence of active depression (current or past year) in 23% and an odds ratio (OR) of 2.77 [46]. Nevertheless, physicians might be reluctant to treat psychiatric disorders in persons with epilepsy, possibly due to fear of triggering seizures [47; 48]. A bidirectional relationship, meaning an increased risk for those with epilepsy developing depression and for those with depression developing epilepsy, has been shown [42]. Because of the considerable impact that depression may have on quality of life [49], it is important both to diagnose and to treat comorbid depression in this patient group and to correct for depression as a confounding variable in research studies.

1.5.2. Sexual dysfunction

Since the early 1950s, it has been realized that epilepsy is associated with an increased rate of sexual difficulties or problems [50]. Nevertheless, in clinical epileptology this topic is generally neglected [51]. The World Health Organization (WHO) defined sexual health as "…a state of physical, emotional, mental and social wellbeing in relation to sexuality" [52]. Sexual satisfaction and healthy sexual functioning are important for the quality of life in adults [53]. A study analysing over 45,000 individual user posts on a web-based message board found that intimacy and sexuality were of concern or a struggle for both patients with epilepsy and/or for their partners[54]. However, both physicians and patients are often reluctant to discuss these matters in clinical encounters [51].

Both the International Classification of Diseases (ICD)-11 proposed by WHO and the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V proposed by the American Psychiatric Association [55; 56] divide sexual dysfunction into four broad categories: 1) sexual desire disorders (e.g., lack or absence of sexual drive), 2) sexual arousal disorders (e.g., inability to obtain an erection), 3) orgasmic disorders (e.g., failure to achieve climax), and 4) sexual pain disorders (e.g., vaginismus or priapism). The subjective and sensitive nature of many of these dysfunctions constitute a major obstacle in identifying sexual disorders, which are also influenced by the relationship to the partner and socio-cultural factors [57].

To assess and characterize sexual dysfunction in the general population and in populations with several chronic diseases, more than 50 screening tools have been developed [58; 59]. However, none of these screening tools and scales has been validated in people with epilepsy. Thus, different rating scales or questionnaires have been used, depending upon the population under study and the research questions being addressed.

While the problem of sexual dysfunction, which is defined in psychiatric diagnostic manuals, has gained more awareness during recent years, the use of different diagnostic and screening tools means that exact evaluations of prevalence remain a challenge.

1.5.2.1. Prevalence of sexual dysfunction in people with epilepsy

One of the first descriptions of sexual dysfunction in people with epilepsy in modern history was a publication in 1954 by Gastaut and Collombin. They described a lack of interest in sexual activity in 26 of 36 (72%) patients with complex partial seizures [50]. Despite various consecutive studies, the exact prevalence of sexual dysfunction in people with epilepsy and the pattern are not well defined. The majority of studies are observational, without control groups, and they mostly emanate from epilepsy clinics.

The prevalence of sexual dysfunction in females in the general population varies from 25% to 63% [60; 61]. The corresponding numbers for males in the general population are approximately 20-30% [60; 61]. In contrast to women, who generally have dysfunction in the domains of desire and pain, males usually have dysfunction related to physical response, and are mainly concerned with erectile dysfunction and premature ejaculation. The variability between studies is probably due to different definitions of sexual problems and different study populations.

The reported prevalence of sexual dysfunction in women with epilepsy varies from 10% to 75% [62-73]. Studies of men with epilepsy reveal a prevalence of sexual dysfunction varying from 3% to 60%, the difference being largely due to methodological heterogeneity among the studies [66; 67; 71; 74-76]. Despite methodological limitations, these studies suggest that persons with epilepsy are 1.5-3 fold more likely to have some form of sexual dysfunction than healthy controls. Erectile dysfunction is the most common sexual dysfunction reported in men with epilepsy, but approximately 10-20% of the patients also report decreased libido.

The great prevalence differences in results reflect differences in the number of patients included and variations in sample characteristics, such as the marital status of the participants, the types and severity of epilepsy, use of anti-seizure drugs, and the types of screening instruments used for evaluating sexual dysfunction. As the majority of studies are based on low numbers of patients, subgroup analyses are difficult. This is probably the reason that many studies are unable to identify any effect on sexual function that is associated with epilepsy severity and/or use of anti-seizure drugs. Overall, studies that have involved patients with uncontrolled seizures, longer duration of epilepsy, higher seizure frequency, focal epilepsy, and patients receiving polytherapy reported higher prevalences of sexual dysfunction.

Disturbances in sexual functioning are an important issue in epilepsy that warrants more attention. The large variation in studies underlines the importance of a representative control group using the same screening tools as in the study sample.

1.5.2.2. Sexual dysfunction in epilepsy – pathophysiological considerations

1.5.2.2.1 Sexual dysfunction as a result of epilepsy

Multiple mechanisms may cause sexual dysfunction in people with epilepsy. Such problems may be a direct result of having epilepsy *per se*. This is supported by the fact that sexual dysfunction usually begins after the onset of seizures and is also present in untreated patients with epilepsy [50; 77; 78]. In addition, there are reports that indicate that sexual dysfunction is independent of anti-seizure drugs and not associated with psychiatric comorbidity [79]. These findings suggest that central mechanisms interfering with pituitary-hypothalamic functions may contribute to sexual dysfunction in these patients. Herzog and others suggested that epileptiform discharges, propagating through amygdalo-hypothalamic pathways, can interfere with pulsatile secretion of gonodatrophic hormones and dopamine [79]. This can cause hypogonadism, hyperprolactinaemia, and sexual difficulties.

Bauer and colleagues estimated hormonal levels in 200 patients with epilepsy who were receiving either one or no anti-seizure drugs and compared them with 105 controls without epilepsy [77]. Patients with epilepsy, including those not using anti-seizure drugs, had low levels of free testosterone. Low free-testosterone levels were associated with high luteinizing hormone (LH) levels, and low testosterone/LH ratio may indicate that epilepsy affects testicular testosterone production by mechanisms other than centrally induced low LH levels.

1.5.2.2.2. Anti-seizure medication

Anti-seizure drugs, especially enzyme-inducing drugs (carbamazepine, phenytoin, and phenobarbital), may influence sex hormonal levels and can produce sexual difficulties by multiple mechanisms [80-83]. Enzyme-inducing drugs increase the levels of sex hormone-binding globulin (SHBG), and thus reduce the levels of unbound active testosterone [82]. These drugs also increase the hepatic metabolism of gonadal and adrenal sex steroids [84]. In addition, anti-seizure drugs with an overall inhibitory effect on the brain are postulated to suppress the pituitary hypothalamic axis, thus producing hypogonadotrophic hypogonadism [85].

Anti-seizure drugs can also influence sexual functions by their effect on serotoninergic pathways. Carbamazepine has been shown to be associated with low levels of free testosterone and high levels of SHBG in normal healthy volunteers, and also in patients with epilepsy [77; 86]. The association between carbamazepine and low levels of sex steroids is further supported by a study that showed significant increases in serum testosterone levels and free androgen values in both men and women after carbamazepine withdrawal [87].

Limited data suggest that valproate may cause impotence in 10% of patients [88]. With regard to the new generation of anti-seizure drugs, only limited data are available regarding their effects on sexual functions. Studies indicate that lamotrigine is least likely to have an adverse effect on sexual function [89]. In fact, it has been shown that patients can experience an improvement in sexual functioning after switching to lamotrigine [90]. Topiramate has been shown to cause sexual dysfunction in 7-13% of patients [91], causing mainly orgasmic disorders in females and erectile dysfunction in males.

The mechanisms behind sexual dysfunction caused by newer non-enzyme-inducing anti-seizure drugs are poorly understood and are likely to be multifactorial [92; 93]. Possibly, most of them reduce central excitatory transmission by acting on sodium and calcium channels or glutamate and GABAergic receptors, resulting in hyposexuality. Both topiramate and zonisamide inhibit carbonic anhydrase enzyme, and may thereby interfere with the production of intracavernosal vasoactive compounds, namely vasoactive intestinal peptide and nitric oxide, which play an important role in peripheral erectile mechanisms [92].

1.5.2.2.3. Comorbid psychiatric illness

People with epilepsy have a higher rate of psychiatric comorbidity, like major depression, anxiety, and psychosis than the general population[7; 94; 95] . Sexual dysfunction, in the form of reduced libido, is one of the typical symptoms of depression, but is also associated with anxiety and psychosis [96; 97]. Psychiatric treatment, like antidepressants (typically selective serotonin reuptake inhibitors; SSRI) or antipsychotic drugs, can contribute and intensify sexual dysfunction [98; 99]. A study of 60 patients with epilepsy compared with 60 healthy controls found more frequent sexual dysfunction among patients with epilepsy [71]. In both groups, sexual dysfunction was associated with depression and anxiety.

Among patients with epilepsy, variables like age of seizure onset, seizure frequency, and/or use of anti-seizure medication were not associated with sexual problems. Also, another study that compared 60 men with epilepsy with 60 controls found a significant correlation between sexual functioning and scores for depression and anxiety, but no association with total testosterone, free testosterone, or bioactive testosterone [100].

1.5.2.2.4 Psychosocial issues

Studies have shown that psychological factors are most important in determining sexual functioning in people with epilepsy [100]. Many patients with epilepsy have low self-esteem, many feel discriminated against and stigmatized, they may have low social competence, and many are socially isolated [101]. In sum, these factors may contribute to a heightened sense of rejection, as well as perceptions of sexual inadequacy and sexual unattractiveness. Additionally, anxiety and fear of having a seizure during sexual interaction may lead to reluctance or avoidance of sexual activity, which can result in feelings of rejection and dissatisfaction in partners.

1.5.2.3. Treatment of sexual dysfunction in epilepsy

The first and foremost approach towards managing sexual dysfunction in people with epilepsy is to uncover the problems via a thorough clinical interview. However, both healthcare providers and patients might find it difficult to talk about sexuality or sexual problems due to cultural or religious barriers [102]. Alternatively, they may feel that the situation is uncomfortable. In these situations in particular, the use of screening instruments may be helpful. If sexual problems are present, the discussion should also, if possible, include the partner, to provide further information and angles on the nature of dysfunction and the likely contributing factors [103].

Patients should be screened and evaluated for psychiatric comorbidity, especially depression and/or anxiety. A detailed drug history is important, as erectile dysfunction may be caused by drugs, such as beta-blockers, diuretics, and antidepressants [99; 104; 105]. Some patients should also be examined by an urologist or gynaecologist for local urogenital problems. Metabolic and/or endocrinological screening may be indicated in selected patients [106]. If possible, strong enzyme-inducing anti-seizure drugs, especially phenytoin, carbamazepine, and phenobarbital, may be switched to non-enzyme-inducing drugs.

In a study of 40 men with epilepsy and hypogonadism, sexual functions improved following treatment with a combination of testosterone and the aromatase inhibitor anastrozole, which blocks the conversion of testosterone to estradiol [107]. Male patients with erectile dysfunction may benefit from symptomatic therapy with phophodiesterase type-5 inhibitor drugs. There are, however, isolated case reports of seizure precipitation by these drugs in non-epilepsy patients [108], and this should be kept in mind. Males with premature ejaculation could respond to short-acting SSRI, such as paroxetine [109].

Besides the clinical perspective, the physician can also think “prophylactic”, like choosing anti-seizure medication that is less likely to decrease sexual function. Lamotrigine or anti-seizure medication without enzyme-inducing properties could lower the risk of sexual problems in patients with epilepsy. Otherwise, there are general recommendations, such as treating depression, but physicians should be aware that SSRI or other psychotropic medications can contribute to sexual problems[110]. Refraining from smoking or using recreational drugs[111-114], reducing overweight[115], decreasing stress, and treating comorbid conditions [116; 117] are other general recommended prophylactic measures. And finally, informing patients about the possible negative effects of their disease on sexual functioning might help them to cope and to find new ways of expressing their sexuality[118].

1.6. Information about epilepsy: the patients' perspective

For the majority of patients with epilepsy, the condition is chronic. Today, concordance, self-management, shared decision making, and patient choice are key terms used in the management of a chronic illness [119-121]. For this to happen, information about the disorder is of vital importance, especially in a complex condition like epilepsy. Although some patients might want to delegate responsibility for treatment decisions to their physician, many patients today want a more collaborative approach [122]. Thorough information enables patients to feel ownership of the decisions that are reached and a feeling of participating in controlling the disease. Even in those not wanting to reach shared decisions, information could alleviate fears and dispel misconceptions. Another factor influencing the quality of life in patients with epilepsy is the level of health literacy, defined as the degree to which individuals can obtain, process, and understand basic health information [123]. As Scrivner et al. point out "Health literacy is, at its core, an issue of communication" [123]. Healthcare providers should adapt their communication and information that is to be delivered to the patients' level of health literacy, in order to ensure that the information provided can be accessed and processed.

If people with epilepsy do not have access to sufficient information and knowledge about the disease, this might have a negative influence on treatment adherence and disease outcome, and result in a poorer quality of life [124]. In contrast, good access to relevant and clear information may increase patient empowerment and reduce stigma [125]. A study from UK showed that although no cause for epilepsy could be found, the patients nevertheless wanted to know as much as possible about epilepsy causes and what might trigger seizures [126]. The authors pointed out that it is important to give patients time to discuss the advantages and disadvantages of different treatment options with doctors who specialize in the subject [126]. Even among those whose seizures are controlled, knowledge about the disease is important and may improve their quality of life. People who have had a seizure may be fearful of having another, even after having been seizure free for many years. Many patients request more and better information about epilepsy [12] to improve coping with challenges associated with the disease. “This is about engaging with patients, listening to their agenda and helping to plan things, (a) to keep them involved in the clinic service, and (b) to keep them involved in their treatment decisions” [127]. Whether patients are informed, which information they get, and how they use it, can all affect health outcome, patient satisfaction, and safety [14; 128].

Most studies that have evaluated the level of epilepsy knowledge among patients have concluded that there are unmet needs for provision of better information and counselling in this patient population [126; 129-136]. Nevertheless, a large study with over 6000 participants, concluded that European people with epilepsy are reasonably well informed about the disease, based on information retrieved by questionnaire via epilepsy support groups in 10 European countries [137]. Most studies assessing the objective knowledge about epilepsy among patients are based on questionnaires [130; 132; 133; 136; 137]. Relatively few studies have investigated the patients’ own perspectives and evaluated whether the patients actually receive the information that they find relevant from healthcare providers, and whether they are satisfied with the information that they receive [125; 126; 129; 134]. We, therefore, performed our online study addressing these issues.

1.6.1. Information on seizure-related injuries and epilepsy-related death

Due to the nature of epilepsy, with unpredictable seizures, often with impaired awareness, patients with epilepsy are obviously prone to accidents and injuries [138; 139]. Most seizure-related injuries are of mild to moderate severity, and lacerations, fractures, dental trauma, concussion, and burns are most commonly reported [140]. Tonic-clonic and atonic seizures are the seizure types most often associated with injuries [141-144]. Epilepsy-related injuries are associated with a lower quality of life [145]. Naturally, those with frequent seizures are the most injury prone, and an individual risk assessment and discussion about precautions are recommended. Various protective measures have been employed, as pointed out in a recent review, but no general consensus has been reached [146].

An increased mortality in epilepsy can be related to the epilepsy aetiology, seizure-related accidents, suicide, status epilepticus, and SUDEP. SUDEP is defined as a sudden, unexpected, non-traumatic, non-drowning death in a person with epilepsy, where autopsy does not reveal another anatomical or toxicological cause of death [147]. It is the most common epilepsy-related death [148]. Although the incidence of SUDEP among people with epilepsy is rather low, with 1.2 per 1000 person-years [3], it is nevertheless of considerable worry for patients and caregivers. There has been a long-lasting debate among health personnel on whether and when to inform patients and their families or caregivers about the risk of SUDEP [149; 150]. A retrospective study revealed that in only 4% of cases was provision of information about risks of SUDEP documented in the clinical record. Having tonic-clonic seizures was significantly associated with receiving information, and there was a trend towards more information among patients with low adherence to treatment [151]. Another study showed that 68.5% of neurologists reported that they discussed SUDEP with only a few or none of their patients [152]. Among Italian paediatricians, 16.2% stated that all patients should be informed about the risk of SUDEP, but only 1.8% reported doing so [153]. Practice guidelines recommend providing information about SUDEP, and also which type of information that should be given [31; 154], and most epilepsy experts seem to agree [155].

Information about SUDEP is a sensitive issue, and many doctors are reluctant to discuss the matter as they consider it to be an extra worry for patients who already are heavily burdened. However, one study showed that such information did not have a negative effect on the participants’ mood or quality of life [156].

1.7. Adherence to drug treatment

Adherence is defined as “the extent to which a person's behaviour taking medication corresponds with agreed recommendations from a health care provider” [157]. Non-adherence is defined as any deviation from the recommendations regarding, both timing and dosage of a prescribed regimen [158]. Non-adherence to anti-seizure drug treatment can result in seizure relapse [159], status epilepticus [160; 161], hospital admission [162], and increased healthcare costs [163; 164]. Non-adherence has also been suspected to be involved in SUDEP [165]. Results from previous studies on non-adherence to drug treatment differ considerably, possibly due to different study populations and different measures used to rate adherence.

Adherence can be measured by asking the patients directly in an interview situation or by using questionnaires, both of which can be subject to recall bias [166-168]. Objective measures include electronic medication-monitoring systems, which are expensive and impractical on a larger scale [169]. Medication possession ratio has also been utilized, i.e., being the day’s supply of medication delivered, divided by the days from when medication was dispensed to end of follow-up period [44].

Non-adherence may be unintentional — for example, the patient forgets to take a dose or accidently takes an incorrect dosage. Moreover, there may be misunderstandings between the physician and patient regarding the agreed dosage or medication, as demonstrated in one of our previous studies [170]. Non-adherence may also be intentional; i.e., for various reasons the patient makes a conscious decision not to follow the agreed treatment plan. This changed dosing regimen may result in lower or even higher serum concentrations of the drug. Chapman and colleagues applied a model based on the patient’s own perception of high or low drug-related concerns (potential adverse events) or necessity (personal need for daily medication) [171].

Factors that have been found to be associated with non-adherence to drug treatment (not differentiated between intentional or unintentional) are: depression [44; 172], anxiety and hippocampal sclerosis [168], young age, use of older anti-seizure drugs [172], having experienced side effects, and polytherapy [173]. Factors associated with good adherence to drug treatment are: refractory epilepsy [174], high socio-economic status, perceived adverse events [169], employment, “medication reminders” [167], learning disability, location of residence, use of newer drugs, use of brand vs. generic drugs [175], a comorbid chronic disease, having a driving license, and having had a seizure after a missed dose [176]. Identification of such factors for both good adherence and non-adherence is important and should be part of comprehensive epilepsy care in order to avoid increased morbidity and mortality among the patients. Nevertheless, it is the individual patient’s perspective on the use of anti-seizure medication that is going to determine adherence and that was therefore the focus of our studies.

Chapter 2: Aims of the thesis

2.1. Primary aims

The overall aim of the research described in this thesis was to determine and evaluate the patients' perspectives on various different epilepsy-related issues.

2.2. Secondary aims

- To evaluate the patients' experiences of different epilepsy-related challenges and to identify possible risk factors (Paper I).
- To explore the prevalence and types of sexual problems, sexual behaviour, and satisfaction with sex life in different groups of patients with epilepsy in comparison with representative samples from the general population, and to identify possible risk factors (Papers II and III).
- To investigate how patients with epilepsy perceive the provision of information about different epilepsy-related issues, to identify possible factors influencing the provision of such information, and to estimate whether the extent of and scope of the information provided about epilepsy-related death corresponds to patients' and caregivers' wishes. (Papers IV and V).
- To assess self-rated intentional and unintentional non-adherence to anti-seizure medication in two different cohorts with epilepsy in relation to possible risk factors for non-adherence (Papers VI and VII).

Chapter 3: Material and methods

3.1. Online survey (Papers I, IV, V, VI)

3.1.1. Study population

This study was based on collaboration between the National Centre for Epilepsy and the Norwegian Epilepsy Association. An online questionnaire was developed and made available on the Association's homepage, as a pop-up for all those who visited the page between April 1st 2017 and September 5th 2017. The homepage is visited by approximately 100,000 users annually. Participants could register as: 1) people with epilepsy, or 2) caregivers, family members, or guardians of people with epilepsy who would answer on behalf of the patients, or 3) caregivers, family members, or guardians of people with epilepsy who would answer on their own behalf (Figure 3). Each participant could complete the questionnaire only once. Questions were selected following a thorough discussion among colleagues at the National Centre for Epilepsy and advisors at the Norwegian Epilepsy Association.

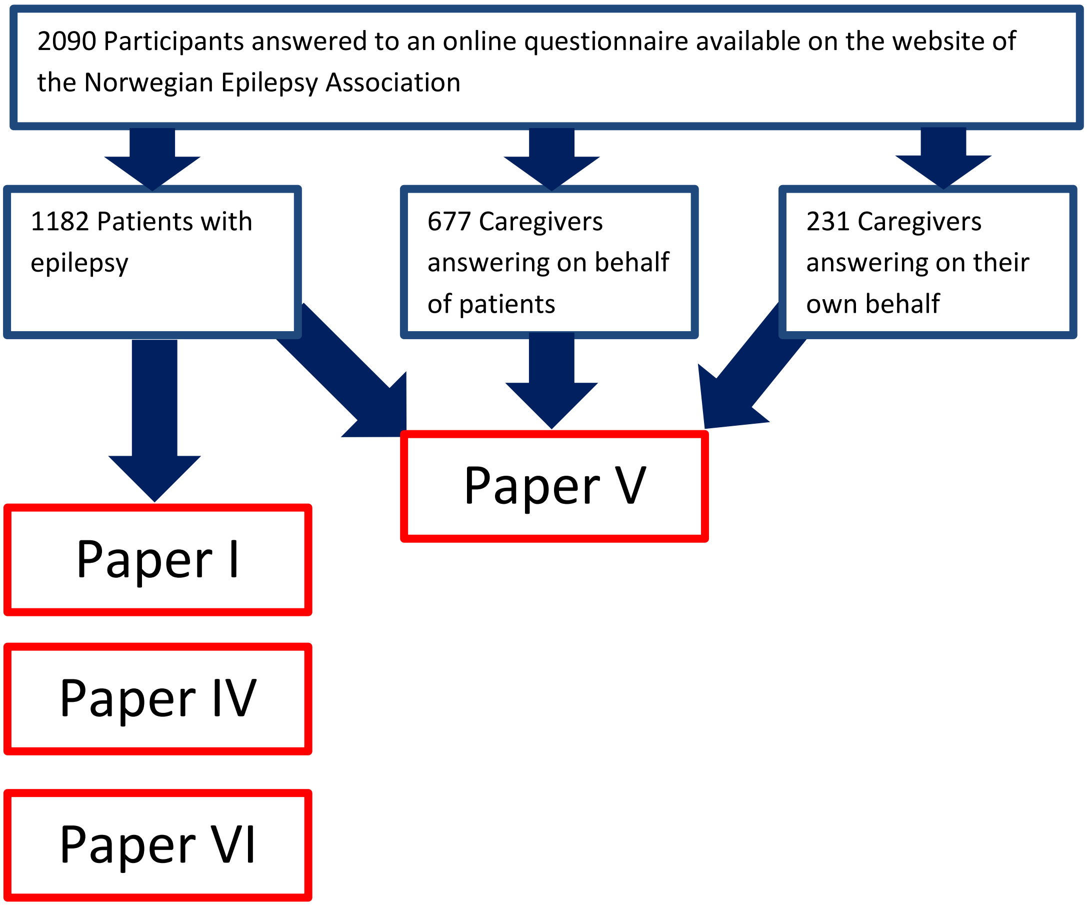

Figure 3. Flowchart of study participants

3.1.2. The questionnaire

The study was done using Questback (http://www.questback.com) with an account used by the Norwegian Epilepsy Association. Table 1 shows the questions on background information and epilepsy-related data taken from the questionnaire to be included in the different articles.

Background information and epilepsy-related data	**Paper I**	**Paper IV**	**Paper V**	**Paper VI**
Gender	X	X	X	X
Age	X	X	X	X
Habitational status	X		X	
Relational status	X	X	X	X
Age at first seizure	X	X	X	X
Duration of epilepsy	X	X	X	X
Epilepsy aetiology	X	X	X	X
Seizure types	X	X	X	X
Seizure frequency	X			X
Seizure freedom during the last 12 months	X	X	X	X
Number of anti-seizure drugs in use	X			X
Type and frequency of follow-up	X		X	
Being involved in treatment decisions				X
Perception of own health				X
Feeling stigmatized				X

Table 1: Information from the questionnaire used in articles I, IV-VI

To obtain information on whether the respondents wished to have access to information about epilepsy-related issues, whether they had been provided with such information, and how they perceived the quality of this information, the participants were requested to answer the following questions: “Have you been informed by your healthcare provider on: “The diagnosis”, “Drug treatment”, “Epilepsy surgery”, “Dietary treatment”, Vagus nerve stimulation”, “Other neurostimulators”, “Treatment with cannabis”, and “Adverse effects””.

Moreover, the participants were asked: “Has your physician or epilepsy nurse provided you with information on the following issues: “Routine use of anti-epileptic drug intake”, “Organized lifestyle”, “Regular sleep”, “Risk of injuries during seizures”, “Risk of death related to epilepsy”, “Contraception and pregnancy”, Concentration and memory problems”, “Depression”, “Anxiety”, “Sexual problems”, “Diet and weight”, “Regulations regarding driving”, and “Alcohol consumption””. The response possibilities were: 1=“No information”, 2=“Some information, but want more”, 3=“Yes, good information”, 4=“I do not remember”, or 5=“Do not want information/not relevant”. For investigating whether the respondents wanted information, the response variables were stratified into 1=“do not want information” (category 5) and 2=“do want information” (categories 1, 2, 3 and 4). For investigating whether the respondents had been given information, the response variables were stratified into 1=“not given information” (category 1) and 2=“been given information” (categories 2 and 3). For evaluating the quality of information, the response variables 2=“Some information, but want more” and 3=“Yes, good information” were compared.

In order to assess whether respondents perceived that their quality of life was affected by a variety of different challenges, the following questions were asked: “To what extent did you experience the following challenges as being problematic for you? “Fear of being alone”, “Problems with concentration”, “Feeling down/blue and/or depressed”, “Problems with memory”, “Sexual problems”, “Difficulties with physical activities”, “Difficulties getting to places”, “Headache and/or vertigo”, “Having difficulties with social interactions”, “Fear of having a seizure”, and “Tiredness””. The response possibilities were: 1=“not at all”, 2=“to a lesser degree”, 3=“somewhat”, or 4=“to a considerable extent”. For further analysis, the response variables were stratified into 1=“not at all and to a lesser degree” (categories 1 and 2) and 2=“somewhat and to a considerable extent” (categories 3 and 4).

In order to investigate whether the respondents unintentionally or intentionally used anti-seizure drugs differently than recommended by, and agreed upon with, their physician, two questions were asked: “Does it happen that you accidentally take your anti-seizure medication differently than agreed with you physician?” and “Does it happen that you intentionally (on purpose) take your anti-seizure medication differently than agreed with your physician?” The response possibilities were: 1=“never”, 2=“rarely”, 3=“sometimes” or 4=“often”. For further analysis, the response variables were stratified into: 1=“never or rarely” (categories 1 and 2) and 2=“sometimes or often” (categories 3 and 4) for unintentional non-adherence and 1=“never” (category 1) vs 2=“rarely, sometimes, or often” (categories 2, 3 and 4) for intentional non-adherence.

In order to obtain information on why the respondents intentionally used the drugs differently than recommended by, and agreed upon with, their physician, the following question was asked: “What is the reason that you take medication differently than agreed upon with your physician? (Multiple answers possible)”. Answer alternatives were: “I have adverse events”, “I am afraid of having side effects”, “I think the medication has no effect”, “I am afraid of experiencing adverse events”, and “I am afraid that the medication might harm me.” In addition, the respondents could provide comments and explanations for non-adherence in a free text part of the questionnaire.

3.1.3. Statistics

IBM SPSS Statistics, version 25, release 25.0.0.1. (SPSS Inc, Chicago, IL, USA) was used for statistical analyses. All p-values reported are based on two-sided tests, with a significance level of 0.05. To test possible group differences, Pearson’s chi-square tests were performed. We further applied Hosmer’s step-down procedure that permits variables significant at the 0.25 level to be included in the multivariate logistic regression model [177]. OR and confidence intervals (CI) at a level of 95% were calculated.

3.1.4. Ethics

This study was assessed by the Regional Committee for Medical and Health Research Ethics (REK). Because the study was anonymous, further approval from REK was not required (Ref.no 2017/563A). After collection the data were transferred to the secure research server at Oslo University hospital for further analysis. We had no access to the IP addresses of the individual respondents, so anonymity was preserved. The information that popped up for visitors to the homepage of the Norwegian Epilepsy Association included background information about the study and the possibility to choose to participate. There was no pressure to participate and no direct benefit was to be derived from participating.

3.2. Questionnaire study on sexual problems among patients with epilepsy (Paper II)

3.2.1. Study population

Between March 2006 and January 2007, consecutive adult inpatients and outpatients at the National Epilepsy Centre in Norway were asked to complete a questionnaire concerning their epilepsy, comorbidities, and possible sexual problems. In addition, the patients’ neurologist was asked to complete a short questionnaire. Inclusion criteria were age 18 years or above, a confirmed epilepsy diagnosis, and being capable of reading and completing the questionnaire.

Corresponding data regarding sexual problems from a representative sample of 1093 Norwegians aged 15–70 years, which had been previously obtained by the poll organization “Market and Media Institute” (MMI; now called Ipsos), was made available to the research group [178] (Figure 4).

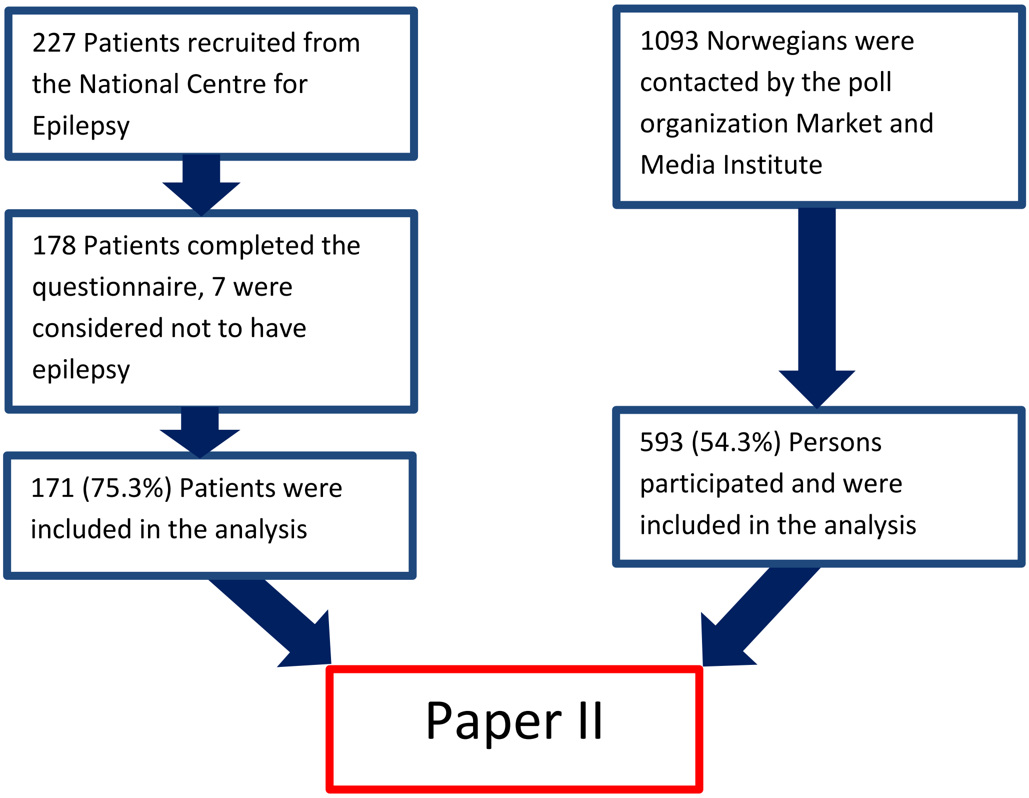

Figure 4. Flowchart of study participants

3.2.2. The questionnaire

The patients answered the same socio-demographic questions as the general population (gender, age, cohabitation, and sexual functioning). In addition, the patients were asked about their epilepsy type, use of anti-seizure and psychotropic drugs, symptoms of depression, and quality of life. The Beck Depression Inventory (BDI) [179], a validated tool with good psychometric properties, was used to measure depression. To assess quality of life we used a visual analogue scale, with a rating from 0 to 10, taken from the Quality of Life in Epilepsy Inventory (QOLIE) 89 [180]. Both inventories, the Beck Depression Inventory and the complete QOLIE 89, have previously been translated to Norwegian and validated [181; 182].

The questionnaires completed by the neurologists contained questions about the individual patient's type of epilepsy and whether the patient had been investigated regarding sexual problems.

3.2.2.1 Operationalization of the questions about sexual problems

Information on sexual problems was obtained from responses to the question: “Have you ever had sexual problems?” The response possibilities were 1=“yes” or 2=“No”.

Information on type of sexual problems (from those who answered “yes” to the first question) was obtained from responses to the question: “What kind of sexual problems? The response possibilities are shown in table 2. Respondents could select more than one answer.

Reduced desire
Problems with orgasm
Premature ejaculation/climax
Late ejaculation/climax
Pain during intercourse
Erectile dysfunction
Vaginal dryness
Feelings of sexual deviance
Other

Table 2: Response possibilities

Patients with epilepsy were also asked whether they had experienced sexual problems within the last month, with the same response possibilities.

Information on satisfaction with sex life was obtained from responses to the question: “All things considered, how satisfied are you with your sex life?” The response categories were the following: 1= “very satisfied”, 2=“quite satisfied”, 3=“neither satisfied nor dissatisfied”, 4=“somewhat dissatisfied” , and 5=“dissatisfied”. The response variables were stratified into 1= “dissatisfied” (categories 4 and 5) and 2= “undecided or satisfied” (categories 1, 2, and 3).

Information on age at first sexual intercourse and on the number of sexual partners during the last 12 months were obtained as continuous variables.

Information on the frequency of sexual intercourse was obtained by the question: “How often did you have intercourse during the last 4 weeks?” The response categories were: 1=“not at all”, 2=“once”, 3=“2 to 4 times”, 4=“5 to 10 times”, and 6=“11 times or more”. The response variables were stratified into 1= “none or once” (categories 1 and 2) and 2= “twice or more” (categories 3, 4, 5, and 6).

Information on the participants’ satisfaction with the frequency of sexual intercourse was obtained by the following question: “How satisfied are you with your frequency of sexual encounters?” The response alternatives were: 1=“too often”, 2=“satisfactory”, and 3=“too infrequent”.

Information on whether the physician had asked the patient about sexual problems was obtained by the following question: “Has the patient been asked about sexual problems?” The response alternatives were: 1=“yes” or 2=“no”. The question continued: “if yes, were sexual problems reported?” The response alternatives were: 1=“yes” or 2=“no”.

3.2.3. Statistics

Group differences were tested by chi-square tests and t-tests for categorical and continuous variables, respectively. OR for sexual problems were estimated by logistic regression analysis, with sexual problems as the dependent variable and quality of life and gender as the independent variables. The results of multivariate analysis are presented as OR with 95% CI and p-values. All tests were two-sided and were performed at a 5% significance level. The Statistical Package for Social Sciences (SPSS version 21) was used for these analyses.

3.2.4. Ethics

This study was approved by the Regional Committee for Medical and Health Research Ethics (REK-Sør) (S-05394). When eligible patients were approached, it was emphasized that participation was voluntary and choosing not to participate would not compromise further follow-up and /or treatment in any way. Sexual behaviour and/or sexual problems are sensitive subjects and patients might object to answering questions about them, especially when not informed about the questions in the survey beforehand. Therefore, we informed patients both on the subject of the survey and that, should they so wish, they could fill in some parts of the questionnaire but ignore questions with which they felt uncomfortable. Possible participants in such a study might feel more inclined to participate when approached by their treating physician, and an alternative could have been to use a third independent person to inform them about the study. As the study did not include any resultant intervention or possibly negative outcome for participants, we regarded our setup as acceptable. Participants were informed that personal information would be handled according to the hospital's data security standards, with deidentified data and that only a separately stored coding list could link patient identification to the reported data. The completed questionnaires and coding list were stored in locked facilities at the hospital. Electronic data were stored on the secure research server at Oslo University Hospital. Participants delivered the completed questionnaire in a sealed envelope. Despite these precautions, it should still be understood that some patients might have felt compromised by being asked for personal information and fear that information might be connected to them could have influenced their responses to some of the questions.

3.3. Anonymous questionnaire studies (Papers III, VII)

3.3.1. Study population

Consecutive adult patients admitted to the National Centre for Epilepsy in Norway were invited to complete an anonymous questionnaire concerning adherence to drug treatment. A second part of this study included additional questions about sexual functioning and sexual problems, and also outpatients from Lillehammer hospital (a second-line neurology specialist service) participated. This study was performed in the period 2015-2017.

Regarding the questions about sexual functioning and sexual problems, data from a representative sample of 4.285 Norwegians aged 18-67 years were obtained from a market-research company, Synovate [183] (Figure 5).

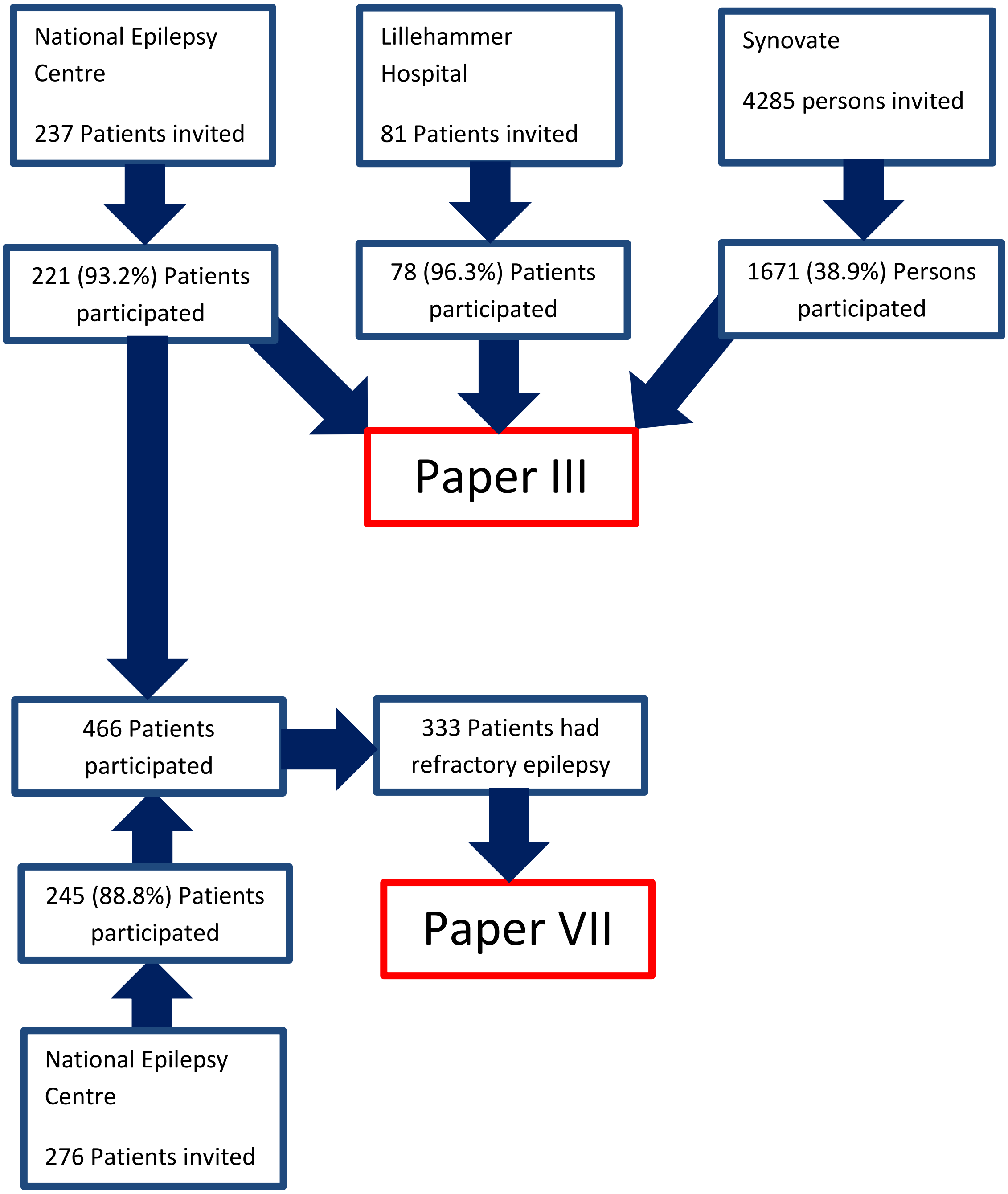

Figure 5. Flowchart of study participants

3.3.2. The questionnaire

Questions in the questionnaire included background information (gender, age), seizure type, seizure frequency, and type and number of anti-seizure drugs in use. Moreover, the respondents were asked to score a visual analogue scale regarding quality of life, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [184], and the Adverse Events Profile (AEP) [185]. In the second part of the study, the following questions were added: level of education, partnership, sexual problems, sexual behaviour, and sexual functioning.

3.3.2.1. Operationalization of the questions on adherence to drug therapy

In order to obtain information on unintentional or intentional non-adherence to anti-seizure drug regimens, two questions were asked: “Do you sometimes inadvertently take your drugs differently than agreed upon with your physician?” and “Do you sometimes intentionally (on purpose) take your medication differently than agreed upon with your physician?” The response possibilities were: 1=“never”, 2=“rarely”, 3=“sometimes”, or 4=“often”. For further analysis, the response variables were stratified into: 1=“never or rarely” (categories 1 and 2) and 2=“sometimes or often” (categories 3 and 4) for unintentional non-adherence and 1=“never” (category 1) vs 2=“rarely, sometimes, or often” (categories 2, 3 and 4) for intentional non-adherence.

3.3.2.2. Operationalization of the questions about sexuality

Information on type of sexual problems was obtained from responses to the question: “Have you experienced one of the following problems?” The response possibilities are shown in table 3.

Reduced sexual desire
Problems with orgasm
Premature ejaculation/climax
Late ejaculation/climax
Pain during intercourse
Erectile dysfunction
Vaginal dryness
Feelings of sexual deviance

Table 3: Response possibilities

The response categories were as follows: 1=“Never”, 2=“rarely”, 3=“often”, 4=“nearly all the time”, and 5=“always”. The response variables were stratified into 1=“never or rarely” (categories 1 and 2) and 2=“often” (categories 3-5).

Information on satisfaction with sex life was obtained from responses to the question: “All things considered, how satisfied are you with your sex life?” The response categories were: 1=“very satisfied”, 2=“quite satisfied”, 3=“neither satisfied nor dissatisfied”, 4=“slightly dissatisfied”, and 5=“very dissatisfied.” The response variables were stratified into: 1=“satisfied” (categories 1 and 2) and 2=“dissatisfied” (categories 4 and 5); response category 3 was not included in further analysis.

Information on the importance of sex in daily life was obtained from the question: “How important do you consider sex to be as a part of your overall life?” The response categories were: 1=“very important”, 2=“quite important”, 3=“neither important nor unimportant”, 4=“slightly unimportant”, and 5=“not important at all”. The response variables were stratified into 1=“important” (categories 1 and 2) and 2=“unimportant” (categories 4 and 5); response category 3 was not included in further analysis. Information on help-seeking behaviour regarding sexual problems was obtained from responses to the question “Have you contacted healthcare providers for help regarding sexual problems?” The response categories were “yes” or “no.

3.3.3. Statistics

IBM SPSS Statistics, version 25, release 25.0.0.1. (SPSS Inc, Chicago, IL, USA) was used for statistical analyses. All p-values reported here are based on two-sided tests, with a significance level of 0.05. To test possible group differences, Pearson's chi-square tests were performed. We further applied Hosmer's step-down procedure that permits variables that are significant at the 0.25 level to be included in the multivariate logistic regression model [177]. ORs and 95% CI were calculated.

3.3.4. Ethics

This study was evaluated by the Regional Committee for Medical and Health Research Ethics (REK). Because the study was anonymous, approval from REK was not required (ref. no.: 2014/1011A). On the first page of the questionnaire, possible participants were informed about the project, and were asked to indicate whether they wanted to participate or not. In order to keep the study anonymous, signatures for the information were not requested. As mentioned in Section 3.2.5., patients asked by the treating physician might have felt more inclined to participate, but delivering the completed questionnaire could have compromised anonymity. The questionnaires were stored at a locked office at the hospital and electronic data were stored on the secure research server at Oslo University Hospital.

Chapter 4: Results

4.1. Challenges in epilepsy - the perspective of Norwegian epilepsy patients.

Henning O, Landmark CJ, Henning D, Nakken KO, Lossius MI.

Acta Neurologica Scandinavica 2019;140:40-47.

We explored the extent to which patients with epilepsy experienced being troubled by different epilepsy-related challenges.

From a web-based survey among patients with epilepsy (n=1182), about 40% reported that they had been seizure free for at least 1 year. Nevertheless, the majority reported that tiredness (71%), memory problems (70%), concentration problems (68%), headache or vertigo (51%), and feeling depressed (59%) were issues that had a negative effect on them, either somewhat or to a considerable degree, in daily life. About one third of the participants described fear of being alone, having sexual problems, or experiencing difficulties in social settings.

A multivariate analysis revealed that female gender, using polytherapy, having had seizures in the previous 12 months, and feeling blue or depressed were significantly associated with these challenges.

4.2. Sexual problems in people with refractory epilepsy.

Henning OJ, Nakken KO, Træen B, Mowinckel P, Lossius M.

Epilepsy & Behavior 2016;61:174-179.

The aim of this paper was to explore the prevalence and types of sexual problems, sexual behaviour, and satisfaction with sex life in a sample of 171 patients with epilepsy in comparison with a representative sample (n=594) from the general Norwegian population. We also looked for possible risk factors associated with sexual problems in the sample with epilepsy. We found a significantly higher prevalence of sexual problems in patients with epilepsy than in the general population in both genders (women, 75.3% vs. 12.0%; men, 63.3% vs. 9.6%). The most commonly reported problems (reported by more than 30%) were reduced sexual desire, problems with orgasm, erection problems, and vaginal dryness. Patients with epilepsy also reported a higher degree of dissatisfaction with their sex life, but, interestingly, the dissatisfaction was less pronounced than would be expected from the reports of sexual problems. In contrast, the proportion reporting dissatisfaction with their sex life in the general population was higher than the proportion reporting sexual problems. We found a correlation between sexual problems and a low quality of life.

In women with epilepsy, sexual problems were also correlated with symptoms of depression. We found no significant correlation between sexual problems and age of epilepsy onset, type of epilepsy, and use of enzyme-inducing anti-seizure medication. Compared with the general population, men with epilepsy reported fewer sexual partners during the last 12 months, and women with epilepsy reported a lower frequency of sexual intercourse. We were unable to identify any single predisposing factor for sexual problems, and we hypothesize that several factors play a role, including factors of both organic and psychosocial nature.

4.3. Sexual function in people with epilepsy: similarities and differences with the general population.

Henning O, Johannessen Landmark C, Træen B, Svendsen T, Farmen A, Nakken KO, Lossius M.

Epilepsia 2019; 60(9):1984-1992.

In this study, we explored the occurrences of different types of sexual problems in patients with both well-controlled epilepsy (n=78) and mostly refractory epilepsy (n=221) and compared the results with a sample from the general population (n=1671).

We found no significant differences between the two epilepsy cohorts regarding prevalence and types of sexual problems. When comparing patients with epilepsy with the general population, the following sexual problems were reported significantly more often in those with epilepsy: problems with orgasm and erectile dysfunction in men, pain during intercourse in women, late ejaculation/climax and feeling sexually deviant in both women and men. For both genders, significantly fewer patients with epilepsy were satisfied with their sex lives compared with the general population, and significantly fewer men with epilepsy reported sex as being an important part of their daily lives. Patients with refractory epilepsy seemed to request help for their sexual problems more frequently compared with the general population, but the difference was statistically significant only for women.

Multivariate logistical regression analysis showed that for women with epilepsy being older than the mean age of the cohort and having symptoms of depression (NDDI-E score over 14) were significant independent variables that were associated with reduced sexual desire. In contrast, for men, reduced sexual desire was associated with quality of life being below the average and being in a relationship. In women, being older than the mean age of the cohort and reporting a low quality of life were significant independent variables that were associated with feelings of sexual deviance. Other factors that were explored, such as being seizure-free during the previous 12 months, using enzyme-inducing anti-seizure medications, using lamotrigine, levetiracetam, or valproate, having a high burden of adverse events (Adverse Events Profile score > 44), or having a lower level of education, were not significantly correlated with any of the types of sexual dysfunction investigated here.

4.4. A call for better information about epilepsy: The patients' perspective - An online survey. Henning O, Alfstad KA, Nakken KO, Lossius MI.

Seizure 2019;69:173-179.

We investigated whether patients with epilepsy who completed a web-based questionnaire (n=1182) wished to be informed about different issues related to the disease, e.g., the diagnosis, treatment options like drugs, cannabis, surgery, diet, vagus nerve stimulation and other neurostimulations, adverse effects of the treatment, lifestyle, contraception, pregnancy, sexual function, cognitive or affective problems, driving regulations, etc. Additionally, we evaluated how they rated the quality of information that they had been given and tried to identify possible factors influencing the provision of information. More than 90% of respondents reported a wish for general information about epilepsy, and more than 75% wanted information about specific issues, like epilepsy surgery. The proportion of respondents reporting that they had received information about specific issues varied according to the issue, from 7% (cannabis use) to 92% (the diagnosis). The difference between the proportion of respondents wishing to have information and the proportion receiving information was rather small (< 20%), and more than 70% of the respondents stated that they were satisfied with the information that they had been given about drug treatment, lifestyle, driving regulations, and sleep habits. Regarding information about diagnosis, contraception and pregnancy, and consumption of alcohol, 50-70% of the respondents were satisfied with the information with which they had been provided. The difference between those wishing to be informed about adverse drug events and those having received information on this topic was moderate (20%–40%), and the quality of information was rated as satisfactory by less than 50%. We found a considerable difference (> 40%) between those wishing information and those being given information regarding various alternative treatments (cannabis, surgery, diet, vagus nerve stimulation, and other neurostimulations), and sexual, cognitive, and affective problems.

Male gender was found to be an independent variable associated with having been provided with information about surgery, vagus nerve stimulation and other neurostimulations, nutrition and body weight, whereas female gender was associated with having been provided with information about contraception and pregnancy. Being older than the mean age of the cohort was associated with having obtained information about surgery, and being younger than the mean age of the cohort was associated with having been informed about adverse drug events, contraception, and pregnancy. Being seizure free was associated with having obtained information about issues concerned with driving regulations and consumption of alcohol, whereas not being seizure free was associated with having been provided with information about non-pharmacological treatments like surgery, diet, and vagus nerve stimulation and other neurostimulations. Having tonic-clonic seizures was associated with having been informed about the diagnosis, lifestyle, sleep, and drinking habits.

4.5. People with epilepsy and their relatives want more information about risks of injuries and premature death.

Henning O, Nakken KO, Lossius MI.

Epilepsy & Behavior 2018;82:6-10.

We investigated whether patients with epilepsy and their relatives want information about the risk of epilepsy-related injuries and premature death, and whether they receive such information. Moreover, we looked for putative factors that may influence the provision of such information.

An online survey was answered by patients with epilepsy (n=1183), caregivers, family members, or guardians of patients with epilepsy, who could either answer on behalf of the patients (n=676) or on their own behalf (n=231). Among all participants, more than 90% wanted such information. Among patients with epilepsy, about 70% reported having received information on seizure-related injuries. About 31% had received information on unexpected death. The corresponding answers among caregivers who answered on behalf of the patients were 81% and 35%, respectively, while the percentages of those who answered on their own behalf were 50% and 28%, respectively.

Factors associated with being most eager to obtain information were: having had tonic–clonic seizures, being young, and being male; in addition, males and younger patients were the best informed. The wish for more information and the likelihood of having received information were not influenced by the severity of the epilepsy.

We found a considerable gap between what patients wanted regarding information and what they had actually received from healthcare providers.

4.6. Non-adherence to treatment regimens in epilepsy from the patient's perspective and predisposing factors: differences between intentional and unintentional lack of adherence.

Henning O, Johannessen Landmark C, Nakken KO, Lossius MI.

Epilepsia 2019; 60(5):e58-e62.

We assessed self-rated intentional and unintentional non-adherence to anti-seizure medication in a population with mostly well-controlled epilepsy (n=1182). The participants completed an online survey available on the website of the Norwegian Epilepsy Association.

About 40% reported that they sometimes or often forgot to take their drugs as scheduled, and about 30% reported that they consciously chose not to follow the treatment plan agreed upon with their physician. In a multivariate analysis, we found that feeling depressed, being younger than the mean age of the cohort, and having memory problems were significantly associated with unintentional non-adherence. Feeling depressed, being male, and having experienced stigmatization were parameters that were significantly associated with intentional non-adherence.

4.7. Refractory epilepsy and non-adherence to drug treatment.

Henning O, Lossius MI, Lima M, Mevåg M, Villagran A, Nakken KO, Johannessen Landmark C.

Epilepsia open 2019; https://doi.org/10.1002/epi4.12367

We assessed the extent of both unintentional and intentional non-adherence among Norwegian patients with refractory epilepsy (n=333) and tried to identify possible risk factors.

About 22% admitted that they sometimes or often forgot to take their drugs as scheduled, while 19% reported that they intentionally did not follow the treatment plan agreed upon with their physician.

A multivariate logistic regression analysis revealed that young age and symptoms of depression (Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) score >14) were significantly correlated with unintentional non-adherence. The only factor associated with intentional non-adherence was young age (younger than 36 years). We found no specific anti-seizure drug to be particularly associated with non-adherence.

Chapter 5: Discussion

5.1. Overview

Our aim with the studies described here was to identify and evaluate some of the challenges faced by people with epilepsy in everyday life. In particular, we wished to explore the patients' perspective regarding problems with adhering to an anti-seizure drug regimen, sexual function, and satisfaction with the information provided by healthcare personnel on various aspects concerned with epilepsy.

To our surprise, we found that even patients with well-controlled epilepsy may struggle with challenges like medical problems, cognitive difficulties, and physical and/or psychosocial limitations. Despite a substantial number of patients reporting sexual problems, generally they seemed to be less concerned than the general population about these issues. Discussing sexual problems is still taboo in Norway, and both health professionals and patients tend to avoid these issues.

Patients with epilepsy report a clear wish for information regarding different aspects of epilepsy. Although for general epilepsy-related information, this need seems to be met by healthcare professionals, regarding more specific issues like epilepsy surgery, comorbidities, psychosocial challenges, and SUDEP, the patients are less satisfied with the information provided. For example, the great majority of patients wanted information about the risk of premature death, but such information was given to only about one third of the respondents in our survey.

We have identified a relatively high rate of non-adherence to drug regimens, both intentional and unintentional, and this seems to occur not only among patients with well-controlled epilepsy, but also in those with refractory epilepsy.

In the following sections, these issues and their implications will be discussed in greater detail.

5.2. Challenges in epilepsy

The main finding from this study was that most persons with epilepsy in Norway experience several everyday challenges that may affect their quality of life. Although 40% of the participants in our study reported being seizure free for at least the preceding 12 months, the majority reported challenges regarding medical and cognitive problems, and, to a lesser extent, psychosocial problems and physical limitations. For clinicians, this information is important to bear in mind as such challenges should be addressed when offering a comprehensive or patient-centred care plan.

5.2.1. Cognitive problems

Cognitive problems, like memory and concentration difficulties, were reported by about 70% of participants with epilepsy in our study.

In a large community-based questionnaire survey among persons with epilepsy in the US (n=1023), 40 - 50% of the respondents reported that the epilepsy and/or the epilepsy treatment affected their ability to think clearly, to remember, to concentrate, and also their mental and emotional wellbeing [11]. The rate of respondents being seizure free for at least one year in that study was similar to the figures in our cohort, i.e. about 40%. The higher proportion of patients reporting such problems in our study might reflect cultural differences, both in self-observation and/or the willingness to report these problems.

The causes of memory problems in persons with epilepsy are complex and probably multi-factorial. They may be related to morphological changes with dysfunctional networks required for storage and/or retrieval of memory, especially in limbic structures [186], to psychiatric comorbidity[187], to the use of anti-seizure medication, or to a combination of these factors. We found that female gender, polytherapy, and not being seizure free were risk factors for cognitive problems, even after controlling for increased psychiatric comorbidity. Surprisingly, we found that memory problems were reported more frequently among those living in stable relationships than in those who stated that they were living alone. One explanation could be that memory problems are more evident and recognizable when there is a life partner.

Cognitive and affective problems often overlap. In some patients, such problems may have a greater impact on their quality of life than the seizures themselves [188; 189]. Several studies have shown that recurring tonic-clonic seizures are associated with a decline in cognitive function [190].

5.2.2. Medical problems

In our study, about 70% of respondents with epilepsy reported being negatively affected by tiredness, while about half reported headache. In a review and meta-analysis on fatigue (extreme and persistent tiredness) in epilepsy, Kwon and co-workers found this occurred in up to 50% of the patients [191]. In seven out of 12 studies included in the meta-analysis, a significant correlation was found between depression and fatigue [192-198]. All these seven studies were performed at epilepsy referral clinics and the patients in at least five of the studies were, to a high degree, refractory [192-194; 197; 198]. In contrast to the results in our study, female gender and number of anti-seizure drugs currently being used were not risk factors [191]. The discrepancies between our results and the results of the studies in the meta-analysis could be due to the specific question asked, as we requested information about tiredness, which is a less-specific term than fatigue.

Results from studies on headache in the epilepsy population, and discussions about a possible causal relationship between epilepsy and migraine are contradictory [199]. In our study, we found a high prevalence of headache, which concurs with the results from a large survey from the US[200]. The prevalence was particularly increased in those who were not seizure free. However, we did not ask more specifically about pre-, peri-, post-, or inter-ictal headache, or about the type of headache.

5.2.3. Psychosocial problems

Nearly 60% of respondents with epilepsy in our study reported feeling depressed. This number is unexpectedly high, especially when taking into account that about 40% of them were seizure free. A recent meta-analysis on depression in epilepsy, including 35 studies, reported a point prevalence of depression of 21.9%. As in our study, there was a higher occurrence of depression in females than in males (26.4% vs 16.7%) [201]. However, the studies are not entirely comparable, as the meta-analysis was based on studies of difficult-to-treat patients. Furthermore, in our study we asked the patients whether they felt depressed or down, and we did not use objective evaluation of depressive symptoms [202]. Thus, it is likely that many of the patients reporting feeling depressed in our survey did not fulfil the diagnostic criteria for depression. This probably explains the high occurrence in our sample. On the other hand, some individuals who do suffer from clinical depression might not recognize the symptoms, and this would result in under-reporting [203].

Feeling depressed was a risk factor for sexual problems, which were reported to occur in 30% of the participants with epilepsy in our survey. This is a lower proportion than we found in our first study among patients with refractory epilepsy, i.e. about 70%. The discrepancy is probably due to quite different study populations. We found that known epilepsy aetiology, older age, and being in a relationship were factors that were associated with sexual problems. Previous studies have also revealed old age and feeling depressed to be risk factors for sexual problems in this patient group [70; 204]. Being in a relationship may make sexual problems more obvious and easier to recognize than in those living alone.

Fisher et al found that 32% of the epilepsy patients in their study reported living with a constant fear of the next seizure [11]. This is a lower proportion than in our sample (nearly 50%). Perhaps surprisingly, being seizure free did not appear to reduce the fear of having a seizure. Female gender and feeling depressed were associated with increased fear. Interestingly, Gaus et al. found a higher rate of seizure worry (afraid of having a seizure within the next month) in men (55%) than in women

(40%), while depressive symptoms were more prevalent in women [205]. Women with epilepsy have a higher rate of affective psychiatric comorbidity than men [49], and the associations between female gender and feeling depressed, fear of being alone, or fear of having a seizure, are probably explained by the large overlap between depression and anxiety.

About one third of our sample reported difficulties with social interactions. As we did not ask the patients to describe these difficulties, we may only speculate about the type and the reasons. In a recent review, the authors emphasize that although social contacts may have a positive effect on health, morbidity, and self-esteem, and may counteract stress; persons with epilepsy are at a risk of reduced social cognitive skills and therefore may be more likely to experience communication and interpersonal difficulties [206].

The rate of anxiety has been shown to be higher in the epilepsy population than in the general population [7; 207; 208]. Fear of being alone may be related to depression or anxiety, or both. Studies about loneliness in epilepsy are rare. However, Fisher et al. found that 24% of persons with epilepsy reported social stigma, fear of other people's reactions, feelings of shame, and loneliness [11]. In our study, feelings of loneliness were more often reported by younger people than older people with epilepsy. This may partly reflect their unfulfilled expectations, and that are also promoted via social media; younger people should be sociable, interactive, and have a large social network.

Overall, psychosocial problems can be a strong barrier against successful integration into society [209], and their importance should not be underestimated.

5.2.4. Physical limitations

In our study, 40-50% of the participants with epilepsy reported problems with being physically active. Several previous studies have shown that persons with epilepsy tend to be less physically active and have a poorer level of physical fitness than controls [210; 211]. However, although two large population-based studies found that persons with epilepsy had a similar level of physical activity as a reference population [212; 213], other studies have shown that fear of seizures and seizure-related injuries are a risk factor for physical inactivity [214]. Lack of a driving license because of a prohibition or restriction due to the diagnosis, is an obvious reason for transport problems and consequently may limit social activities among persons with epilepsy. This is of particular importance in many rural parts of Norway where public transport is sparse or not available.

5.2.5 Other epilepsy-related challenges

Our studies provide an insight into an important and probably underestimated aspect of epilepsy care: everyday challenges that are not necessarily directly related to seizures. Such challenges add to the burden of epilepsy, and addressing these challenges and identifying coping strategies and ways of mitigating them should be a natural part of a comprehensive epilepsy-care plan. In the previous sections, I have discussed cognitive, medical, psychosocial, and physical issues. These overlap to varying extents, and it is important that they are not viewed as single entities that do not interact and impact on each other – for example, physical limitations may isolate individuals, thereby affecting psychosocial wellbeing. Another aspect that may encompass all four of the above sections – cognitive, medical, psychosocial, and physical, has formed a major part of this research and is therefore considered in a separate section, below, although is a challenge that obviously affects, and is affected by many other factors, namely sexual problems.

5.3. Sexual problems among people with epilepsy

5.3.1. Prevalence and type of sexual problems

The results from our studies show that people with epilepsy report having sexual problems up to six times as often as people in the general population. This is in line with the results from previous studies, although the proportion reporting such problems varies between studies. This is mostly due to differences between study populations and different definitions of the term “sexual problem” [65-68; 74; 75; 84; 100; 215-219]. However, in women with epilepsy there have also been reports of no increase in rates of sexual problems [215], or even lower rates, compared with women without epilepsy, particularly among those using lamotrigine and levetiracetam [90; 220]. In one of these studies, about 80% of the patients had been seizure-free during the last 6 months, indicating a study population with easy-to-treat epilepsy [220]. No information of seizure frequency was provided in the other study [90]. Three studies on this topic have been published during the last few years. Two of them showed a significant increase of sexual dysfunction in women with epilepsy [72; 216], whereas one showed no difference regarding sexual problems between women with epilepsy and women in the general population [70].

Having the opportunity to include large population-based control groups (n=593 and n=1671) is an important advantage in our studies. Other studies have used either small control groups or biased control groups. For example, a Brazilian study compared sexual functioning in males with epilepsy (recruited from an epilepsy clinic) with sexual functioning in healthy controls. The controls consisted of men with pregnant wives recruited from the waiting room of a pre-conception clinic [218]; naturally, this introduced a selection bias.

Both the rate and type of sexual problems differed between our two studies. Nearly all types of sexual problems (reduced sexual desire, problems with orgasm, premature ejaculation, erectile dysfunction, pain during intercourse, and vaginal dryness) were significantly increased in patients with epilepsy in our first study. In the second study, however, only rates of problems with orgasm, late ejaculation/climax, pain during intercourse, erectile dysfunction and feelings of sexual deviance were significantly increased. Rates of lack of sexual desire, premature ejaculation/climax, and inadequate vaginal lubrication were similar to rates reported in the general population.

Calabro et al. compared 30 male outpatients with epilepsy to 30 male controls and found sexual problems to be present in 21/30 vs. 11/30, respectively [74]. This is in agreement with our results. The predominant problem in Calabro's sample was delayed ejaculation and reduced desire. However, the sample was small and probably underpowered. Nikoobakht et al. reported erectile dysfunction among 43 % of 80 married men between 22 and 50 years of age with epilepsy. There was, however, no control group in that study [76]. In accordance with our results, Zelena et al. found a prevalence of sexual problems in 52 % of 29 women with epilepsy. Insufficient lubrication (35 %) and lack of desire (28 %) were the main problems in that sample [73]. Morell et al. reported increased dyspareunia in combination with insufficient arousal in a sample of women with epilepsy. This finding was particularly prominent in those with focal epilepsy, suggesting a physiological explanation for their findings [69].

Sexual deviance is a rather non-specific type of sexual problem and may reflect that psychological factors are involved in perceptions of sexuality, rather than indicating a specific problem. We found that low self-esteem and low quality of life were both associated with sexual problems among the patients in our studies. A review from 2007 revealed that studies about feeling sexually deviant among persons with epilepsy were sparse and mostly related to those with temporal lobe epilepsy [221].

Our two studies were performed over an interval of nearly a decade. The rate of sexual problems in the general population has also increased from the first to the second study. A study looking at self-reported sexual dysfunction pre-treatment in men with prostate cancer in two surveys nearly 20 years apart found a similar result, with a significant increase in reported sexual dysfunction[222].

These observations could be caused by an alteration in attitude to reporting sexual dysfunction due to sociocultural changes and a lower degree of perceived stigmatization[222]. An increased awareness of possible "flaws", with a wish for normality, might increase critical self-observation and facilitate reporting of problems in sexual functioning [223].

In contrast to this, we found a slight reduction in sexual problems reported by the patients. A contributing factor could have been a decrease in the usage of older anti-seizure drugs, like carbamazepine, phenobarbital, or phenytoin in this period [224]. These drugs are strong enzyme inducers, and may therefore have a negative influence on sexual function [225].

5.3.2. Sexual problems – the impact on quality of life and mood

Quality of life is a multifaceted concept that incorporates physical, psychosocial, and economic factors. In our study, we used only the scale of overall quality of life that had been calculated from two items to assess this. This has been shown to provide as good a reflection of quality of life as that provided by more extensive questionnaires [181]. We found that our study patients with sexual problems had low quality of life, but whether the sexual problems caused the low quality of life, or the quality of life caused the sexual problems, cannot be determined.

Sexual problems are known to be associated with depression [226]. As people with epilepsy have a higher prevalence of depression [7], an increased rate of sexual problems in this patient group is to be expected. In both our studies on sexual problems, we found a significant association between symptoms of depression and sexual problems among women with epilepsy. These results are in agreement with results from various prior studies [71; 74; 75; 100]. For example, Zelena et al. found only depression, as assessed by the Beck Depression Inventory (BDI), being significantly associated with reduced sexual function in women with epilepsy, and sexual problems were not associated with specific seizure types, hemispheric lateralization in focal epilepsy, seizure frequency, or hormonal status [73]. Similarly, we did not find any correlation between sexual problems and seizure type, seizure frequency, or use of enzyme-inducing anti-seizure medication, but it should be noted that we did not control for hormonal status. Although depression cannot fully explain the higher rate of sexual problems identified in people with epilepsy, it might be an important influencing factor [75].

Our findings and the reports in the literature underline that, in addition to changes in hormonal status, other factors, like affective disorders and or possibly psychosocial challenges, can contribute to sexual problems in people with epilepsy.

5.3.3. Other risk factors for sexual problems

We were not able to find an association between seizure type, seizure control, use of different anti-seizure drugs, high burden of adverse drug events, or degree of education, and the frequency and types of sexual dysfunction. However, results from some previous studies indicate that hyposexuality is associated with temporal lobe epilepsy, particularly in those with amygdala involvement [225; 227].

Enzyme-inducing anti-seizure drugs may reduce free testosterone by increasing sex hormone binding globuline (SHBG), and thus lower libido [82; 83; 225]. However, the relationship between libido and testosterone levels is not linear [100]. Clinical experience indicates that compromised sexual function may occur in some patients using these drugs, whereas others might be unaffected [228]. This may explain the lack of correlation between sexual problems and the use of such drugs in our study. Herzog et al. found that men using enzyme-inducing drugs, such as carbamazepine or phenytoin, had lower scores on sexual functioning than normal controls and those treated with lamotrigine [84].

Overall, the results of both our study and of other studies indicate an increased rate of sexual problems in patients with epilepsy. Explanations for this finding are often based on a biomedical model, emphasizing factors like the epilepsy and anti-seizure medication altering the hormonal status and thereby affecting sexual functioning [225]. However, our findings suggest that this model does not explain the causes for sexual problems sufficiently. We therefore suggest that a biopsychomedical model, which also incorporates psychological factors, such as mood, anxiety, and behaviour, as well as expectations and satisfaction regarding sexual life, may be more appropriate. According to the Diagnostic and Statistical Manual of Mental Disorders, one of the criteria for the diagnosis of sexual dysfunction is “marked distress or interpersonal difficulty” [55]. In our studies, we did not ask about distress regarding sexual problems, and this probably resulted in over-reporting of sexual problems both in our sample and in the control group. People experience a range of different sexual problems, but provided that these do not result in distress or dissatisfaction regarding sex life, then they should not be problematized.

5.3.4. Are people with epilepsy satisfied with their sexual lives?

We asked our study participants about their level of satisfaction with their sexual lives. In the general population, the number of people reporting dissatisfaction with their sex lives exceeded the number reporting sexual problems; i.e., some people who did not report sexual problems were nevertheless dissatisfied with their sex life. In our sample of patients with epilepsy, the opposite picture emerged. More patients reported being satisfied with their sex life than was expected from the rate of sexual problems. Whereas the rate for sexual problems in the epilepsy group was six times higher than the rate in the general population, the rate of sex life dissatisfaction was “only” doubled. Interestingly, similar findings have been reported in the elderly general population from a study among men and women aged between 60-75 years old, living in Norway, Denmark, Belgium, and Portugal [229].

Unfortunately, the definition of “satisfaction” varies between studies [72; 76; 220; 230], which makes inter-study comparison challenging. It is possible that at least some people with epilepsy may adapt to the sexual problems that they experience. This may result in an acceptance, lower expectations, and less distress or dissatisfaction regarding their sex life.

Therefore, in our second study we asked the participants for their opinions on the importance of sex in daily life. Compared with the general population, among men with epilepsy significantly fewer considered that sex was an important part of daily life. To the best of our knowledge, this has not been previously reported, and the reasons are not clear. It could be that having experienced sexual problems, men with epilepsy may attempt to diminish its importance or, for psychological reasons, be less inclined to initiate sexual activity [231]. We did not, however, find a similar situation with women. One reason could be that intimacy in a relationship is of greater importance for sexual functioning for women [232]. However, a recent study found that although sexual desire was more prevalent among men, there was no gender difference in the association between intimacy and sexual desire [233].

5.3.5. Age at sexual debut

In neither of our two studies was age at sexual debut among patients with epilepsy significantly different from that among the controls. De Vincentiis et al. compared a sample of 35 Brazilian female teenagers with epilepsy with an age-matched control sample, and found that 41% of the teenagers with epilepsy reported having had sexual intercourse; among these, the median age for first intercourse was 15 years, which was the same as in the control group[215]. Different findings are reported by Lossius et al. who found that Norwegian pupils with epilepsy reported a higher rate of sexual intercourse than in controls, and also a lower age of sexual debut [234; 235]. They speculated that this might be due to a higher prevalence of risk-seeking behaviour among those with epilepsy [234; 235].

In our study, the proportion of those never having had sexual intercourse was higher in the epilepsy group than in the general population, and this was particularly so among those with refractory epilepsy. Most previous studies examining this issue are based on sexually active patients, and thus exclude those who have never had vaginal sexual intercourse. Data on this subject is sparse. One survey reported that about 15% of women with epilepsy had never had sexual intercourse [63].

5.3.6. Do patients with epilepsy discuss their sexual problems with their physicians?

Only 16% of the patients in our first study reported that they had been asked by their physician about sexual functioning. This number might be even lower during regular consultations, as informing the patients about the survey could have triggered discussion about sexual functioning. Nevertheless, our findings support the results from previous studies [51; 63]. Thus, the possibility that epilepsy and use of anti-seizure medication may cause sexual problems might not be understood or considered of relevance by many clinicians [51].

We have no information regarding why clinicians so rarely discuss this subject with their patients. Fischer et al. interviewed medical students about their intention to address sexuality in clinical practice, and found that the further the students had come in their education, the less likely they were to have considered talking about sexuality in practice; the students reported low levels of self-perceived competence to address sexual issues [236]. A systematic review revealed that despite the majority of healthcare providers considering sexuality to be of importance, it was not discussed routinely. This was assumed to be due to lack knowledge and expertise within this complex area of medicine and the fear of being perceived as intrusive or asking inappropriate questions [237]. However, clinical experience indicates that patients usually welcome questions about their sexuality, and they rarely decline discussions on this subject [100; 118].

In our second study, we asked whether respondents had requested help with sexual problems. Our results suggest that both the general population and patients with epilepsy are hesitant regarding seeking help from healthcare providers about sexual problems, and these results are in line with those from other studies [51; 63; 238]. Although we found it encouraging that woman with mostly refractory epilepsy seemed more willing to seek help with sexual problems, this attitude should be promoted in all patients.

5.4. Information about epilepsy

5.4.1. Information about epilepsy in general and regarding specific issues

5.4.1.1. How do patients with epilepsy perceive information from healthcare providers?

Our study shows that although the wish for information about various aspects of epilepsy among people with epilepsy in Norway is generally high (70-90% of patients wish to have information), their needs are only partially met by healthcare providers.

To the best of our knowledge, only a few studies have investigated the patients' wishes for information. A qualitative study (n=35) showed that many patients would like more information about treatment options, and they wanted to hear more about the advantages and disadvantages of the different anti-seizure medicines [126]. In a quantitative European survey (n=461), 54% of patients wanted more information about epilepsy in general, and treatment options in particular [135].

Nearly all patients in our survey reported that they wanted general information about the disease. However, in addition, many of the respondents wanted information on specific topics that most physicians probably had not considered as being particularly relevant for them; e.g., non-medical treatments (epilepsy surgery, neurostimulator treatment, or dietary treatment) or treatment with cannabis. At least 70% reported that they would like to have information on each of these topics, despite about 40% of the patients having been seizure free for at least 12 months.

Few studies have been published that explore the patients' perspective regarding provision of information. In 2000, Poole et al. conducted a survey among people with epilepsy in the UK, either in primary care (n=1652) or specialist care (n=742) to determine whether they had received information on various epilepsy-related issues; information on the proportion of patients in these groups with freedom of seizure is not provided in the publication. Regarding general epilepsy-related information, 51.7% of patients in the primary care group had received such information and 59.4% in the specialized care group. Information on topics like driving restrictions, free drug prescriptions, adverse effects of anti-seizure medication, effects of consumption of alcohol, and photosensitivity had been obtained by 70-80% of the respondents [134]. A similar study was conducted in 2015 based on people with epilepsy attending an epilepsy specialist centre (n=102) [129]. In this group, 67.6% had received information on epilepsy-related issues overall, with more than 80% having obtained information on driving restrictions, alcohol consumption, and adequate sleep [129]. Although both these studies provided factual information about the provision of information, they did not investigate the patients' perspective, regarding their wishes or requirements for information, or the information requirements of their families or carers.

Although the proportion of people with epilepsy who received general epilepsy-related information in our study was slightly higher than that reported in the studies of Poole et al. and Bennett et al., it is important to take into account the topics being considered[129; 134]. The overall information in our study differed from that used in these two studies. The difference between information that was wanted and information that was obtained on specific topics was greatest regarding psychosocial and cognitive issues, as well as non-pharmacological treatments. Although these issues overlap to a certain extent with adverse effects of drugs, our results nevertheless indicate that discussion of these issues seems to be an unmet need of those participating in our study.

Although seizure control is a natural goal for both patients and doctors, many patients seem to be more concerned about adverse effects of drugs [135]. This may explain why we found a discrepancy of more than 20% between the proportion of patients who wanted information on this subject and the proportion of patients who were provided with information about the side effects of drugs.

5.4.1.2. Factors influencing the provision of information

Many studies aim at assessing the extent of knowledge that people with epilepsy have about their condition, rather than whether or not this information is made available to them by their healthcare providers [130; 132; 133; 136; 137]. One study revealed that lack of knowledge was significantly associated with high mean age, low level of educational achievement, prolonged duration of epilepsy, occurrence of “major” seizures, and high seizure frequency [137]. None of these studies found any association between epilepsy-related information and gender. In contrast, we found that, apart from interest in non-medical treatments, male patients had received information about nutrition and weight more often than female patients had been provided with such information. In Norway, more men than women are overweight [239], and it is possible that some physicians may claim that male patients are less aware of weight and dietary issues.

With respect to age, we found an association between young age and having obtained information about contraception and pregnancy, adverse effects of drugs, and sleeping habits. This seems to be similar to results from some previous studies [133]. It is possible that younger persons are more inclined to ask for information and/or healthcare providers might prioritize ensuring that younger patients are properly informed. However, a recent study revealed that higher age is a positive indicator for health literacy [123]. This is thought to be achieved by the continuous interaction between heathcare providers and patients over a longer time frame. Health literacy as a prerequisite to obtain, process, and understand basic health information depends on different factors, probably the most important of which is being sufficiently educated [123]. Experiencing tonic-clonic seizures might underline the severity of the disease, and thereby the need for information, as was apparent in our study.

Epilepsy surgery as a possible treatment option for persons with refractory epilepsy has long been reported to be underutilized [240]. Studies that have assessed neurologists’ knowledge of, and attitude towards, epilepsy surgery have generally indicated a rather cautious outlook. This represents a barrier towards referral of patients to epilepsy surgery [241; 242], and such attitudes are also likely to influence the extent to which information is provided on this issue. A wish for information about epilepsy surgery among those patients with recurrent seizures was natural, but there is no obvious explanation why a higher proportion of male patients were provided with information about epilepsy surgery and neurostimulation (including vagus nerve stimulation) than women. The provision of information regarding cannabis treatment, and the quality of information that was provided, was considered particularly inadequate by the respondents. This may reflect that this treatment is currently not registered as a part of approved epilepsy treatment in Norway.

The average duration of epilepsy among participants in our study was 20 years. With such a long duration of the disease, it might be expected that they would be well informed about various aspects of epilepsy. However, there is also the risk that healthcare providers assume that information has been provided at an earlier stage and focus more on informing patients with newly diagnosed epilepsy about various issues.

5.4.1.3. Methods of delivering information

Even in an epilepsy population where 40% is seizure-free, there is a considerable need for relevant information. How information is best delivered is a matter of debate. Educational programmes, like the Modular Service Package Epilepsy (MOSES) for German-speaking countries, self-management in epilepsy (SMILE) for English-speaking adults, or the interactive, animated epilepsy education programme (IAEEP) for children, have been developed and proved effective [243-245]. An informed patient can take an active part in discussing a treatment strategy. In addition, he or she can be an ambassador for further distributing information on epilepsy. How information is received by the patients, and whether it enables them to participate in shared decision making, is also dependent on the way in which physicians communicate[246]. Whether patients are informed at all, the information with which they are provided with, and how they use it, all affect health outcome, patient satisfaction, and safety [14; 128]. Knowledge may alleviate stress and provide a feeling of security and control; this in turn may raise the seizure threshold.

5.4.2. Information on seizure-related injuries and epilepsy-related death

5.4.2.1. Our results in context

Among the many unfortunate consequences of epilepsy are seizure-related injuries and, at worst, premature death. Our survey demonstrated that only one third of the study cohort had been provided with information about epilepsy-related risk of death, despite over 90% of the respondents wanting to be provided with such information. The term SUDEP (sudden unexpected death in epilepsy) was deliberately not used in our survey in order to include all types of epilepsy-related deaths. In our study, we received answers from three different groups of respondents: patients with epilepsy (about 40% were seizure free); family members or guardians answering on behalf of patients (for this the group, the patients for whom answers were being provided were younger, mostly below 18 years old, less likely to live alone, and only 23% were seizure free); family members or guardians answering on their own behalf. Although the first two groups differed regarding age and seizure freedom, the wish to have access to relevant information was common, indicating that patients with less refractory epilepsy also wanted such information.

It is not surprising that the proportion of patients that had received information about the risk of seizure-related injuries was higher than those who had received information about the risk of premature death, as injuries are a less sensitive issue than death.

To the best of our knowledge, the only other web-based study on this issue was performed in the USA among members of a selected population, the Epilepsy Therapy Network [247]. That study had a comparable number of respondents to ours, but fewer seizure-free patients (25%), probably indicating selection of patients with more severe epilepsy than in our study. In the USA-based study, 1299 patients and 547 caregivers responded to an internet-based survey, and 93 patients and 64 caregivers answered the questionnaire while waiting at an epilepsy clinic [247]. Among the internet respondents 71% had heard about SUDEP and the equivalent proportion of the clinical population was 39%. Caregivers were more likely to have heard about SUDEP (76%) than patients (65%). Overall, between 2 and 3 % did not want to be informed about the risk of SUDEP, regardless of the individual risk [247].

The proportion of patients in our study who did not want to receive information about epilepsy-related risks was quite low (9% for death and 8% for injuries). This is in line with earlier studies, indicating that the great majority of the epilepsy population wants such information [248-250], including those who are seizure free. After our study was published, Surges et al. reported from a survey at an epilepsy clinic (n=372), that 51% wanted to be informed, 41% did not want information on SUDEP and 8% were unsure [251]. In their cohort, only 13% had been informed about SUDEP. In contrast Long and colleagues asked patients or caregivers who had no knowledge of SUDEP (n=94) [252]. All respondents wanted to be informed, and also felt that it was their right to be informed, even including 36% who felt that such information would make them more anxious [252].

Of our patients wanting information about premature death, about 69% reported that they had not been informed about this issue. This is somewhat higher than in other studies; 50% in the study of Keddie et al [248], 47.6% in the study of Xu et al [250], and 32% in the study of Kroner et al [247]. This might be because less patients in our sample have refractory epilepsy and may have been considered to be at lower risk of premature death by their physicians. Only about 14% of all patients in our study felt that they had been well informed about the risk of sudden death. However, the quality of the information they had received is not known. In a recent study from an epilepsy unit in Spain, 88% stated that they had not been informed about SUDEP [253], which is a similar proportion to that reported from the study by Surges et al[251]. Overall, the data from published studies and our own research show that the extent to which patients with epilepsy are informed about SUDEP varies considerably, and is generally quite low.

5.4.2.2. Factors influencing whether patients are informed

In our cohort, those experiencing tonic-clonic seizures were more likely than others to want information about the risk of injuries and premature death. Although they were more likely than others to have received information about the risk of injuries, this was not the case for premature death, despite tonic-clonic seizures having been shown to be associated with an increased risk for premature death [254].

In contrast to the results from another study [250], we found that being young increased the probability of being informed about these risks, and also the wish to obtain such information. Patients cohabitating with family or partners were also more likely to have been provided with information about the risk of injuries or wished to obtain more information on this risk. This could be due to an increased awareness of the problems that seizures might inflict on others in the household; to the best of our knowledge, this aspect has not previously been studied.

We found that men were more likely to have obtained information about the risks of both death and injuries than women. This has not been found in previous studies on these issues [247; 250]. However, some studies have shown that male patients are more likely to be non-compliant with treatment regimens than women [176], and therefore physicians might consider providing male patients with information on seizure-related risks as a means to encourage treatment adherence. A retrospective case note analysis found that there was a trend towards informing non-compliant patients about the risks for SUDEP [151].

5.4.2.3. Is it reasonable to withhold information?

Physicians might be reluctant to inform about SUDEP because they do not want to make their patients worried or depressed. However, patients might want to be informed about the possible risks, even if that information may give rise to feelings of anxiety [252]. A recently published study of patients (n=231) who were provided with information about SUDEP, showed that at a follow-up 6 months after they had received the information, drug adherence had improved, but anxiety, depression, and quality of life scores remained unchanged [156].

For most people with chronic diseases like epilepsy, comprehensive knowledge of the disease is important in order to reduce feelings of insecurity and to enable a better way of managing everyday life. We can only speculate regarding why the majority of the patients in our study had not received information on the risk issues. The explanations are probably complex. We believe that physicians, particularly neurologists, play a critical role in patient education, encouraging self-management, and ensuring that patients and their carers or family are aware of the risks, and how to tackle those risks associated with epilepsy [148; 255]. Assessment of the risk factors during routine clinical practice can bring about behavioural changes that reduce individual risk factors [256]. In order to reduce the risk of unfavourable incidents occurring, it is important to discuss these matters with the patients and the relatives and to encourage them to take responsibility themselves for the condition, e.g., to avoid seizure triggers. In a recent review, patients scored the information that they had received about SUDEP during a semi-structured interview as useful (81%) or satisfactory (84%), and 94% considered it important to receive such information [253].

5.5. Adherence and non-adherence

The main finding from our first study among patients with mostly well-controlled epilepsy was that almost one third chose not to follow their agreed treatment plan, but had decided to take their anti-seizure medication differently than prescribed (intentional non-adherence). In addition, about 40% reported that they sometimes or often forgot to take their drugs as scheduled (unintentional non-adherence).

In our second study, one fifth of patients with refractory epilepsy reported intentional non-adherence rarely, sometimes or often, while also one fifth reported unintentional non-adherence sometimes or often.

To our knowledge, our study is the first to differentiate between intentional and unintentional non-adherence in epilepsy. We believe that this distinction is important, as the reasons underlying non-adherence can be better explored, and, more importantly, the appropriate measures can be implemented to improve the management of this patient group.

Results from previous studies have shown considerable variation regarding estimates of poor adherence to treatment in epilepsy populations. A recent review reported non-adherence in 26-79% of patients [158]. Different study populations, different definitions of adherence, and different methods of measuring non-adherence may account for this wide variability. For example, a French study showed that 79% of 263 participants always followed the prescribed regimen, and those who were non-adherent (21%) stated that adverse effects were the main reason [257]. A recent German study found that 44% (n=226) had irregular intake of anti-seizure medication, and that young age and adverse drug effects were the most important risk factors for non-adherence [173].

Various approaches have been used to try to determine adherence to treatment schedules. Self-reports, as used in our study, might under-estimate the proportion of non-adherence. This may be particularly so for unintentional non-adherence, as those who forget to take their drugs might also not remember their forgetfulness when completing the questionnaire. Patients may also be reluctant to admit intentional non-adherence. However, anonymized data collection, as used in our study, may be one approach to encouraging participants to complete the questionnaire accurately. It has been claimed that the degree of adherence to a prescribed drug regimen is dependent upon the individual patient's attitude to the necessity of treatment and their fear of adverse effects [258].

Among patients with well-controlled epilepsy we found that feeling depressed, young age, and memory problems were risk factors for unintentional non-adherence, whereas intentional non-adherence occurred more often in depressed male patients and in patients who felt stigmatized. Among patients with refractory epilepsy, we found young age and depression to be risk factors. This is in line with the results other studies [44; 159; 173]. However, in contrast with other studies [173; 257], we found neither adverse events nor individual drugs to be risk factors for non-adherence.

It is not clear why males are more prone to intentional medication non-adherence than females. It could be speculated that men are more willing than women to take risks and less willing to follow recommended treatment schemes. Indeed, it has been demonstrated that young men with epilepsy are more prone to risk-taking behaviour than women [259]. Furthermore, persons with epilepsy who experience stigmatization might feel that following a daily drug regimen may reinforce the stigma and this feeling might predispose them to be non-adherent.

We found a correlation between non-adherence and young age and symptoms of depression. This is in line with other studies [44; 159; 173]. However, in contrast to other studies, we did not find a high score of adverse events [173; 257] to be a risk factor for non-adherence.

In various studies on non-adherence, the rate of freedom from seizures among the patients included in the study is either not stated [173] or is around 30% [171; 257]. Studies on non-adherence to treatment of refractory epilepsy are sparse. A study from US, defining refractory epilepsy as those currently using three or more anti-seizure medications, regardless of seizure frequency, revealed a significantly higher rate of adherence to treatment in these patients than in patients using fewer drugs [174].

The ILAE task force defined drug-resistant epilepsy in 2010 as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules" [260]. Unfortunately, we did not have sufficient information on previously tried anti-seizure medications among our patients to apply this definition. Therefore, we chose to define refractory epilepsy as having had seizures during the previous year despite use of anti-seizure drugs.

The reasons why patients with refractory epilepsy are more adherent to treatment than those with more easy-to-treat epilepsies are unknown, although recurrent seizures confirm the need for treatment. In our studies, the patients with refractory epilepsy has an early epilepsy onset (median debut at 15 years vs. 21 years in non-refractory epilepsy), and regular intake of anti-seizure medication may have become an established daily routine. Moreover, those with refractory epilepsy are usually followed more closely by an epileptologist and are probably provided with more thorough information on the necessity for carefully following the agreed anti-seizure medication schedule. Also, fear of sudden unexpected death and more regular therapeutic drug monitoring might result in better adherence to drug treatment.

In this patient group, minimizing non-adherence is important for improving seizure control and thereby reducing the risk of seizure-related complications.

5.6. Methodological considerations

5.6.1. Online survey (Papers I, IV, V, VI)

Various limitations are associated with this study. Only about 2.5 % of the almost 50,000 visitors to the homepage participated in the survey. However, 50,000 visitors constitute about 1% of Norway's population; it is possible that during the study period, searches for "epilepsy" on the Norwegian Google site, resulted in the homepage of the National Epilepsy Association being the first listed. That would mean that everybody in Norway looking for information about epilepsy, not just patients and family members, may have visited the homepage of the NEA during the study period. This may indicate that the majority of those visiting the homepage did not have epilepsy. However, as we do not have any information about visitors who chose not to participate, we cannot exclude a selection bias. The proportion of seizure-free patients (41%) was lower than expected in a representative sample of the Norwegian epilepsy population, and may indicate a bias towards patients with more severe epilepsy being included in the study. Further limitations are possible problems with the validity of questionnaires based on close-ended questions. A potential bias could also be selection of those with a greater need for information and/or interest in reporting back to the health system than the “average” person with epilepsy.

All information gathered during the study is based directly on the input of the respondent. Therefore, we have no verification that the respondent actually reported the correct seizure type or even actually had epilepsy at all. Nor do we have any control over whether participants had or had not received information from health personnel, and no verification regarding the quality of the information that respondents had received from healthcare providers. It is simply assumed that those who use their time in completing the questionnaire are actually interested in contributing to increased knowledge about these aspects of epilepsy.

Recall bias will also influence the reported information on adherence. For nearly all questions, there were some participants who did not respond. This could be due to coincidence, carelessness, or lack of attention by the respondents. But it could also mean the respondents that did not answer regarded those questions as being too sensitive or intrusive, or perhaps not relevant to their situation. This would then be a selection bias and could affect the results.

5.6.2. Questionnaire study on sexual problems among patients with epilepsy (PaperII)

Questionnaires have the disadvantage that misunderstandings or unintended scoring cannot be identified or corrected for by follow-up questions, as can be incorporated in an interview. However, as sexuality may be a sensitive subject to discuss openly, a questionnaire might result in the data obtained being more correct than that supplied via an interview. The use of a large control group strengthens the findings of our study.

Our study population was recruited from a tertiary epilepsy centre. This implies selection of patients with difficult-to-treat epilepsy, and therefore our results may not be representative for the general epilepsy population of Norway. The sample from the general population was slightly younger than the sample with epilepsy, but the difference was not significant.

Another limitation is that the sample from the general population was derived from a study that was performed in 1997, about 10 years before the data from the group with epilepsy were collected. It is possible that during the intervening ten years between data collection times, opinions on, or the prevalence of, sexual problems within the Norwegian population might have altered, and thereby affected the results of our study.

In this study, we asked about sexual problems without tailoring the questions towards the definition of sexual dysfunction in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) which requires a minimum duration of 6 months and that the symptoms are accompanied by distress[55]. As we used the same phrasing that had been used in the survey in the general population “did you ever experience”, this means that we are considering lifetime prevalence. This will be expected to be higher than point prevalence, and there might be considerable recall bias. However, this would be the same in both the patient group and the control group.

Factors like quality of life, symptoms of depression, and different aspects of sexuality, like libido or satisfaction with sex life, are relatively subjective and interrelated, and therefore it may be inappropriate to treat them as independent variables. However, associations between these variables were also considered within the context of the study. In order to assess the quality of life we did not use the complete quality of life in epilepsy inventory (QOLIE) 89, but only the score for overall quality of life calculated from two items. Although this has been shown to provide a relatively good reflection of quality of life compared with that determined by extensive questionnaires, some particular aspects might still be missing [181].

The questionnaire for the physicians required a diagnosis of either focal epilepsy or generalized epilepsy; unclassified epilepsy was not an option. This may have forced physicians to choose either focal or generalized epilepsy, even in cases where there was doubt. It should be expected that not all patients can be classified as having either focal or generalized epilepsy, as was shown in a study of a population of Norwegian women with epilepsy, where, despite efforts to classify correctly, 13% were still rated as difficult to classify [261].

5.6.3. Anonymous questionnaire studies (Papers III, VII)

In these studies, we also used questionnaires which, as previously mentioned, have the disadvantage that misunderstandings or unintended scoring cannot be identified nor corrected for by follow-up questions. As we have no information about the patients who chose not to participate in the study, we cannot exclude a selection bias. Again, as all information was provided by the participants, we have no way of being sure that the information provided on seizure type was correct, and the potential for recall bias regarding seizure frequency and other information cannot be excluded.

Regarding the study about non-adherence, we selected patients with refractory epilepsy, which was defined as having had seizures during the last 12 months despite use of anti-seizure medication. Ideally, we should have used the definition of drug-resistant epilepsy used by the ILAE task force (failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules) [260]. However, to use this definition we would have needed information on type of epilepsy and previously used anti-seizure medication (“appropriately chosen”) and dosage, serum concentrations, and possible adverse events of current and previously used anti-seizure medication (“tolerated, appropriately … used”). Unfortunately, this information was not available in our study.

As the majority of patients were using anti-seizure medications in polytherapy, possible correlations between individual anti-seizure medications and non-adherence were difficult to detect and the size of the sample was probably too small. Another obvious source of error in studies on non-adherence is that patients might be reluctant to admit non-adherence, whether intentional or unintentional. As some patients reported intentionally taking their antiepileptic medication differently than agreed upon with their physician this could result in a lower or higher dosage, or in an unchanged daily dosage but a different daily dosing regimen.

With regard to the study on sexual function, we must be aware that as sexuality may be a sensitive subject to discuss openly, using a questionnaire might provide more correct data than a face-to-face interview due to the anonymous nature of a questionnaire. However, the disadvantages of the questionnaire approach, as discussed before, still remain. Although use of data from a large control group from the general population strengthens the findings of our study, the sample size from the well-controlled epilepsy cohort (Lillehammer hospital) was smaller than the cohort with mostly refractory epilepsy recruited from the National Epilepsy Centre, and this may have skewed our results. In addition, the two epilepsy populations have a small degree of overlap. In the group with mostly refractory epilepsy, about 25% had been seizure free during the last 12 months, while in the group with well-controlled epilepsy, 40% were not seizure free.

Female respondents that answered questions on erectile dysfunction and male respondents that answered questions regarding vaginal dryness might have misunderstood the questions, or might have answered regarding their partners.

In order to determine the age of sexual debut we asked for age at the first intercourse. This might have been interpreted by respondent as vaginal penetration, and this would exclude persons with another sexual orientation than heterosexuality.

In this study we asked for sexual problems without tailoring the questions according to the definition of sexual dysfunction (at least 6 month duration and accompanied by distress), and thereby probably obtained an over representation of sexual problems. By using the same phrasing that had previously been used in the population-based survey “have you experience” we are looking at lifetime prevalence. Although there might be considerable recall bias, this would have affected both the patient group and the control group.

Another limitation is that data from patients were collected 7-9 years (2015-2017) after the survey in the general population (2008). During the intervening years, the prevalence of sexual problems and/or views on sexual functioning might have changed, thereby affecting the results.

In order to assess quality of life, we asked participants to score a visual analogue scale from 0 to 10. Although this approach can provide an overall impression, the results are less reliable than a complete quality of life questionnaire, like the QOLIE that includes 89 questions. We also asked participants to complete the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [184] and the Adverse Events Profile (AEP) [185] to assess possible symptoms of depression and the extent of perceived adverse events. Both tools were translated to Norwegian, translated back to English, and checked by a native speaker. However, no further validation in Norwegian patients was performed.

6. Conclusions

- Epilepsy-related challenges, such as cognitive, medical, and psychosocial problems and physical limitations, are a concern to patients, even those who had more controlled epilepsy. Among the risk factors for these challenges were feeling depressed, use of polytherapy, not being seizure free, and female gender.

- People with epilepsy suffer more from sexual problems than the general population, however the prevalence of the problem is variable. The importance of sex in daily life was apparently lower for people with epilepsy, and they were not as dissatisfied with their sex lives as might have been expected on the basis of the sexual problems reported. Quality of life and symptoms of depression were identified as risk factors for sexual problems.

- The extent to which patients with epilepsy have been informed about different epilepsy-related issues varies considerably, as does the perceived quality of the information provided. Different factors, among them gender, age, and seizure control, were identified as factors that influence the provision of information. Nearly all patients or caregivers wished to be informed about the risk of premature death related to epilepsy, but only about one third of patients or caregivers reported having received information on this important subject.

- In a cohort with more well-controlled epilepsy, about 30% reported intentional non-adherence to agreed treatment regimens and 40% reported unintentional non-adherence. Among identifiable risk factors were feeling depressed, having memory problems, being young, being male, and having experienced stigmatization. Among patients with refractory epilepsy, non-adherence, either intentional or unintentional, was lower at about 20%.

7. Future perspectives

In this project we investigated the perspectives of people with epilepsy regarding challenges related to epilepsy, comorbidity like sexual problems, provision of information by healthcare services, and adherence to treatment. Patients provided the information for these investigations by filling in closed-end questionnaires, partly anonymously.

Based on the results obtained here, I would suggest that further studies that go into greater detail by using mixed methods, like interviews or focus groups, to explore the reasons behind different answers may provide valuable, more nuanced insights. Obtaining this information will enable us to improve the tailoring of patient care such that the needs of the individual person are met and that the relevant challenges are properly addressed.

Although the need for patients and caregivers to be provided with information about SUDEP is unequivocal, there is sparse data on how patients cope with this information, which, in principle, could be very daunting. Follow-up after being provided with information on SUDEP should include assessment of how the patients handle this information with regards to changes in their behaviour, and also evaluation of possible changes in their psychosocial and psychiatric burden.

Some studies have shown an increased prevalence of sexual problems in patients with epilepsy, but there are nearly no studies on treatment in this area. This probably reflects the very limited access to facilities treating sexual problems. Organization of a multidisciplinary treatment resource could provide patients with long sought-after help. In addition, such a facility could offer possibilities for more detailed research and better evaluation and understanding of the different contributing factors.

There has been a tremendous increase in awareness regarding the necessity for information in epilepsy. Layperson organizations, like the Norwegian Epilepsy Association (www.epilepsi.no), have been advocating, and supporting measures for, delivering and spreading information about epilepsy and different epilepsy-related issues. At the same time, network organizations, such as the Norwegian epilepsy network (www.epilepsinett.org), are aiming at delivering personalized information by including multidisciplinary specialists. Both strategies should be evaluated as to whether, either individually or together, they meet the patients' expectations and needs.

Unfortunately, everyday clinical care in the "normal" neurology service does not usually leave sufficient time to address all the individual challenges being faced by our patients. A specialized epilepsy centre, based on a comprehensive-care concept and with a dedicated multidisciplinary team, should be the backbone of a national epilepsy-care service, being both a referral centre for the difficult-to-treat patients and for patients with special needs. With such a service, the goal of patient-centred care for epilepsy patients could be within reach.

8. Reference List

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9. Papers

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ORIGINAL ARTICLE

Challenges in epilepsy—The perspective of Norwegian epilepsy patients

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Objectives: For most people with epilepsy (PWE), problems that are not directly related to seizures may constitute major challenges in everyday life. The purpose of this study was to determine the extent of these challenges and any risk factors for their occurrence among PWE in Norway, based on the patients' own perspective.

Materials and Methods: We used a web-based survey to ask PWE visiting the homepage of the Norwegian Epilepsy Association about different everyday challenges. A link to the survey was accessible via the members' homepage for a 4-month period during 2017.

Results: One thousand one hundred eighty-two PWE responded to the questionnaire. Although more than 40% of the cohort reported that they had been seizure free for at least 1 year, the majority reported that tiredness (71%), memory problems (70%), concentration problems (68%), headache or vertigo (51%), and feeling depressed (59%) continued to represent challenges. In addition, fear of being alone, sexual problems or difficulties in social settings were reported by about one-third of the patients. Reporting having these challenges was significantly associated with female gender, polytherapy, experiencing seizures during the previous 12 months and feeling blue or depressed.

Conclusions: The results of this study, reflecting a self-selected Norwegian population, provide insights into the challenges not directly associated with seizures that impact on the quality of life of PWE. The impacts of such challenges may be underestimated as components of the entire burden of epilepsy.

KEYWORDS
challenges, epilepsy, quality of life, treatment

1 | INTRODUCTION

Epilepsy is one of the most common neurological disorders with a prevalence of about 0.7%.[1-3] Medication with antiepileptic drugs (AEDs) is the cornerstone of epilepsy treatment, and almost 70% of patients become seizure free with appropriate AED therapy.[4] Nevertheless, even among seizure-free patients, the disease may have an adverse impact on daily activities and feeling of well-being. This is reflected in the definition of epilepsy proposed by International League Against Epilepsy (ILAE) in 2005, in which epilepsy was defined as an enduring predisposition to generate epileptic seizures and by neurobiological, cognitive, psychological and social consequences of the condition.[5] By including the consequences of the disease in their definition, ILAE emphasized that the consequences of epilepsy encompass far more than seizures.[5]

Due to the unpredictability of seizures, many patients have a constant fear of them occurring, even if there has been a prolonged period of being seizure free.[6] Moreover, some PWE may experience chronic adverse effects from the AED or other treatment, and the disorder may present obstacles to education, work, driving, establishing a family, and development and maintenance of social relationships. In addition, epilepsy may adversely affect an individual's self-esteem and self-image.[6-9]

Data on how people with epilepsy (PWE) perceive their daily challenges are available from various studies.[6,9-13] Questionnaires used to evaluate quality of life like the QOLIE-31 do to some degree also cover similar aspects.[14] They are often used in various populations.[15] The aim of this study was to use an online survey among a self-selected Norwegian population to determine the extent to which PWE experience challenges not directly related to seizures, but that impact on their quality of life. Awareness of this problem may contribute to more comprehensive patient care. It might help to consider patients' needs by providing information and measures for improved quality of life.

2 | MATERIAL AND METHODS

2.1 | Study population

This study was a collaboration between the National Epilepsy Centre in Norway and the Norwegian Epilepsy Association (NEA), the organization for patients with epilepsy in Norway. From 1 April to 5 September 2017, all visitors to NEA's homepage were guided to an online questionnaire regarding epilepsy and epilepsy-related challenges. Information about the survey and a link to it were also available via the Facebook site of NEA. The target population included all PWE who visited the website. Each participant could complete the questionnaire only once.

2.2 | The electronic questionnaire

The survey was anonymous. The questions were closed-ended and were decided following thorough discussion with experts at the National Epilepsy Centre and advisors at NEA. The questionnaire consisted of 42 questions. Completion of the questionnaire was estimated to take approximately 15-20 minutes.

Questions in the first part of the questionnaire were designed to elicit background information on the PWE (eg, gender, age group, being in a relationship) and also covered the patient's epilepsy (type, duration, age at first seizure and current seizures), treatment and follow-up. Respondents were then asked about whether quality of life was affected by a variety of different challenges. These included fear of having a seizure, fear of being alone, problems with concentration and/or memory, feeling down/blue and/or depressed, sexual problems, difficulties with physical activities, transport problems, physical symptoms such as drowsiness, headache, and/or vertigo and having difficulties with social interactions.

The answer options were based on a modified Likert scale, with the possibilities: "not at all"; "to a lesser degree"; "somewhat"; and "to a considerable extent." In further analysis of the questionnaires, the answers were dichotomized to either "not at all and to a lesser degree" vs "somewhat and to a considerable extent." This dichotomization was done according to the clinical relevance the different challenges pose to patients and physicians.

The study was approved by the Regional Ethics Committee (ref. no.:2017/563).

The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.3 | Statistical analyses

IBM SPSS Statistics version 25, release 25.0.0.1. (SPSS Inc) was used for statistical analyses. All *P*-values reported here are based on two-sided tests, with a significance level of 0.05. To test possible group differences, Pearson's chi-square tests were performed. Odds ratios for predictors for perceived challenges were estimated using bivariate and multivariate logistic regression analyses.

Variables tested were gender, use of polytherapy (two or more AEDs), above or below the mean age of the participants, known epilepsy aetiology, having tonic-clonic seizures, having been seizure free for the previous 12 months, feeling blue/down or depressed and being in a relationship. Feeling down/blue or depressed was not tested as a variable for fear of being alone, problems with concentration and/or memory and tiredness as these challenges may not to be independent.

3 | RESULTS

3.1 | General aspects

The NEA website recorded 48 249 visits during the study period, and 1182 PWE participated in the survey. Not all participants answered all questions. Demographic and clinical characteristics of the participants are summarized in Table 1. More than 40% of respondents reported being seizure free in the previous year.

The majority (>50%) of respondents reported that their quality of life was reduced, somewhat or to a considerable extent, by tiredness, memory and concentration problems, feeling down/blue and/or depressed, and by headaches and/or vertigo. About 30% reported fear of being alone, sexual problems and difficulties in social interactions (Figure 1). Responses to the main categories of symptoms and reports are presented below.

3.2 | Cognitive problems

Cognitive problems like memory (70%, n = 811/1157) and concentration (68%, n = 779/1153) problems were among the predominate challenges reported by a large majority of the patients (Figure 1).

TABLE 1 Demographic and clinical characteristics of the PWE participants (n = 1182) in the survey

Characteristics	Response to specific question n (%)	n (%)	Mean (range)
Age (y)	1156 (97.8)		41.8 (11-93)
Male gender	1150 (97.3)	372 (31.5)	
In a relationship	1157 (97.9)	697 (59.0)	
Living together with others	1146 (97.0)	782 (68.2)	
Age at first seizure (y)	1152 (97.5)		21.0 (1-80)
Number of years with epilepsy	1129 (95.5)		20.4 (0-72)
Seizure types	1180 (99.8)		
Focal, aware		346 (29.3)	
Focal, impaired awareness		425 (36.0)	
Tonic-clonic		719 (60.9)	
Absences		263 (22.3)	
PNES		55 (4.7)	
Other		86 (7.3)	
Do not know		108 (9.1)	
Seizure-free throughout the previous year	1179 (99.7)	479 (40.6)	
Seizure frequency	674 (57.0)		
Daily/weekly		211 (31.3)	
Monthly/more seldom		463 (68-7)	
Epilepsy aetiology	1174 (99.3)		
Known		543 (46.3)	
Unknown		631 (53.7)	
Monotherapy	1074 (90.9)	597 (55.6)	
Medical follow-up at least once per year	850 (71.9)	708 (83.3)	

Abbreviation: PNES, Psychogenic non-epileptic seizures.

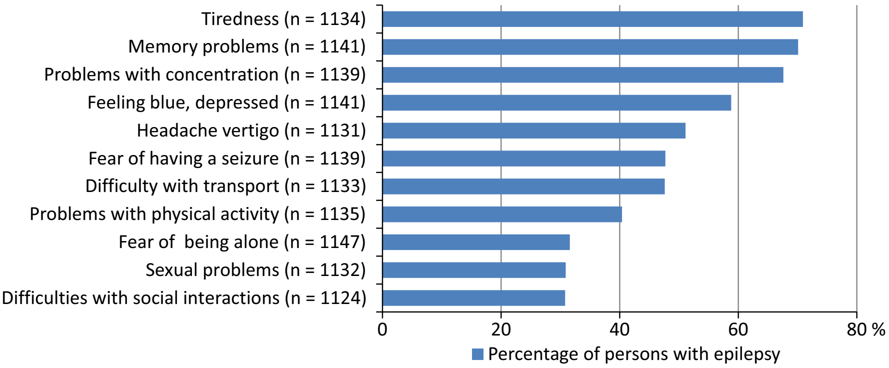

FIGURE 1 Challenges perceived by patients (n = 1183) somewhat/to a large degree in %

Multivariate logistic regression analysis indicated that female gender and not being seizure free were independent variables associated with perceived cognitive problems. Polytherapy was associated with memory problems, but not with concentration problems (Table 2).

3.3 | Medical problems

Participant reported medical problems like tiredness (71%, n = 826/1165) and headache or vertigo (51%, n = 590/1154) (Figure 1). Multivariate logistic regression analysis indicated that female gender and not being seizure free were among independent variables associated with perceived medical problems (Table 2).

3.4 | Psychosocial problems

Participants reported psychosocial problems like feeling blue or depressed (59%, n = 677/1151), fear of having a seizure (48%, n = 551/1156), sexual problems (31%, n = 352/1139), fear of being alone (32%, n = 362/1147) and difficulties in socializing with others

TABLE 2 Columns showing different independent variables as factors associated with reported perceived life challenges (dependent variables) shown in rows

Independent variables	Gender	Monotherapy vs polytherapy	Younger vs older than the mean age	Known vs unknown aetiology	Having vs not having tonic-clonic seizures (TCS)	Being vs not being seizure free the last 12 mo	Feeling blue, depressed	Being vs not being in a relationship
Dependent variables								
Fear of being alone	Female gender OR 1.599; CI: 1.169-2.188; *P* = 0.003		Younger than mean age OR 1.597; CI: 1.186-2.155; *P* = 0.002		Having TCS OR 1.429; CI: 1.060-1.925; *P* = 0.019			
Problems with concentration	Female gender OR 1.991; CI: 1.495-2.650; *P* < 0.001				Having TCS OR 1.384; CI: 1.043-1.837; *P* = 0.024	Not seizure free OR 1.470; CI: 1.108-1.952; *P* = 0.008		
Feeling blue, depressed	Female gender OR 1.339; CI: 1.016-1.765; *P* = 0.038	Polytherapy OR 1.408; CI: 1.077-1.841; *P* = 0.012			Having TCS OR 1.309; CI: 1.000-1.713; *P* = 0.050	Not seizure free OR 1.436; CI: 1.099-1.878; *P* = 0.008		
Memory problems	Female gender OR 1.906; CI: 1.421-2.558; *P* < 0.001	Polytherapy OR 1.546; CI: 1.151-2.076; *P* = 0.004				Not seizure free OR 1.790; CI: 1.340-2.390; *P* < 0.001		Being in a relationship OR 1.387; CI: 1.035-1.858; *P* = 0.028
Sexual problems			Older than mean age OR 1.744; CI: 1.247-2.438; *P* = 0.001	Known aetiology OR 1.463; CI: 1.095-1.955; *P* = 0.010			Feeling blue, depressed OR 2.973; CI: 2.174-4.066; *P* < 0.001	Being in a relationship OR 1.598; CI: 1.175-2.173; *P* = 0.003
Problems with physical activity					Having TCS OR 1329; CI: 1.002-1.762; *P* = 0.049	Not seizure free OR 1.450; CI: 1.094-1.922; *P* = 0.010	Feeling blue, depressed OR 2.926; CI: 2.210-3.872; *P* < 0.001	
Difficulty with transport		Polytherapy OR 1.511; CI: 1.152-1.983; *P* = 0.003				Not seizure free OR 2.281; CI: 1.728-3.011; *P* < 0.001	Feeling blue, depressed OR 2.096; CI: 1.599-2.747; *P* < 0.001	
Headache, vertigo	Female gender OR 2.229; CI: 1.674-2.967; *P* < 0.001					Not seizure free OR 1.404; CI: 1.066-1.849; *P* = 0.016	Feeling blue, depressed OR 2.354; CI: 1.797-3.083; *P* < 0.001	

(Continues)

TABLE 2 (Continued)

Independent variables	Gender	Monotherapy vs polytherapy	Younger vs older than the mean age	Known vs unknown aetiology	Having vs not having tonic-clonic seizures (TCS)	Being vs not being seizure free the last 12 mo	Feeling blue, depressed	Being vs not being in a relationship
Difficulties with social interactions		Polytherapy OR 1.384; CI: 1.027-1.866; *P* = 0.033					Feeling blue, depressed OR 4.733; CI: 3.386-6.616; *P* = 0.000	Not being in a relationship OR 1.457; CI: 1.078-1.972; *P* = 0.014
Fear of having a seizure	Female gender OR 1.687; CI: 1.264-2.251; *P* < 0.001		Younger than mean age OR 1.779; CI: 1.328-2.386; *P* < 0.001	Unknown aetiology OR 1.355; CI: 1.035-1.773; *P* = 0.027			Feeling blue, depressed OR 2.477; CI: 1.886-3.254; *P* < 0.001	
Tiredness	Female gender OR 1.608; CI: 1.197-2.160; *P* = 0.002	Polytherapy OR 1.376; CI: 1.024-1.850; *P* = 0.034	Younger than mean age OR 1.574; CI: 1.132-2.192; *P* = 0.007			Not seizure free OR 1.589; CI: 1.188-2.124; *P* = 0.002	▨	

🟩Significantly associated ($P < 0.05$). ☐Not significant ($P \geq 0.05$). ▨Variable not independent with regards to reported challenges (dependent variables).

(31%, n = 354/1149) (Figure 1). Multivariate logistic regression analysis indicated that feeling down/blue or depressed was strongly associated with all other psychosocial problems, apart from fear of being alone, which was not tested due to the possibility of overlap. Results regarding whether other variables were associated with psychosocial problems were inconsistent (Table 2).

3.5 | Physical limitations

Participants reported physical limitations like problems with transportation (48%, n = 550/1156) and difficulties with physical activities (40%, n = 466/1153) (Figure 1).

Multivariate logistic regression analysis indicated that feeling down/blue and/or depressed and not being seizure free were the independent variables associated with the different categories of physical limitations (Table 2).

4 | DISCUSSION

The main finding from this study was that most PWE in Norway experience several considerable everyday challenges that affect their quality of life. These challenges include cognitive and psychosocial problems, in addition to physical limitations. Our sample was recruited from persons visiting the homepage of the Norwegian Epilepsy Association, thus representing a selected group searching for information.

Although 40% of the participants in our cohort reported being seizure free for at least a year, most reported challenges with cognitive difficulties and, to a lesser extent, psychosocial problems and physical limitations. This information should serve as a reminder to healthcare providers working with PWE that the focus should not be solely on seizures, but that these additional challenges should also be included in healthcare plans.

4.1 | Cognitive problems

Cognitive problems, like memory problems and problems with concentration, were reported by about 70% of patients in this study, which is in line with results from other studies.

The high prevalence of memory problems in our study cohort is similar to that reported from other studies.[16] In a large community-based questionnaire survey among PWE in the United States (n = 1023), between 40% and 50% of respondents reported that epilepsy affected their ability to think clearly, to remember, to concentrate, and their mental and emotional well-being.[6] The possible causes of memory problems in PWE are complex and potentially multi-factorial. They may be related to dysfunction in the networks required for storage and or retrieval of memory,[17] to cerebral morphological changes, to psychiatric comorbidity and/or to the use of AEDs. We found that female gender was a risk factor for cognitive problems, even after controlling for increased psychiatric comorbidity. Polytherapy and not being seizure free indicates refractory epilepsy. We were surprised to find that in our cohort of PWE, memory problems were more often reported among those in a relationship than in those who stated that they were not in a relationship. One explanation could be that memory problems are more evident and noticeable if a person is in a relationship.

Cognitive and affective problems often overlap. Cognitive problems might be related to the epilepsy itself and its underlying aetiology, to AEDs, to psychiatric comorbidity or to a combination of these factors. For some patients, such problems may have a greater impact on their quality of life than the seizure themselves.[18,19] Several studies have shown that cognitive problems occur frequently (70%-80%) in PWE,[20] with recurring tonic-clonic seizures particularly associated with a decline in cognitive function.[20]

4.2 | Medical problems

In a review and meta-analysis on fatigue (extreme and persistent tiredness) in epilepsy, Kwon and co-workers found fatigue occurred in up to 50% of the patients.[21] In seven of the studies included in the meta-analysis, a significant correlation was found between depression and fatigue. In one study, seizure frequency was an associated risk factor.[21] In contrast with the results of our study, gender and number of AEDs being in use were not risk factors in that study.[21] However, we asked about tiredness, which is a less specific term than fatigue.

Results from studies on headache in the epilepsy population are contradictory.[22] In our study, there was a high prevalence of reported headache, particularly in those who were not seizure free.

4.3 | Psychosocial problems

A recent meta-analysis on depression in epilepsy, including 35 studies, reported a point prevalence of depression of 21.9%, with a higher occurrence of depression in females than males (26.4% vs 16.7%), as found in our study.[23] However, the studies are not entirely comparable, as the meta-analysis was based on studies of difficult-to-treat patients. Furthermore, in our study we asked the patients whether they felt depressed or down/blue and did not use a more objective evaluation of depressive symptoms.[24] It is likely that many of the patients reporting feeling depressed in our survey do not have clinical depression, and this probably explains the high occurrence (nearly 60%) in our sample.

Feeling depressed was also a risk factor for sexual problems, which were reported by 30% of the participants. This is a lower proportion than found in a previous study among drug-resistant patients with epilepsy (63%-75%).[25] As well as feeling depressed being associated with sexual problems, other significant associations with sexual problems were being above the mean age of the cohort, having a known epilepsy aetiology and being in a relationship. Both older age and feeling depressed are known to be associated with sexual problems in PWE.[26,27] As being in a relationship may provide patients with more opportunities for sexual activity, this may mean that any sexual problems are recognized more readily than in those living alone. In a study by Fisher et al,[6] 32% of the patients reported living with a constant fear of the next seizure; this is a lower proportion than in our sample (nearly 50%). Perhaps surprisingly, being seizure free did not reduce the fear of having a seizure. Feeling depressed could increase this fear, and female gender was also associated. Interestingly, Gaus et al[28] found a higher rate of seizure worry (afraid to have a seizure next month) in men (55%) vs women (40%) with epilepsy, while depressive symptoms were increased in women. The association to female gender which we found in our study with regard to feeling depressed and fear of being alone or fear of having a seizure is probably explained by the large overlap between depression and anxiety and the higher rate of affective psychiatric comorbidity among women.[29]

About one-third of our sample reported difficulties with social interactions. As we did not ask the patients to specify the difficulties, we may only speculate about the reasons. In a recent review by Steiger and Jokeit,[30] the authors emphasize that although social contacts have a positive effect on health, morbidity, and self-esteem and may counteract stress, PWE are also at a risk of reduced social cognitive skills and therefore may be more likely to experience communication and interpersonal difficulties. Overall, comorbid depression can be a strong barrier against many aspects of successful integration in society.[31]

Many studies have shown a higher rate of anxiety in the epilepsy population than in the general population.[32,33] Fear of being alone may be more related to feelings of depression, rather than anxiety as a defined clinical diagnosis. Studies about loneliness in epilepsy are rare. Fisher et al[6] found that 24% of PWE reported social stigma, fear of other people's reactions and feelings of shame and loneliness. Surprisingly, in our study feelings of loneliness were more often reported by younger PWE. This may partly reflect their unfulfilled expectations, also promoted via social media, that younger people are sociable, interactive and have a large social network.

4.4 | Physical limitations

In our study, around 40%-50% of the participants reported problems with physical activity. Two large population-based studies found that PWE had a similar level of physical activity as a reference population.[35,36] However, other studies have shown that PWE tend to be less physically active and have a poorer level of physical fitness than controls.[37,38] Fear of seizures is reported to be a risk factor for physical inactivity.[39] Driving regulations mean that not being seizure free is an obvious reason for transport problems among PWE.

4.5 | Limitations of the study

The percentage of seizure-free patients (40.7%) was lower than expected in a representative sample of the general Norwegian epilepsy population. This may indicate a bias towards patients with more severe epilepsy being included in the study. Even if our study is comparable to previous studies with a similar proportion of seizure-free patients,[6] a selection bias may nevertheless have had an impact on our results. It is reasonable to assume that patients with active epilepsy have a higher degree of challenges and entailed an overestimation of problems.

Further limitations are the lack of a reference population answering the same questionnaire, the known problems with the validity of questionnaires comprised of close-ended questions, and a potential selection bias towards persons with a greater need for information than the "average" PWE. During the study period, nearly 50 000 unique users visited the website of the Epilepsy Association. This is about 1% of Norway's population. An explanation may be that during this period, when searching for epilepsy on the Norwegian Google site, the homepage of the Epilepsy Association was the first to pop up. However, only 1182 PWE chose to participate in the study. We have no information about the PWE who chose not to participate, while interest in participating in the study and answering the questionnaire might reflect that the participant perceives that they have considerable challenges in everyday life.

5 | CONCLUSIONS

The results of this study, reflecting a self-selected Norwegian population, provide insights into an important and probably underestimated component of epileptology, namely the everyday challenges that are faced by PWE and are not directly related to seizures. We found that even seizure-free patients struggle with considerable psychosocial, cognitive and physical problems. Such challenges add to the burden of epilepsy and addressing these challenges and identifying coping strategies and ways of mitigating the challenges should be a natural part of a comprehensive epilepsy care.

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CONFLICT OF INTEREST

Oliver Henning has received speaker's honoraria from Eisai, UCB and Livanova. Cecilie Johannessen Landmark has received speaker's honoraria from Eisai and GW Pharma. Morten Ingvar Lossius has been giving talks and participated in expert panels for Eisai and UCB. Karl Otto Nakken has no conflict of interest to disclose.

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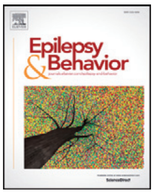

Sexual problems in people with refractory epilepsy

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ABSTRACT

Sexual dysfunction is an important but often neglected aspect of epilepsy. The objective of this study was to explore the prevalence and types of sexual problems in patients with epilepsy and compare the results with similar data obtained from a representative sample of the general population.

At the National Centre for Epilepsy in Norway, 171 of 227 consecutive adult inpatients and outpatients with epilepsy (response rate: 75.3%) and their neurologists participated in a questionnaire study about epilepsy and sexuality. The results were compared with data available from 594 adult Norwegians who had completed the same questionnaire.

Patients with epilepsy had a significantly higher prevalence of sexual problems (women: 75.3% vs. 12.0%; men: 63.3% vs. 9.6%). The most commonly reported problems (>30%) were reduced sexual desire, orgasm problems, erection problems, and vaginal dryness. The patients reported considerable dissatisfaction regarding sexual functioning. Significantly more sexual problems were found in patients of both sexes with reduced quality of life and in women with symptoms of depression. We found no significant association between sexual problems and age of epilepsy onset, type of epilepsy, or use of enzyme-inducing antiepileptic drugs. Whereas age at sexual debut did not differ between the patients with epilepsy and the general population, men with epilepsy had a lower number of partners during the last 12 months, and the proportion of women with a low frequency of intercourse was higher in the group with epilepsy.

In conclusion, sexual problems are significantly greater in Norwegian patients with epilepsy than in the general adult population. As no single epilepsy type or treatment could be identified as a specific predisposing factor, it seems likely that there are multiple causes underlying our results, including both organic and psychosocial factors.

1. Introduction

Since the early 1950s, it has been realized that epilepsy is associated with an increased rate of sexual dysfunction and sexual problems [1]. Nevertheless, in clinical epileptology, this subject is generally neglected. One definition of sexual dysfunction is 'discontent or dissatisfaction with any emotional, physical, or relational aspect of sexuality' [2]. It should be noted that sexual dysfunction is a medical diagnosis described both in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [3] and the World Health Organization's International Classification of Disorders (ICD-10) [4]. In order to receive a diagnosis of sexual dysfunction according to the DSM-5 system, the sexual problem must have been experienced for a period of at least six months and be associated with significant distress in the patient [3]. However, most of the scientific reports on the prevalence and incidence of sexual dysfunction are based on questionnaire surveys and self-reported sexual problems in the study population. For this reason, it is more correct to use the term 'sexual problems' (SP) than 'sexual dysfunction' when reporting such estimates.

Estimates of the occurrence of SP reported in the general population are variable, ranging from 10% to 52% in men and from 25% to 63% in women [5–8]. The variation in estimates probably reflects differences in definition of SP, variable study populations, and the use of different methods for assessing SP. In addition, different countries have cultural differences regarding sexuality [6] that might influence the results [7]. The occurrence of SP in people with epilepsy has usually been estimated as being greater than in the general population, although one study [9] reports a lower rate of SP in men with epilepsy than in controls. Other studies found increased rates of SP from 25% to 57% [10–13] or increased odds ratio from 2.13 to 17.33 [14,15] in men with epilepsy. The results of studies in women with epilepsy are often more descriptive and report a higher rate of women being less open to psychosexual stimulation [16] and having an increase in sexual hypoactivity [17]. In addition, some studies do not find differences in the reporting of SP between women

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with and without epilepsy [18], whereas others find rates of SP ranging from 23.1% to 51.7% [19,20].

The primary aim of this study was to compare the prevalence of different aspects of sexual functioning in a population with epilepsy with similar data obtained from a representative sample from the general population in Norway. A secondary aim was to identify predictors of SP in patients with epilepsy.

2. Materials and methods

2.1. Study population

Consecutive adult inpatients and outpatients attending the Norwegian National Centre for Epilepsy (SSE) were recruited to the study by their respective physicians. The inclusion criteria were that the patients had to have an epilepsy diagnosis, be 18 years of age or older, and be able to understand and complete a questionnaire. The study was approved by the regional and local ethics committee.

Initially, 227 patients with epilepsy agreed to participate in the study, of whom 178 (75.3%) completed the questionnaire. There was no difference regarding gender between those who completed the questionnaire and those who did not, but those who did not return the questionnaire were slightly older (mean age: 43.6 years vs. 41.5 years; difference not significant) and, although not statistically significant, had a higher frequency of generalized epilepsy (34.7% vs. 26.2%). Results from seven patients were subsequently excluded as they were considered not to have epilepsy. Thus, results from 171 patients were included in the analysis.

For comparison with the sample with epilepsy, data from a representative sample of 1093 Norwegians aged 15–70 years, obtained by the poll organization Markeds og Mediainstituttet (MMI), were made available to the research group [2,21]. The response rate in the MMI survey was 54.2% (593 persons). Data on the persons who dropped out in this survey are not available.

The sociodemographic characteristics in terms of gender, age categories, and cohabiting status of the two samples are presented in Table 1.

2.2. The questionnaire

In the questionnaire used in the group with epilepsy, the patients were asked about their epilepsy, their use of antiepileptic drugs (AEDs) and psychotropic drugs, SP, sexual behavior, sexual functioning, and sexual well-being.

Beck Depression Inventory (BDI) [22], a validated tool with good psychometric properties, and QOLIE 89 (Quality of Life in Epilepsy Inventory) were used to measure depression and quality of life in the patients with epilepsy. These inventories had been previously translated to Norwegian and validated [23,24]. For our study, we used only the scale ‘overall quality of life’ from the QOLIE 89, which consists of two items: a visual analogue scale (VAS) and a choice between five different quotations regarding quality of life during the previous 4 weeks. From the results of these, a score for quality of life (QoL) can be calculated ranging from 0 to 100. We dichotomized the variable, with cutoff at the median of all results.

Lastly, each participating patient's neurologist was asked to complete a short questionnaire to provide information about their patients' epilepsy, seizure types and frequency, and treatment with AEDs and psychotropic drugs.

2.3. Operationalization of the sexuality questions

In order to define the measurement of sexual functioning, the following aspects were specifically investigated:

1) Sexual problems: This was investigated with the following question: “Have you ever had sexual problems? What kind of problems?” The possible answers are shown in Table 3, with the addition of ‘no problems’. In the population with epilepsy, an additional question was whether the person had experienced SP during the previous month.
2) Satisfaction with sex life: This was investigated with the following question: “All things considered, how satisfied are you with your sex life?” The response alternatives were the following: ‘very satisfied’, ‘quite satisfied’, ‘neither satisfied nor dissatisfied’, ‘somewhat dissatisfied’, and ‘dissatisfied’.
3) Other sexual variables: Age at first sexual intercourse and the number of sexual partners during the last 12 months were answered as continuous variables. Frequency of sexual intercourse during the last 4 weeks had the following alternative responses: ‘none’, ‘once’, ‘2 to 4 times’, ‘5 to 10 times’, and ‘11 times or more’.
4) Satisfaction with the frequency of sexual intercourse: This was investigated with the following question: “How satisfied are you with the frequency of sexual encounters?” The response alternatives were the following: ‘too often’, ‘satisfactory’, and ‘too infrequent’.

2.4. Statistics

Group differences were tested by chi-square tests and t-tests for categorical and continuous variables, respectively. Odds ratios (ORs) for SP were estimated by logistic regression analysis, with SP as the dependent variable and QoL and gender as the independent variables. The results of multivariate analysis are presented as ORs with 95% confidence intervals and p-values. All tests were two-sided and were performed at a 5% significance level. The Statistical Package for Social Sciences (SPSS version 21) was used.

3. Results

The clinical characteristics of the group with epilepsy are summarized in Table 2. The prevalence of SP was significantly higher in the patients with epilepsy than in the general population: 63.3% vs. 9.6% in men ($p < 0.001$) and 75.3% vs. 12.0% in women ($p < 0.001$), respectively (Fig. 1). Reporting of nearly all types of SP was significantly higher in the

Table 1
Gender and age distribution as well as partnership status in the two samples.

	Group with epilepsy (N = 171) n (%)	General population (N = 593) n (%)
Female	83 (48.6)	332 (56.1)[b]
Cohabitating	90 (55.8)[a]	355 (59.9)
<40 years of age	79 (46.2)	334 (56.3)
40–49 years of age	53 (31)	112 (18.9)
>50 years of age	39 (22.8)	147 (24.8)

No significant differences between the groups.

[a] 161/171 answered.

[b] 592/593 answered.

Table 2
Clinical characteristics of the group with epilepsy (N = 171).

Epilepsy characteristics	n (%)
Generalized epilepsy	45 (26.2)
Focal epilepsy	126 (73.8)
AED monotherapy	68 (39.8)
3 or more AEDs	22 (12.6)
Epilepsy onset <10 years of age	44 (26.9)[a]
Use of enzyme-inducing AEDs	48 (28.0)
BDI > 14	44 (25.7)
QoL > 5	124 (73.4)[b]

AED: antiepileptic drug, BDI: Beck Depression Inventory, QoL: quality of life.

[a] 165/171 answered.

[b] 169/171 answered.

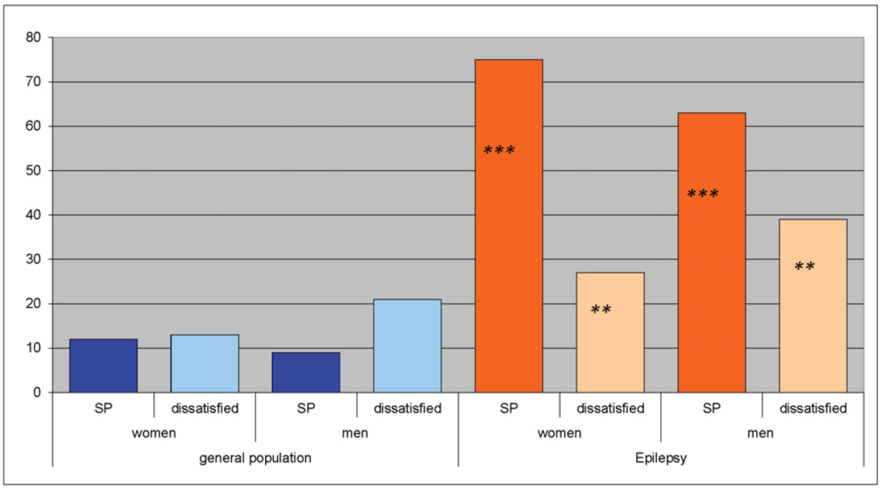

Fig. 1. Prevalence of sexual problems (SP) and dissatisfaction with sex life (%) in the general population and in the patients with epilepsy. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$.

group with epilepsy than in the general population (Table 3). Noteworthy are the high rates of reduced sexual desire and problems with orgasm reported in the sample with epilepsy by both sexes and high rates of vaginal dryness and pain during intercourse reported by women. In the group with epilepsy, SP within the last month were reported by 57.1% of the women and 52.9% of the men.

In the general population, 13% of the women and 21% of the men reported being dissatisfied or somewhat dissatisfied with their sex lives. Among the respondents in the group with epilepsy, the corresponding figures were 27.4% for women ($p = 0.004$) and 38.8% for men ($p = 0.002$) (Fig. 1).

In the total population with epilepsy, a significant increase in lifetime or current SP was found in patients scoring <66.25 on the overall QoL index ($p < 0.05$). For women, we also found a significant increase in lifetime or current SP in patients scoring higher than 14 on the BDI. There were no significant associations between those experiencing SP and specific types of epilepsy, age at epilepsy debut, usage of enzyme-inducing AEDs, usage of selective serotonin reuptake inhibitors (SSRI), or whether the patient was in a relationship or single (Supplementary data).

The OR for association between low QoL and SP was calculated in a statistical regression model, and an OR of 2.96 (confidence interval (CI): 1.55–5.67) was derived for low QoL in patients with current SP and an OR of 2.70 (CI: 1.30–5.59) for low QoL in patients with lifetime SP. Gender had no significant influence.

Table 3
Type of sexual dysfunction in women and men in the two populations.

	Group with epilepsy (N = 171)		General population (N = 593)	
	Women n (%)	Men n (%)	Women n (%)	Men n (%)
Sexual dysfunction	64 (75.3)	57 (63.3)	40 (12.0)***	25 (9.6)***
Reduced sexual desire	44 (51.8)	23 (25.6)	21 (6.3)***	4 (1.5)***
Problems with orgasm	30 (35.3)	12 (13.3)	14 (4.2)***	1 (0.4)***
Premature ejaculation	0 (0)	14 (15.6)	1 (0.3)	9 (3.5)***
Late ejaculation	3 (3.5)	5 (5.6)	2 (0.6)	0 (0)***
Pain during intercourse	23 (27.1)	1 (1.1)	16 (4.8)***	4 (1.5)
Erectile dysfunction	–	31 (34.4)		6 (2.3)***
Vaginal dryness	26 (30.6)	–	0 (0)***	–
Feeling sexually deviant	7 (8.2)	5 (5.6)	2 (0.6)***	4 (1.5)
Other	10 (11.8)	3 (3.3)	8 (2.4)**	3 (1.2)

p-Values calculated within the same gender between the general population and the group with epilepsy.

*** $p < 0.001$.

** $p < 0.01$.

* $p < 0.05$.

Table 4 shows that the age of sexual debut did not differ significantly between the groups. The number of sexual partners during the last 12 months was significantly lower in males with epilepsy than in the general population (Table 4).

Although the proportion of women with a lower frequency of sexual intercourse during the last 4 weeks was significantly higher in those with epilepsy, there were no differences in being satisfied with the frequency of intercourse between the two groups (Table 4).

Physicians reported having asked 27 (16%) of the patients about sexual functioning. Among these 27 patients, 18 (66%) were reported to have complained about SP, and nine had not. From the patients' medical records, it was found that 2 of these 9 patients (22.2%) who had not complained about SP when asked by their physician had nevertheless reported SP when completing the questionnaire.

4. Discussion

4.1. Prevalence of sexual problems

In this study, we found a significantly higher lifetime prevalence of SP in the patients with epilepsy than in the general population. This applied to different types of SP, such as reduced sexual desire, problems with orgasm, premature ejaculation, erectile dysfunction, pain during intercourse, and vaginal dryness.

Our results are similar to those from previous studies, although the rate of reported SP varies considerably (8–80%) [9,12–16,25–28]. However, there are also reports of no increased rates, or even lower rates, of SP in women with epilepsy [28], particularly among those using lamotrigine and levetiracetam [18,29].

4.2. Types of sexual problems

Among women with epilepsy, the most prevalent problem was reduced sexual desire, followed by problems with orgasm, vaginal dryness, and pain during intercourse. The most frequently reported problems among the men were erectile dysfunction, followed by reduced sexual desire, premature ejaculation, and problems with orgasm.

Calabro et al. [13] compared 30 male controls (SP reported by 11/30) with 30 male outpatients with epilepsy (SP reported by 21/30); thus, the rate of SP in the patient group was higher by 56%. This is in agreement with our results. The dominating problems in Calabro's cohort were delayed ejaculation and reduced desire. However, the sample was small and probably underpowered. Nikoobakht et al. [11] reported erectile dysfunction among 42.5% of 80 men with epilepsy. There was, however, no control group in this study.

Table 4
Differences in sexual debut age, number of partners, frequency of intercourse, and satisfaction-with-intercourse frequency between the general population and population with epilepsy.***

	Group with epilepsy (N = 171)		General population (N = 593)	
	Women mean (SD)	Men mean (SD)	Women mean (SD)	Men mean (SD)
Age at sexual debut (years)	17.51 (2.94)	18.55 (4.95)	17.33 (S3.77)	17.93 (4.25)
Number of sexual partners during previous 12 months	1.37 (1.37)	1.06 (1.07)	1.34 (2.20)	1.92 (4.12)**
Frequency of intercourse during previous 4 weeks	Women n (%)	Men n (%)	Women n (%)	Men n (%)
None or once	37 (47.4)	33 (41.2)	107 (32.9)*	99 (38.7)
Twice or more	41 (52.6)	47 (58.8)	218 (67.1)*	157 (61.3)
Satisfaction with the frequency of intercourse	Women n (%)	Men n (%)	Women n (%)	Men n (%)
Too infrequent	28 (39.4)	43 (54.4)	212 (38.9)	125 (49.2)
Satisfying	42 (59.2)	32 (40.5)	184 (59.2)	127 (50.0)
Too often	1 (1.4)	4 (5.1)	6 (1.9)	2 (0.8)

*** $p < 0.001$.
** $p < 0.01$.
* $p < 0.05$.

In accordance with our results, Zelena et al. [19] found a prevalence of SP in 52% of 29 women with epilepsy. Insufficient lubrication (34.5%) and lack of desire (28%) were the main problems in that cohort. Morrell and Guldner [30] reported increased dyspareunia in combination with insufficient arousal in a cohort of women with epilepsy. This finding was particularly prominent in those with focal epilepsy, suggesting a possible physiological deficit.

4.3. Overall satisfaction with sexual functioning

Among the general population, the number of persons reporting dissatisfaction with their sex lives exceeded the number reporting SP; that is, some persons who did not report SP were, nevertheless, not satisfied with their sex lives. In our cohort of patients with epilepsy, the opposite picture emerged with the patients reporting more satisfaction with their sex lives than might be expected from the rate of SP. Whereas the rate for SP in the group with epilepsy was six times higher than the rate in the sample from the general population, the rate of dissatisfaction was only doubled. The definition of 'satisfaction' has varied among previous studies [18], which means that comparison between studies is challenging. It is possible that people with epilepsy may adapt to, and accept, a state of SP, and/or they may have lower expectations regarding their sex lives.

4.4. Quality of life and depression

Quality of life is a multifaceted concept that incorporates psychosocial, economic, and medical factors. We used only the scale of overall quality of life that had been calculated from two items in order to assess the quality of life among participants in our study. This has been shown to provide a relatively good reflection of even extensive questionnaires [23]. Patients with epilepsy with SP reported a low quality of life, but the direction of the association (whether SP cause the low quality of life or whether the low quality of life leads to SP) cannot be determined.

Among the women with epilepsy, we found a significant association between symptoms of depression and SP. A similar but nonsignificant trend was also found in men. These results are in agreement with those from some prior studies [13,26,27,31]. Jensen et al. [9] found a nonsignificant increase in scores in the Brief Symptom Inventory (BSI) in women with epilepsy and SP but not in men, possibly due to the small sample size. Zelena et al. [19] found only depression, as assessed by the BDI, being significantly associated with reduced sexual function in women with epilepsy. Sexual problems were not associated with a specific seizure type, lateralization in focal epilepsy, seizure frequency, or hormonal status.

Sexual problems are known to be associated with depression [32]. As people with epilepsy have a higher prevalence of depression [33], an increased rate of SP is to be expected. Although depression cannot fully explain the greater rate of SP identified in people with epilepsy, it might be an important contributing factor [26].

4.5. Age at sexual debut and number of partners

We found no significant differences between patients with epilepsy and controls regarding age of sexual debut and number of partners during the last 12 months. de Vincentiis et al. [28] reported sexual debut at the age of 14.6 years in patients with epilepsy vs. 15.1 years in controls among Brazilian female teenagers, but this difference was not significant. Similarly, Lossius et al. found a lower age of sexual debut among Norwegian pupils with epilepsy compared with controls and speculated that this finding might be due to more risk-seeking behavior among those with epilepsy [34].

Studies comparable with ours that assess the number of sexual partners are apparently lacking. Interestingly, while there was nearly no difference in number of sexual partners among women regardless of epilepsy status, men with epilepsy had significantly fewer sexual partners during the previous 12 months. Thus, the ability of women with epilepsy to find sexual partners does not seem to differ significantly from the general population. However, men with epilepsy seem to differ from the general population in this respect and might experience more problems in finding sexual partners than men in the general population.

4.6. Frequency of sexual intercourse

While there was a trend towards a lower frequency of sexual intercourse among patients with epilepsy compared with the population without epilepsy, the difference was only significant for women. There are few studies addressing this topic. Reis et al. [15] found that men with epilepsy treated with carbamazepine had less sexual intercourse than controls. de Vincentiis et al. [28] found no difference in frequency of sexual intercourse between female teenagers with epilepsy and controls, but only 10 sexually active patients were included in this study, and those who were sexually inactive may have been excluded. Bergen et al. [17] found that, in a group of women with epilepsy, about 20% were sexually inactive.

The results of these studies should be interpreted with caution because of the low number of patients with epilepsy. However, it appears that, despite people with epilepsy reporting a high degree of SP and dissatisfaction with their sex lives and that some women with epilepsy have a lower frequency of sexual intercourse, the majority have sexual intercourse at a frequency that is comparable with the general population and that most consider this frequency to be satisfactory.

4.7. Potential explanations of our findings

We did not find an association between SP and a particular type of epilepsy. However, results from previous studies indicate that hyposexuality is associated with temporal lobe epilepsy, particularly in those with amygdala involvement [35,36]. Surprisingly, we did not find a correlation between SP and use of enzyme-inducing AEDs. Such drugs reduce free testosterone by increasing sex-hormone-binding globulin and thus lower libido. However, the relationship between libido and testosterone levels is not linear, and some patients using these drugs might experience compromised sexual function, whereas others might not [37]. This could explain why a clear correlation was not apparent in the data from our study.

A combination of several mechanisms probably underlies the relatively frequent occurrence of SP in patients with epilepsy. The epilepsy etiology, seizures, drug treatment, and psychosocial factors, including depression, sexual anxiety, and stigma associated with epilepsy, may all contribute.

4.8. A neglected issue during the consultation

Only 16% of the patients in our study were asked about sexual functioning, according to their physicians. This number might be even lower during regular consultations, as informing the patients about the survey could have triggered discussion about sexual functioning. Nevertheless, our findings support the results from previous studies [17,38]. Thus, the possibility that epilepsy and AED use may decrease libido might not be understood or considered of relevance by many clinicians [38].

We have no information regarding why the clinicians associated with our study so rarely discussed this subject with their patients. Indeed, it is reported that patients usually welcome questions about their sexuality and rarely decline discussion of the subject [27].

4.9. Limitations of the study

Questionnaires have the disadvantage that misunderstandings or unintended scoring cannot be corrected for by using follow-up questions, as can be incorporated in an interview. However, as sexuality may be a sensitive subject to discuss openly, a questionnaire might give more correct data than an interview. Use of a large control group strengthens the findings of our study.

Our study population was recruited from a tertiary epilepsy center. This implies selection of patients with difficult-to-treat epilepsy. Thus, our results may not be representative of the general population with epilepsy of Norway.

The sample from the general population was slightly younger than the sample with epilepsy, but the difference was not significant.

Another limitation is that the sample from the general population is derived from a study that was performed in 1997, about 10 years before the data from the group with epilepsy were collected. It is possible that, during the intervening ten years, opinion on, or the prevalence of, SP within the Norwegian population might have changed and thereby influenced the results of our study. However, there is no evidence to suggest that this is likely to be the case.

Factors like quality of life, symptoms for depression, and different aspects of sexuality like libido or satisfaction with sex life are relatively subjective and interrelated, and therefore, it may be inappropriate to treat them as independent variables. However, associations between these variables are also considered within the context of the study.

The questionnaire for the physicians did require a diagnosis of either focal or generalized epilepsy. Unclassified epilepsy was not an option, which could have forced physicians to choose either focal or generalized, even in cases where there was doubt.

5. Conclusions

The results from our study indicate that there is a considerably higher rate of SP in patients with epilepsy than in the general population. The most commonly reported SP for patients with epilepsy are reduced sexual desire, problems with orgasm (both sexes), vaginal dryness, pain during intercourse (females), erectile dysfunction, and premature ejaculation (males). Nevertheless, the higher rate of SP in the group with epilepsy is not reflected in the extent of dissatisfaction with sexual functioning among this group.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2016.05.038.

Conflict of interest

The authors have no conflict of interest or any financial disclosures, sponsors or grants regarding this manuscript.

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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Sexual function in people with epilepsy: Similarities and differences with the general population

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Abstract

Objective: The potential impact of epilepsy on sexual function is important for patient welfare, but often neglected. This study explored the occurrences of different sexual problems in patients with both well-controlled and mostly refractory epilepsy, and compared these with equivalent information from the general population.

Methods: Between 2015 and 2017, a total of 221 adult inpatients and outpatients, mostly with intractable epilepsy, at the National Centre for Epilepsy in Norway, and 78 outpatients with well-controlled epilepsy at Lillehammer hospital participated in a questionnaire survey on sexual function. Information on the individual patient's epilepsy was collected. The results were compared with equivalent data on sexual function from 1671 adult Norwegians in the general population.

Results: Patients with epilepsy reported a significantly higher frequency of problems with orgasm, dyspareunia, erectile dysfunction, and feelings of sexual deviance. However, reduced sexual desire, premature ejaculation/climax, and vaginal dryness occurred at similar frequencies in the general population. After controlling for gender, we found no significant association between sexual problems and seizure control or use of enzyme-inducing antiepileptic drugs. In both genders, feelings of sexual deviance were associated with lower quality of life. Fewer patients with epilepsy were satisfied with their sex lives. The perception of sex as an important part of daily life was similar among women with epilepsy and women from the general population, whereas significantly fewer men with epilepsy than men in the general population reported that sex was an important part of their daily lives. Women with mostly refractory epilepsy reported asking for help with their sexual problems significantly more often than women in the other groups.

Significance: Some sexual problems occur significantly more often in patients with epilepsy than in the general population and feelings of sexual deviancy occur more frequently. No epilepsy-related factors could be identified as specific predictors.

KEYWORDS

comorbidity, epilepsy, quality of life, sexual dysfunction, sexual problems

1 | INTRODUCTION

Since the early 1950s, epilepsy has been reported to be associated with an increased rate of sexual problems.[1] However, this subject is generally neglected among neurologists.[2] Estimates of the occurrence of sexual dysfunction reported in the general population are highly variable, ranging from 10% to 52% in men and from 25% to 63% in women.[3–5] This variation probably reflects differences in how sexual dysfunction has been defined, different study populations, and different methods for assessing such problems. In addition, there are cultural variations regarding sexuality among different world regions that might also influence the results.[3,6]

Data on sexual problems in people with epilepsy are limited. Although two studies reported reduced rate of sexual problems, or even better sexual functioning, in people with epilepsy,[7,8] nevertheless, there seems to be agreement that sexual problems occur more frequently in epilepsy patients than in the general population.[9–13] Two further studies report no significant differences regarding sexual functioning between people with epilepsy and controls.[14,15]

We have previously shown a significantly higher prevalence of sexual problems in women with epilepsy than in controls (75% vs 12%), and in men with epilepsy than in controls (63% vs 10%).[11] The large differences found in that study were probably due to selection bias, as the study included patients with severe epilepsy and a slightly different way of assessing sexual problems.

The aim of the current study was to determine the prevalence of sexual problems and sexual satisfaction in three different groups of adults: (a) patients from a tertiary referral epilepsy center with *mostly* refractory epilepsy; (b) patients with well-controlled seizures; and (c) a control group from the general Norwegian population.

In addition, we investigated whether particular epilepsy-related risk factors were associated with any of the sexual problems considered in this study.

2 | METHODS

2.1 | Study population

Between 2015 and 2017, epilepsy patients were recruited to this study from two locations. These were the following. (a) The Norwegian National Epilepsy Center in Sandvika, Norway; this is a tertiary national referral center, and patients recruited from here tend more often to have refractory epilepsy. (b) The outpatient clinic at Lillehammer hospital; this is a second-line neurology specialist service, and patients recruited from here tend to have well-controlled epilepsy. Inclusion criteria were that the patients had received an epilepsy diagnosis, that they were at least 18 years of age, and that they were capable of understanding and completing a questionnaire.

Key Points

- Various sexual problems were more prevalent in patients with epilepsy than in the general population
- Sexual desire in patients with epilepsy was similar to that in the general population
- The occurrence of sexual problems is not associated with seizure control and antiepileptic drug treatment
- Patients with refractory epilepsy asked more often for professional help to deal with sexual problems than patients with well-controlled epilepsy

Because the study was anonymous, approval from the regional ethical committee was not required (ref. no.: 2014/1011A).

For comparison with the two epilepsy cohorts (mostly refractory epilepsy and well-controlled epilepsy), data from a representative sample of 4285 Norwegians 18-67 years of age, were obtained from the market-research company, Synovate.[16]

2.2 | The questionnaire

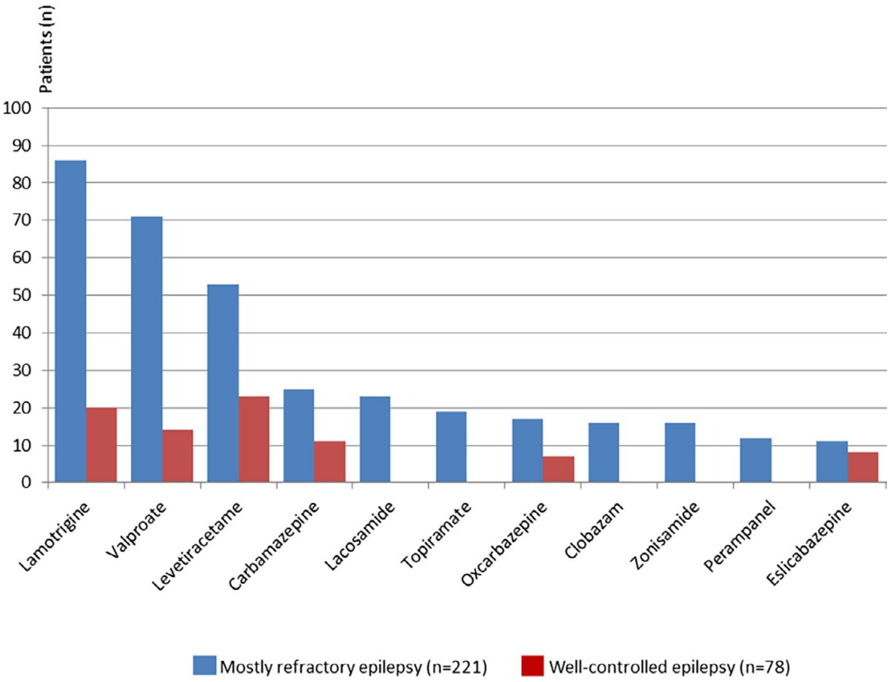
The patients answered the same questions that had been included in the Synovate questionnaire for the general population regarding sociodemographic characteristics (gender, age, level of education), and also regarding sex life (partnership, sexual problems, sexual behavior, and sexual functioning). In addition, the patients scored their perceived quality of life (QoL) on a visual analog scale and were also asked supplementary questions regarding their epilepsy (seizure frequency, use of antiepileptic drugs [AEDs]; carbamazepine, phenobarbital, phenytoin, and primidone were defined as enzyme-inducing AEDs.[17] In the questionnaire patients also reported symptoms for depression and adverse events.

A score over 14 in the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)[18] was used to detect depression. The adverse events profile (AEP)[19] was used to describe the degree of perceived adverse events; a score over 44 was considered an adverse effects overload. Three or more empty rows in the AEP led to exclusion of the answer for calculation of adverse effect burden.

2.3 | Operationalization of the sexuality questions

Information on *sexual problems* was obtained from responses to the question: “Have you experienced one of the following problems?” The eight problems listed are shown in Figure 1. The response categories for each problem listed

FIGURE 1 Reported use of antiepileptic drugs (n) by patients with mostly refractory epilepsy and patients with well-controlled epilepsy. Only drugs used by at least 5% of patients are shown



were: 1 = "Never," 2 = "rarely," 3 = "often," 4 = "nearly all the time," and 5 = "always." The response variables were stratified into 1 = "never or rarely" (categories 1 and 2), and 2 = "often" (categories 3-5).

Information on *satisfaction with sex life* was obtained from responses to the question: "All things considered, how satisfied are you with your sex life?" The response categories were: 1 = "very satisfied," 2 = "quite satisfied," 3 = "neither satisfied nor dissatisfied," 4 = "slightly dissatisfied," and 5 = "very dissatisfied." The response variables were stratified into 1 = "satisfied" (categories 1 and 2) and 2 = "dissatisfied" (categories 4 and 5); response category 3 was not included in further analysis.

Information on *the importance of sex in daily life* was obtained from responses to the question: "How important do you consider sex to be as a part of your overall life?" The response categories were: 1 = "very important," 2 = "quite important," 3 = "neither important nor unimportant," 4 = "slightly unimportant," and 5 = "not important at all." The response variables were stratified into 1 = "important" (previous categories 1 and 2) and 2 = "unimportant" (previous categories 4 and 5); response category 3 was not included in further analysis.

Information on *help-seeking behavior regarding sexual problems* was obtained from responses to the question "Have you contacted health-care providers for help regarding sexual problems?" The response categories were: "yes" or "no."

2.4 | Statistics

IBM SPSS Statistics, version 25, release 25.0.0.1. (SPSS Inc) was used for statistical analyses. All *P*-values reported here are based on two-sided tests, with a significance level of .05. To test possible group differences, Pearson's chi-square tests or independent sample *t*-tests were performed. Variables like gender; above or below the mean age of the participants; having been seizure-free for the previous 12 months; AEP score of 45 or more; NDDI-E score of 15 or more and QoL under the mean score; use of lamotrigine, levetiracetam, or valproate; and use of enzyme-inducing AED were tested using Pearson's chi-square test. We applied Hosmer's step-down procedure, which means that variables significant at the 0.25 level were included in the multivariate logistic regression model.[20] Odds ratios for factors associated with perceived sexual dysfunction were estimated using bivariate and multivariate logistic regression analysis with 95% confidence intervals.

3 | RESULTS

3.1 | Characteristics of survey participants

Of 237 patients invited to the study at the National Epilepsy Center (cohort with mostly refractory epilepsy), 221 (93.2%) participated, and of 81 patients invited to the study at Lillehammer hospital (cohort with well-controlled epilepsy) 78 (96.3%) participated. The response rate in the general population survey by Synovate was 39% (1671 persons of 4285 invited to participate).

Data on those who chose not to complete the surveys are not available.

An overview of the sociodemographic characteristics of the three groups of respondents (mostly refractory epilepsy cohort, well-controlled epilepsy cohort, general population) is presented in Table 1.

TABLE 1 Overview of the sociodemographic characteristics of the three groups of respondents

	Mostly refractory epilepsy patients (n = 221)	**Well-controlled epilepsy patients (n = 78)**	**General population (n = 1671)**
Gender			
Female, n (%)	130 (58.8)[‡]	47 (60.3)[†]	776 (46.4)
Male, n (%)	91 (41.2)[‡]	31 (39.7)[†]	895 (53.6)
Age,			
mean (SD; min.-max.)	39.1 (13.5; 18-72)[a,**,†]	43.3 (16.7; 18-77)[§]	42.6 (12.2; 18-67)
Level of education			
University, n (%)	80 (36.5)[b,*,§]	17 (21.8)[§]	971 (58.1)
Below university, n (%)	139 (63.9)[b,*,§]	61 (78.2)[§]	700 (41.9)
Partnership			
Cohabitating or in a relationship, n (%)	142 (56.1)[c,§]	54 (69.2)[†]	1316 (78.8)
Single, n (%)	73 (34.0)[c,§]	24 (30.8)[†]	355 (21.2)
Have had intercourse, n (%)	198 (90.8)[a,§]	68 (93.2)[e,†]	1620 (97.6)[g]
Age of sexual debut,mean (SD; min.-max.)	17.7 (3.2; 12-36)[d]	17.9 (3.4; 13-33)[f]	18.0 (3.6; 7-65)[h]

Notes: P-values calculated between the group from the National Epilepsy Center and the group from the second-line service (Pearson's chi-square or independent samples *t*-test).

P-values describe statistically significant differences between the general population and the epilepsy cohorts using Pearson's chi-square or independent samples *t*-test.

[a] 218/221 answered.
[b] 219/221 answered.
[c] 215/221 answered.
[d] 192/221 answered.
[e] 73/78 answered.
[f] 64/78 answered.
[g] 1659/1671 answered.
[h] 1602/1671 answered.
*$P < .05$.
**$P < .01$.
[†] $P < .05$.
[‡] $P < .01$.
[§] $P < .001$.

Clinical characteristics of both epilepsy cohorts regarding seizure freedom, seizure frequency, use of enzyme-inducing AED, NDDI-E score, AEP score, and QoL are shown in Table 2.

Use of number of different AED used and AED used by at least 5% in the two populations with epilepsy are shown in Table 3 and Figure 1.

As expected, seizure freedom was more common among the more refractory epilepsy patients than in well-controlled epilepsy patients (60% vs 24%). Moreover, the cohort with well-controlled epilepsy patients reported a better quality of life (higher rate of QoL over the mean) than the more refractory epilepsy patients (Table 2).

3.2 | Sexual problems

The following sexual problems were reported significantly more often by the patients with epilepsy than by respondents from the general population: problems with orgasm and erectile dysfunction in men, pain during intercourse in women, late ejaculation/climax, and feeling sexually deviant in both women and men (Figure 2). There were no significant differences between the two epilepsy cohorts regarding prevalence and types of sexual problems. For both genders, significantly fewer patients with epilepsy were satisfied with their sex life compared with satisfaction among the general population, and significantly fewer men with epilepsy reported that sex was an important part of their daily life. Patients from the cohort with more refractory epilepsy reported asking for help with sexual problems more frequently, although the difference was only statistically significant for women (Figure 3).

3.3 | Risk factors associated with sexual dysfunction

Multivariate logistic regression analysis indicated that patients age over the mean age (OR 2.744, CI 1.308-5.757;

TABLE 2 Clinical characteristics of the epilepsy groups (n = 299)

Epilepsy characteristics	Mostly refractory epilepsy patients (n = 221) n (%)	Well-controlled epilepsy patients (n = 78) n (%)
Seizure-free during previous 12 mo	51 (24.5)[e,***]	42 (60.0)[i]
Enzyme-inducing AEDs[a]	30 (13.6)	13 (16.7)
NDDI-E <15[b]	156 (73.2)[f]	55 (82.1)[j]
AEP >44[c]	77 (42.5)[g]	19 (30.3)[k]
QoL over mean (6.7)[d]	104 (49.5)[h,*]	46 (63.9)[l]

P-values describe statistically significant differences between the two groups of epilepsy patients.

[a] Enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, phenobarbital, primidone).

[b] Neurological Disorders Depression Inventory for Epilepsy.

[c] Adverse events profile.

[d] Quality of life.

[e] 208/221 answered.

[f] 213/221 answered.

[g] 181/221 answered.

[h] 210/221 answered.

[i] 70/78 answered.

[j] 67/78 answered.

[k] 63/78 answered.

[l] 72/78 answered.

*$P < .05$.

***$P < .001$.

P = .008) and an NDDI-E score over 14 (OR 3.904, CI 1.692-9.009; P = .001) were significant independent variables that were associated with reduced sexual desire in women with epilepsy. In men with epilepsy, QoL under mean (OR 3.484, CI 1.161-10.417; P = .026) and being in a relationship (OR 3.791, CI 1.018-13.586; P = .047) were significant independent variables associated with reduced sexual desire. Multivariate logistic regression analysis indicated that patients age over the mean age (OR 2.762, CI 1.122-6.802; P = .027) and a QoL under mean (OR 2.777, CI 1.027-7.518; P = .044) were significant independent variables associated with feelings of sexual deviance in women with epilepsy.

Being seizure-free during the previous 12 months; use of enzyme-inducing AEDs; use of lamotrigine, levetiracetam, or valproate; a high burden of adverse events (AEP > 44); and level of education were not significantly correlated with any of the types of sexual dysfunction investigated here.

4 | DISCUSSION

The results from our study support previous findings indicating that patients with epilepsy have a significantly higher frequency of sexual problems than adults in the general population.[10–13,21] Independent of seizure control, significantly more respondents in the epilepsy groups reported problems with orgasm, dyspareunia, late ejaculation/climax, erectile dysfunction, and feelings of sexual deviance. However, the occurrence of problems with premature ejaculation/climax and vaginal lubrication was similar in the epilepsy patients to that of the general population. Surprisingly and in contrast to other studies,[10,11,15] we also found that the proportion of people reporting a lack in sexual desire in epilepsy patients and in the general population was similar.

TABLE 3 Number of antiepileptic drugs in use in epilepsy patients

	Mostly refractory epilepsy patients (n = 221) n (%)	Well-controlled epilepsy patients (n = 78) n (%)
Number of antiepileptic drugs in use:		
0	20 (9.0)	9 (11.5)
1	75 (33.9)	44 (56.4)
2	92 (41.6)	22 (28.2)
3	31 (14.0)	3 (3.8)
4	3 (1.4)	-

We found that there was no association between seizure control or use of AEDs (including enzyme-inducing AEDs) or the degree of adverse effects and the frequency of reporting different types of sexual dysfunction. Enzyme-inducing AEDs may reduce free testosterone by increasing sex-hormone–binding globulin and thus lower libido.[22] However, the relationship between libido and testosterone levels is not linear, and therefore some patients using these drugs might experience compromised sexual function, whereas others might

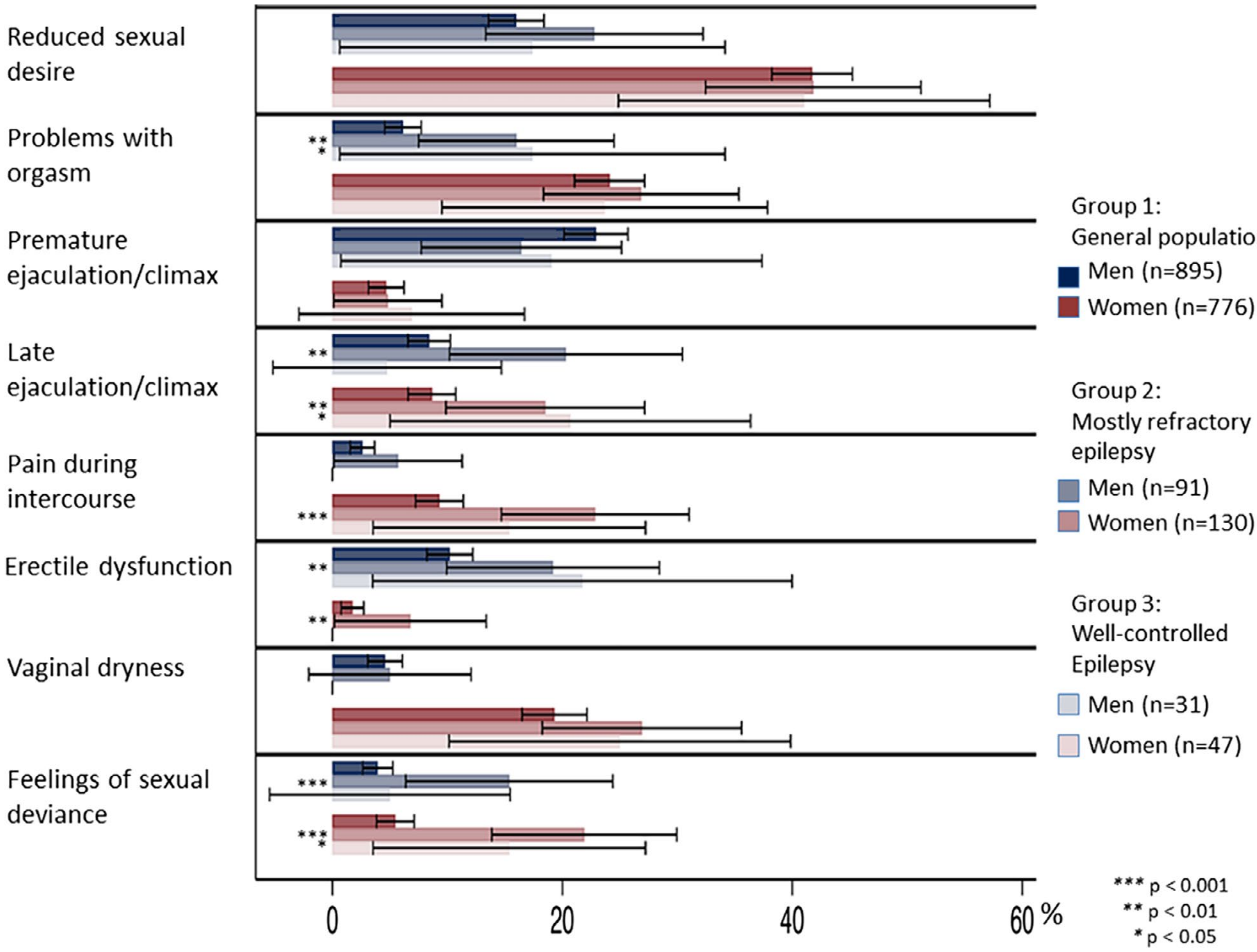


FIGURE 2 Sexual problems reported (%) by patients with mostly refractory epilepsy, patients with well-controlled epilepsy, and the general population, divided by gender. Error bars show a 95% confidence interval for the different groups. Statistical comparisons (shown by asterisks) are between the epilepsy groups and the general population within each gender

not.[23] This may explain the lack of correlation between sexual problems and use of enzyme-inducing AEDs in our study. In addition, Herzog et al found a significant difference in sexual function and testosterone levels between men treated with lamotrigine and normal controls vs men treated with carbamazepine or phenytoin.[24] Lack of similar findings is probably due to the small sample size in our study.

Pain during intercourse among women can be caused by insufficient lubrication. A decreased physiological response to sexual stimuli in women with epilepsy has been suggested as a possible explanation for vaginal dryness.[25] Although an increase in reports of vaginal dryness was apparent among the women with epilepsy in this study, the difference from that of the general population was not significant.

In our study, patients with epilepsy more frequently reported feeling sexually deviant, compared to what was reported in the general population. This is a rather nonspecific type of sexual problem and may simply reflect that psychological factors are involved in perceptions of sexuality, rather than indicating a specific problem. This may be related to our finding that low quality of life was associated with sexual dysfunction among the epilepsy patients. A review from 2007 found that feeling sexually deviant in relation to epilepsy was sparse in the literature and mostly related to temporal lobe seizures.[26] In addition, reports on localized brain injuries or dysfunctions give variable reports. Although frontal lesions might to a larger degree result in hypersexuality,[27,28] temporolimbic lesions were found to be associated with change of sexual preferences.[27] However, there are other reports showing hypersexuality in patients with temporal lobe dysfunctions and change of sexual preferences after basal frontal damage.[29,30]

In our study, the epilepsy group, especially those with more refractory epilepsy, reported less satisfaction with their sex life than respondents in the general population. This result was expected and supports findings from previous studies.[11,31]

Compared with the general population, women with epilepsy did not differ in their opinion from the general population, but significantly fewer men with epilepsy than men in

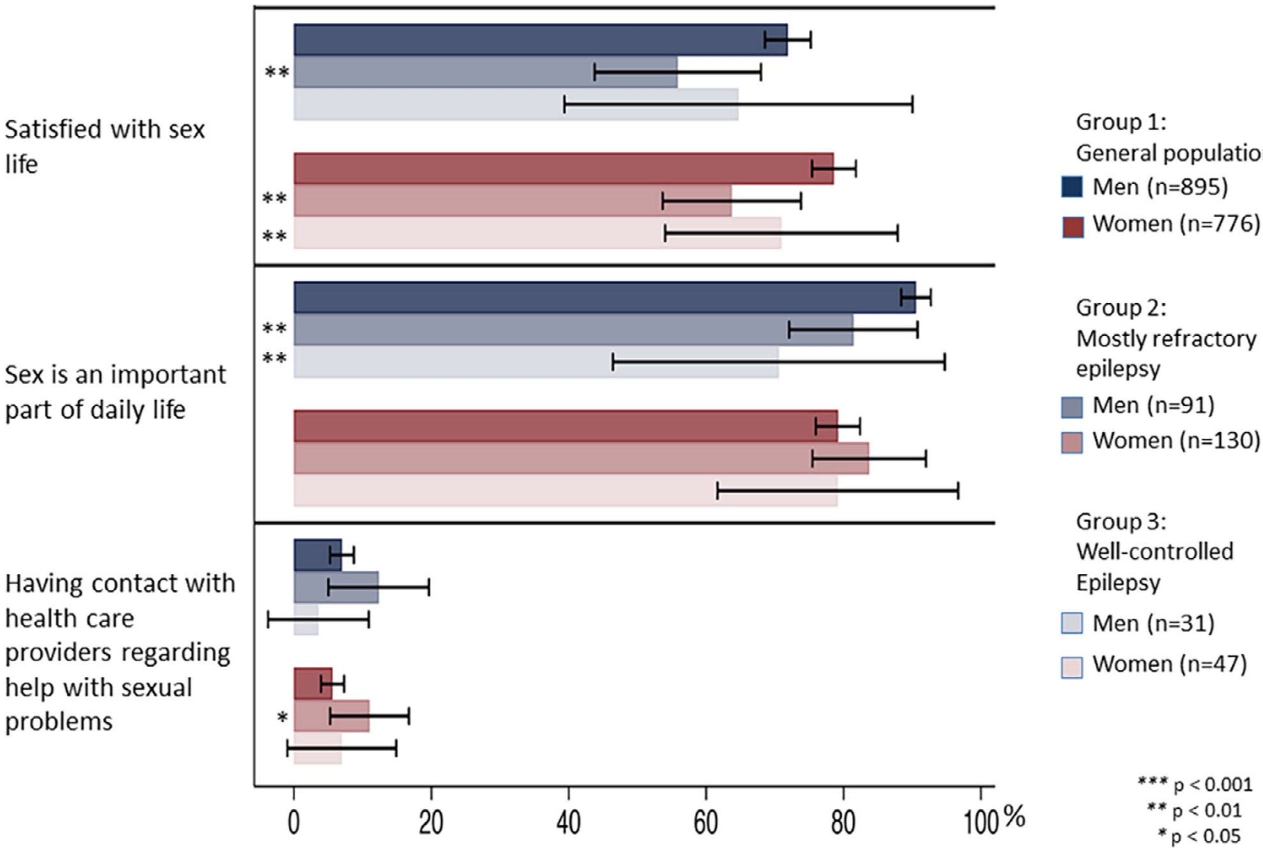


FIGURE 3 Satisfaction with sex life, importance of sex in daily life, and contact with health care providers regarding sexual problems as reported (%) patients with mostly refractory epilepsy, patients with well-controlled epilepsy, and the general population, divided by gender. Error bars show a 95% confidence interval for the different groups. Statistical comparisons (shown by asterisks) are between the epilepsy groups and the general population within each gender

the general population considered that sex was an important part of daily life. The reasons for this are not clear and such findings have not, to our knowledge, been reported in other studies. It may be speculated that, having experienced sexual problems, men may attempt to diminish its importance or, for psychological reasons, be more inclined not to initiate sexual activity. However, it should be noted that there is a significant difference between genders regarding the importance of sex as part of daily life in the general population, and this will influence the results.

The proportion of respondents that had never had sexual intercourse was higher in the epilepsy group, particularly among those from the more refractory epilepsy (National Epilepsy Center) cohort, than in the general population. Most previous studies examining sexual problems and epilepsy are based on sexually active patients, and thus exclude those patients who have never had sexual intercourse. One survey reported that about 15% of women with epilepsy in their study claimed that they had never had sexual intercourse.[9]

In addition to the effect of AEDs on the neuroendocrine regulation, a sexual dysfunction might also be caused by the epilepsy itself. Especially temporolimbic epileptiform discharges might interrupt hypothalamic regulation of pituitary secretion.[32] Although some larger controlled studies did not look at seizure localization or lateralization,[10,11,13,15] right-sided temporal lobe epilepsy has been associated with a higher degree of sexual dysfunction.[33]

In both the general population and among patients with epilepsy, it appears that seeking help from health care providers about sexual problems is uncommon,[2,9,34] and our results reiterate this. Although we found it encouraging that women with mostly refractory epilepsy seemed more willing to seek help regarding sexual problems, it is clear that this should also be promoted among men with well-controlled epilepsy (the group with lowest contact with health care providers regarding sexual problems). It is possible that the relatively high contact with health care providers regarding sexual problems for both men and women apparently shown here may actually reflect the close contact that these patients have with health care providers rather than that these patients actively seek assistance.

Our study has some other limitations. Questionnaires have the disadvantage that misunderstandings or unintentional scoring cannot be corrected by follow-up questions, as can be done in an interview. Female respondents who answered questions on erectile dysfunction and male respondents who answered questions regarding vaginal dryness might have misunderstood the questions, or might have answered regarding their partners. However, because sexuality may be a sensitive subject to discuss openly in an interview setting for some respondents, a questionnaire might provide more accurate data than an interview; some respondents might answer more honestly in an anonymous questionnaire than in an interview setting.

Although use of data from a large control group from the general population strengthens the findings of our study, the sample size from the well-controlled epilepsy cohort (Lillehammer Hospital) was smaller than the cohort with mostly refractory epilepsy recruited from the National Epilepsy Center, and this may have skewed the results. In addition, the two epilepsy populations have to a small degree some overlap. In the group with mostly refractory epilepsy, about one-fourth were seizure-free the last 12 month, whereas in the group with rather well-controlled epilepsy, 40% were not seizure free.

Another limitation of the study is that the data from the general population are derived from a survey that was performed in 2008, about 7-9 years before the data from the groups with epilepsy were obtained. It is possible that during the intervening years, the prevalence of sexual problems in the Norwegian population might have changed and thereby affected the relevance of the comparative data. However, there is no evidence to suggest that this is likely to be the case.

In conclusion, our study supports previous findings that patients with epilepsy are significantly less likely to be satisfied with their sex lives. More epilepsy patients report feelings of sexual deviance, having problems with pain during intercourse, and problems with orgasm and late ejaculation/climax than in the general population. However, we were unable to identify any epilepsy-related factors as specific predictors for these problems. Although male patients with mostly refractory epilepsy were more likely to ask for professional help with sexual problems than male patients with well-controlled epilepsy, no other differences between the two epilepsy populations were identified.

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CONFLICTS OF INTEREST

Oliver Henning has received speaker's honoraria from Eisai, UCB, and LivaNova. Cecilie Johannessen Landmark has received speaker's honoraria from Eisai and GW Pharma. Morten Ingvar Lossius has given talks and participated in expert panels for Eisai and UCB. Torleiv Svendsen has received honoraria for attending advisory boards and/or speaker`s honoraria from Eisai, GlaxoSmithKline, and UCB. Karl Otto Nakken, Anette Farmen, and Bente Træen have no conflicts of interest to disclose.

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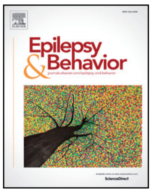

People with epilepsy and their relatives want more information about risks of injuries and premature death

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ABSTRACT

For most people with chronic diseases such as epilepsy, thorough knowledge of the disease is important in order to reduce feelings of insecurity and to enable better management of everyday life. Whether and when to inform patients and their families about all the risks associated with epilepsy is a matter of controversy.

Using a web-based survey, patients with epilepsy (PWE) (n = 1183) and carers, family members, or guardians of PWE, who could either answer on behalf of the patients (CBP) (n = 676) or on their own behalf (CAR) (n = 231) were asked whether they wanted information about the risk of epilepsy-related injuries and premature death and also whether they had received such information.

Ninety percent or more of PWE, CBP, and CAR reported that they wanted such information, and 50% of CAR, 81% of CBP, and 70% of PWE had received some information about seizure-related injuries. Regarding risk of unexpected death, 31% of PWE, 35% of CBP, and 28% of CAR had received information on this issue. Those with tonic–clonic seizures were most eager to obtain information on these matters, and those best informed about epilepsy-related risks were males and the youngest part of the cohort. The wish for more information or the likelihood of having already received information was independent of the individual's seizure situation.

This study demonstrates that there is a considerable gap between what the patients want regarding information and what they are actually given by healthcare providers.

1. Introduction

Although sudden unexpected death in epilepsy (SUDEP) is a rare complication, it is a source of considerable worry [1]. Although some studies indicate that the large majority of patients want to be informed about SUDEP [2–6], it is still a matter of controversy whether and when to inform patients and their families about all the risks associated with epilepsy [7]. Guidelines often recommend providing such information, and most experts would agree with this [1,8]. Nevertheless, the reality seems to be otherwise. According to Morton and coworkers [9], neurologists are reluctant to inform their patients about these issues, as 68.5% of them discussed SUDEP with only a few or none of their patients [9]. A survey among Italian pediatricians treating children with epilepsy revealed that 16.2% stated that all patients should be informed about the risk of SUDEP, but only 1.8% actually did so [10].

The purpose of this study was to assess the extent to which patients with epilepsy (PWE) and their family members (or carers or guardians) wanted information about epilepsy-related risks and whether this need was met by healthcare professionals.

2. Material and methods

The study was a collaboration with the Norwegian Epilepsy Association (NEA) (i.e., the Norwegian branch of the International Bureau for Epilepsy (IBE); lay people). Between April 1st 2017 and September 5th 2017, an online questionnaire was available on the homepage of NEA, popping up for all those who visited the page. Visitors to the page were asked to complete a questionnaire regarding risk of epilepsy-related injuries and premature death. Information about the survey was also available via Facebook. The home page of the NEA is, while not an official information from the Norwegian health services, still an important source of information visited by approximately 100,000 users per year. At the time of the survey, the page did not contain specific information about injuries or SUDEP.

Participants could register as 1) PWE or carers, family members or carers, or guardians of PWE, who could either 2) answer on behalf of the patients (CBP), or 3) on their own behalf (CAR). Each participant could complete the questionnaire only once. Questions included background information and covered the patient's epilepsy, treatment,

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and follow-up, the information that had been received about the risk of seizure-related injuries or death, and whether they wanted such information. The options regarding information were “do not want information”, “have not received information”, “received information but wanted more”, “received good information”, and “do not remember”.

We assumed that PWE, CBP, or CAR who selected any option other than “do not want information” wanted such information. Those selecting “do not remember” or “do not want information” were excluded when calculating the percentage of PWE, CBP, or CAR who had or had not received information.

To investigate possible group differences, chi-square tests were performed. All reported p-values are 2-sided. Odds ratios (ORs) for factors indicating the wish to obtain more information or for having been informed about the increased risk of injury and premature death were estimated using bivariate and multivariate logistic regression analysis. Variables tested were gender, cohabitation or not, above or below the mean age of the participants, known epilepsy etiology, having tonic–clonic seizures, and having been seizure-free for 12 months or more. The study was evaluated by the regional ethics committee (ref. no.: 2017/563).

Table 1
Demographic and clinical characteristics of the participants in the survey (n = 1859).

Characteristics		
Population (n)	Patients (1183)	Carers answering on behalf of the patients (676)
Age in years (yrs) (mean; range)	41.76 (2–93)[a]	16.23 (0–79)[k]
Male gender (%)	373 (32.4)[b]	350 (52.9)[l,**]
Living alone (%)	365 (31.8)[c]	42 (6.4)[m,**]
Under 18 years of age (n; %)	28 (2.4)[d]	437 (66.7)[k,**]
Age at first seizure (yrs) (mean; range)	20.99 (1–80)[e]	7.39 (0–78)[n]
Number of years with epilepsy (mean; range)	20.40 (0–72)[f]	9.09 (0–69)[o]
Seizure types, n (%)		
• Focal, not impaired consciousness	347 (29.4)[g]	210 (31.5)[p]
• Focal, impaired consciousness	425 (36.0)[g]	306 (45.9)[p]
• Tonic–clonic	720 (61.0)[g]	410 (61.6)[p]
• Absences	263 (22.3)[g]	275 (41.3)[p]
• PNES[a]	55 (4.7)[g]	22 (3.3)[p]
• Other	86 (7.3)[g]	112 (16.8)[p]
• Don't know	108 (9.1)[g]	31 (4.7)[p]
Seizure-free last year, n (%)	480 (40.7)[h]	151 (22.7)[k,**]
Epilepsy etiology, n (%)		
• Known	544 (46.3)[i]	260 (39)[q,*]
• Unknown	631 (53.7)[i]	407 (61)[q]
Follow-up at n (%)		
• Neurologist (child or adult)	804 (68.1)[g]	554 (83.3)[k]
• Epilepsy nurse	150 (12.7)[g]	115 (17.3)[k]
• General practitioner	393 (33.3)[g]	125 (18.8)[k]
• No regular follow-up	224 (19.0)[g]	64 (9.6)[k]
Frequency of follow-up		
• Less than once per year	143 (16.8)[j]	26 (4.5)[r]
• Once per year	371 (43.6)[j]	175 (30.4)[r]
• 2–4 times per year	297 (34.9)[j]	300 (52.1)[r]
• More than 4 times per year	40 (4.7)[j]	75 (13)[r]

PNES = psychogenic nonepileptic seizures.
[**] $p < 0.001$.
[*] $p < 0.01$.
[a] 1157/1183 answered.
[b] 1115/1183 answered.
[c] 1151/1183 answered.
[d] 1157/1183 answered.
[e] 1153/1183 answered.
[f] 1130/1183 answered.
[g] 1181/1183 answered.
[h] 1180/1183 answered.
[i] 1175/1183 answered.
[j] 851/1183 answered.
[k] 655/676 answered.
[l] 662/676 answered.
[m] 661/676 answered.
[n] 644/676 answered.
[o] 634/676 answered.
[p] 666/676 answered.
[q] 667/676 answered.
[r] 576/676 answered.

3. Results

In the study period, the NEA web site had 48,249 hits, and 2090 persons agreed to take part in the survey. Of these, 1183 (56.6%) were PWE, 676 (32.3%) were CBP who answered on behalf of someone with epilepsy, and 231 (11.1%) were CAR (family members, guardians, or carers answering for themselves). Demographic and clinical characteristics of the participants are summarized in Table 1, and results from the questions regarding information about seizure-related risks are presented in Table 2.

Of all PWE, CBP, and CAR participants, at least 90% wanted information about epilepsy-related risks like injuries (Fig. 1) or death (Fig. 2). Among those wanting information with regard to the risk of seizure-related injuries, 70% of PWE, 81% of CBP, and 50% of CAR had obtained at least some information, and 47%, 55%, and 24%, respectively, reported that the information that they had received on this topic was good. Among those wanting information regarding risk of seizure-related death, 31% of PWE, 35% of CBP, and 28% of CAR had received at least some information (Fig. 2), and 16%, 17%, and 11%, respectively, reported having received good information on this issue (Fig. 2).

Having tonic–clonic seizures was the only independent factor in a multivariate logistic regression analysis associated with wanting information about the risk of death (OR: 2.22; confidence interval (CI): 1.57–3.12; $p < 0.001$). Other factors did not reach statistical significance (data not shown).

Male gender (OR: 1.28; CI: 1.02–1.60; $p = 0.033$), having epilepsy of known etiology (OR: 1.27; CI: 1.01–1.58; $p = 0.040$), and being younger than the mean age of participants (OR: 1.31; CI: 1.04–1.64: $p = 0.019$) were all significant independent factors in a multivariate logistic regression analysis for having obtained information about the risk of epilepsy-related death.

Having tonic–clonic seizures (OR: 4.10; CI: 2.72–6.17; $p < 0.001$), living together with others (OR: 2.12; CI: 1.20–3.77; $p = 0.010$), and being younger than the mean age of participants (OR: 1.62; CI: 1.10–2.40; $p = 0.016$) were all significant independent factors for wanting information about the risk of epilepsy-related injuries.

Male gender (OR: 1.48; CI: 1.15–1.89; $p = 0.002$), having tonic–clonic seizures (OR: 1.44; CI: 1.13–1.84; $p = 0.004$), living together with others (OR: 1.58; CI: 1.20–2.08; $p < 0.001$), and being younger than the mean age of participants (OR: 1.52; CI: 1.19–1.94; $p < 0.001$) were all significant independent factors for having been provided with information about the risk of epilepsy-related injuries.

The wish for more information or having been informed about either risk was independent of being seizure-free or not or having consultations with a neurologist or an epilepsy nurse at least once per year (data not shown).

3.1. Discussion

Epilepsy may have many unfortunate consequences. Among these are seizure-related accidents and, at worst, premature death. To reduce the risk of such unfavorable incidents, it is important to discuss these matters with the patients and the relatives to empower them to take responsibility themselves for the condition, e.g., to avoid seizure triggers. To assume that they are well informed about the risks associated with epilepsy could be precarious.

In Norway, most PWE (about 2/3 in our cohort) are followed up by neurologists (child and adult) while the remainder is followed up by general practitioners (GPs). Nevertheless, our survey demonstrated that only one-third of the study cohort had been provided with information about epilepsy-related risk of death. The term SUDEP was deliberately not used

Table 2
Results from a questionnaire regarding information on risk of injuries and premature death associated with epilepsy.

	Patients (n = 1183)	Family, guardians, or carers on behalf of patients (n = 676)	Family, guardians, or carers (n = 213)
Risk of injuries, n (%)			
• Don't want info	81 (7.0)[a]	45(7.0)[b]	21 (9.9)[c]
• No info provided	290 (25.2)[a]	107 (16.6)[b]	94 (44.1)[c]
• Some info provided, want more	223 (19.4)[a]	146 (22.6)[b]	50 (23.5)[c]
• Good info provided	459 (39.9)[a]	309 (47.8)[b]	45 (21.1)[c]
• Don't remember	98 (8.5)[a]	39 (6.0)[b]	3 (1.4)[c]
Risk of premature death, n (%)			
• Don't want info	100 (8.7)[d]	47 (7.2)[e]	22 (10.4)[f]
• No info provided	659 (57.3)[d]	362 (55.8)[e]	132 (62.3)[f]
• Some info provided, want more	144 (12.5)[d]	100 (15.4)[e]	31 (14.6)[f]
• Good info provided	157 (13.7)[d]	93 (14.3)[e]	21 (9.9)[f]
• Don't remember	90 (7.8)[d]	47 (7.2)[e]	6 (2.8)[f]

[a] 1151/1183 answered.
[b] 646/676 answered.
[c] 213/213 answered.
[d] 1150/1183 answered.
[e] 649/676 answered.
[f] 212/213 answered.

in the survey in order to include all types of epilepsy-related deaths. Besides family members or guardians answering on their own behalf (CAR), we had two groups answering about patients: either patients themselves (PWE) or carers answering on behalf of the person with epilepsy (CBP). These two groups differ in some aspects as shown in Table 1. Patients in the CBP group are younger, mostly less than 18 years of age, and less likely to be living alone (i.e., the CBP group consists mostly of parents representing their children). Interesting is that these also have a more refractory epilepsy with 23% reporting one year seizure freedom vs. 40% among PWE. Groups do also differ in gender, with PWE being composed of more women (67.6%). We can only speculate about the reasons for this, but one could be the idea that women are possibly more conscientious and more likely to participate in surveys. Still, there is no significant difference between both groups in their wish to get informed, showing that patients whose epilepsy is less refractory also do feel a need to get informed about risks related to epilepsy.

It is not surprising that the proportion of participants that had received information about the risk of seizure-related injuries was higher than those who had received information about risk of premature death, as injuries are a less sensitive issue than death.

To the best of our knowledge, the only other web-based study on this issue was performed in the USA among members of a selected population, the Epilepsy Therapy Network [3]. That study had a comparable number of respondents to ours but fewer seizure-free patients (24.7%), probably indicating a selection of more patients with refractory epilepsy than in our study.

The proportion of patients in our study who did not want to receive information about epilepsy-related risks was quite low (9.4% for death and 7.7% for injuries). This is in line with earlier studies, indicating that the great majority of the population affected by epilepsy wants such information [2,4,6], including those patients who are seizure-free.

About 69% of our patients wanting information reported that they had not been informed about the risk of premature death. This is higher than in other studies; 50% in the study of Keddie et al. [2], 47.6% in the study of Xu et al. [6], and 32.2% in the study of Kroner et al. [3]. This might be due to the fact that the patients in our sample have less refractory epilepsy and are, therefore, probably considered to be at lower risk of premature death by their physicians. Only about 14% of all patients felt that they had been well informed. However, the quality of the information that they had received is not known.

Compared with the whole cohort, those experiencing tonic–clonic seizures were more likely to want information about the risk of injuries and premature death. They were more likely than others to have received information about the risk of injuries but not about premature death, despite tonic–clonic seizures being associated with an increased risk of premature death [11]. In contrast to the results from another study [6], our data indicate that being younger increased the probability

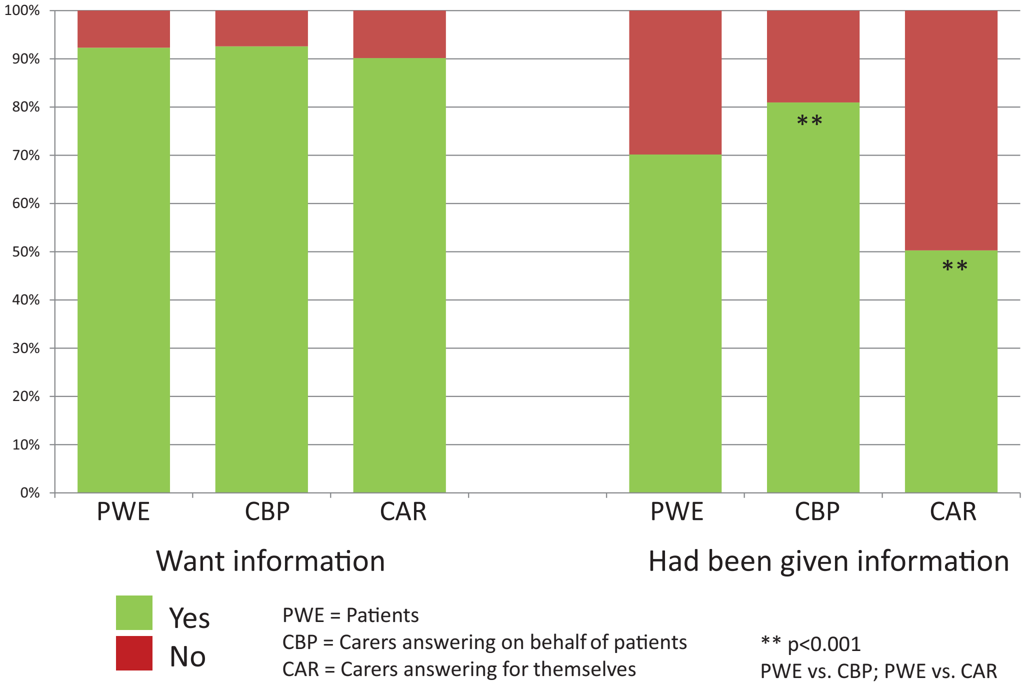

Fig. 1. The diagram shows the percentage of patients (PWE), carers answering on behalf of patients (CBP), and carers answering for themselves (CAR) wanting and obtaining information on risk of injuries associated with epilepsy.

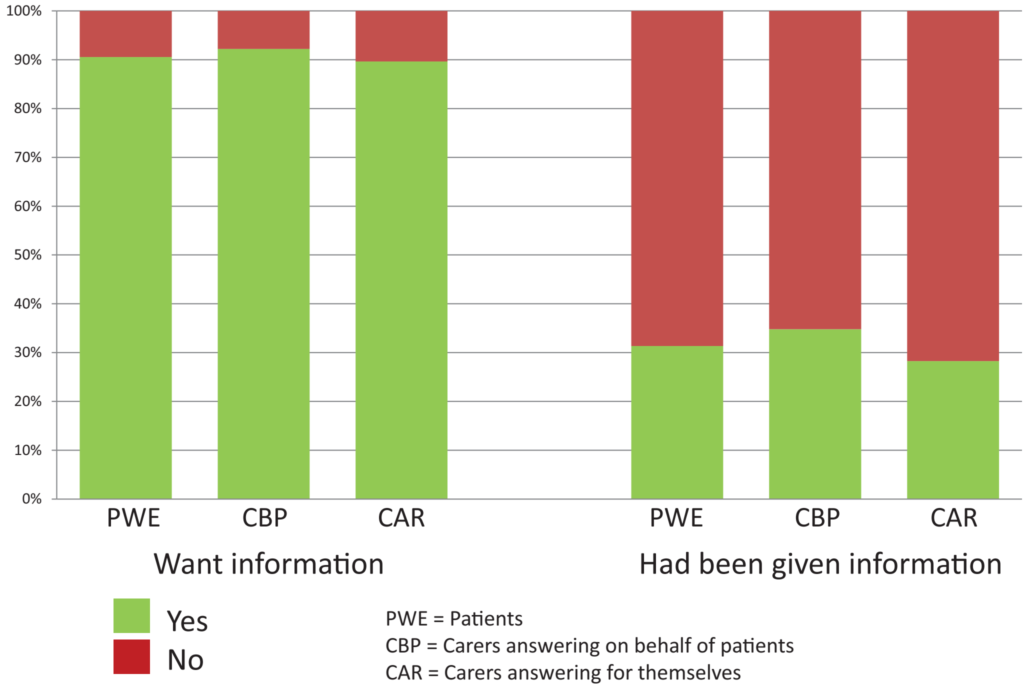

Fig. 2. The diagram shows the percentage of patients (PWE), carers answering on behalf of patients (CBP), and carers answering for themselves (CAR) wanting and obtaining information on risk of unexpected death associated with epilepsy.

of being informed about these risks and also the wish to obtain information about the risk of injuries.

Cohabitating with family or others also increased the probability of having obtained information or wishing to obtain more information about the risk of injuries. This could be associated with an increased awareness of the problems that seizures might inflict on others in the household. To the best of our knowledge, this aspect has not been previously studied.

We found that men were more likely than women to have obtained information about the risks of both death and injuries. This has not been found in previous studies investigating information regarding SUDEP [3,6]. Some studies have shown that male patients are more likely to be noncompliant than women [12]. Thus, physicians might consider providing male patients with information on seizure-related risks as a means to increase adherence to the treatment.

For most people with chronic diseases like epilepsy, comprehensive knowledge of the disease is important in order to reduce feelings of insecurity and in order to enable better management of everyday life. We can only speculate regarding the reasons why the majority of the patients in this study had not received information on the risk issues. The explanations are probably complex, but one contributory factor could be that consultations may be too brief and shallow to enable discussion of such serious issues. Moreover, some physicians may not have sufficient knowledge on these issues, and health personnel may be reluctant to give their patients information that might be considered as an extra burden to them.

We believe that physicians, neurologists in particular, play a critical role in patient education to encourage self-management and to ensure that patients are aware of the risks and how to modify those risks [13,14].

3.2. Limitations of the study

Although a web-based questionnaire was used with the intention of obtaining data from a representative sample of Norwegian PWE, the percentage of seizure-free patients (40.7%) was still lower than expected in a sample representative of the general Norwegian epilepsy population and may indicate a bias towards patients with more severe epilepsy. Nevertheless, we still think that our study is at least as representative as previous studies, as these tend either to have been based on fewer patients or on a selection of patients from tertiary epilepsy centers, i.e., those with difficult-to-control epilepsy [2,4,6]. Further limitations in our study are the known problems with validity of close-ended questionnaires such as lack of answer alternatives. Finally, we did not have the possibility to control whether the patients actually were or were not informed by healthcare providers as memory problems are quite frequent in PWE. Still, even if our study does not take into account whether information has been actually given to the patient, it gives an accurate account on how the patient and carers perceive being informed.

4. Conclusion

The results of this study provide a brief insight into a very important topic and demonstrate that there is a considerable gap between what the patients want regarding information and what they are actually given by healthcare providers. This should be a wake-up call for all those who are working in the care of people with epilepsy.

Acknowledgments

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Disclosures

None of the authors have any conflict of interest to disclose. We have not received any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2018.02.023.

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SHORT RESEARCH ARTICLE

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Refractory epilepsy and nonadherence to drug treatment

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Abstract

In patients with epilepsy, nonadherence to agreed antiepileptic drug (AED) treatment may result in seizure relapse, and at worst sudden unexpected death. The aim of this study was to examine the extent of both unintentional and intentional nonadherence among Norwegian patients with refractory epilepsy and try to identify possible risk factors. At the National Centre for Epilepsy in Norway, 333 consecutive adult in- and outpatients with refractory epilepsy participated in an anonymous survey about adherence to drug treatment. Twenty-two percentages admitted that they sometimes or often forgot to take their drugs as scheduled, and 19% reported that they, rarely, sometimes or often intentionally did not follow the AED treatment plan agreed upon with their physician. Young age and depression were significantly correlated with unintentional nonadherence. Intentional nonadherence was associated with young age (36 years or younger). We found nonadherence not to be associated with any specific AED. In conclusion, about one-fifth of patients with refractory epilepsy admitted that they did not adhere to the agreed drug treatment plan, either intentionally or unintentionally. Measures to reduce nonadherence in this patient group may improve seizure control and should be tailored to address both unintentional and intentional lack of adherence.

KEYWORDS

adherence, drug treatment, epilepsy, refractory

1 | INTRODUCTION

With a global prevalence of 0.6%-1.2%, epilepsy is one of the most common neurological disorders.[1] About 60%-70% of patients with epilepsy can become seizure-free with appropriate treatment with antiepileptic drugs (AEDs).[2] The remaining 30%-40% with drug-resistant epilepsy often experience psychosocial challenges in addition to recurrent seizures. These patients have an elevated risk of injuries, and at worst sudden unexpected death (SUDEP).

Adherence to treatment is defined as: "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider".[3] Consequently, nonadherence to treatment is defined as any deviation from healthcare provider recommendations, both regarding timing or dosage of a prescribed regimen.[4] There are many potential consequences of nonadherence to AED treatment plans, including seizure relapse, status epilepticus, hospital admission, and increased healthcare costs. In addition, SUDEP has been related to nonadherence.[4–9]

Nonadherence may be due to misunderstandings between the physician and the patient regarding the agreed dosage or medication.[10] Chapman et al demonstrated low adherence being related to doubts about AED necessity, concerns about AED treatment, limitations in capability and resources, and perceiving not to be involved in treatment decisions.[11] Nonadherence may be unintentional, that is, the patient forgets to take a dose or inadvertently takes an incorrect dosage. However, nonadherence can also be intentional; the patient—for various reasons—chooses not to follow the agreed AED treatment plan.[12]

We have previously demonstrated nonadherence, intentionally in 30% and unintentionally in 40% of responders in an Internet survey. That cohort was assumed to represent a general epilepsy population.[12] Norwegian patients with the most severe epilepsies are referred to the National Centre for Epilepsy. The extent of nonadherence to AED treatment in this subpopulation has not previously been studied. Thus, we were aiming at determining the extent of both unintentional and intentional nonadherence to AED treatment among patients with refractory epilepsy. Additionally, we looked for predisposing factors for nonadherence in this selected patient population.

2 | MATERIAL AND METHODS

2.1 | Study population and the questionnaire

Consecutive adult patients admitted to the National Centre for Epilepsy in Norway, a tertiary referral center, were invited to complete a questionnaire regarding age, gender, epilepsy and seizure type, seizure frequency, and use of AEDs. In addition, they were asked to respond to a visual analog scale about quality of life (QoL), the Neurological Disorders Depression Inventory for Epilepsy (NDDIE), and the adverse events profile (AEP). Only patients who were considered able to read, understand, and fill out the questionnaire by themselves were recruited for the study. Patients with learning disabilities and patients who did not have sufficient Norwegian language skills were excluded. The time frame for the study was 2015-2017.

Information on whether the respondents unintentionally or intentionally used AEDs differently than recommended by and agreed upon with their physician was determined from responses to the following two questions: 1) “Do you sometimes inadvertently take your antiepileptic medication differently than agreed upon with your physician?” and 2) “Do you sometimes intentionally (on purpose) take your antiepileptic medication differently than agreed upon with your physician?”

Patients could choose between the following alternative answers for each of these questions based on a four-point Likert scale: “never,” “rarely,” “sometimes,” or “often.”

During the analysis, we dichotomized the answers into two groups: “never or rarely” vs “sometimes or often” for unintentional nonadherence, and “never” vs “rarely, sometimes, or often” for intentional nonadherence.

The different dichotomization was due to different clinical implications. In unintentional nonadherence, it is of clinical relevance whether this happens rarely or more regularly. Intentional nonadherence on the contrary is a conscious decision to take medication either differently or not at all. In this situation, the willingness of the patients was important, even if would occur seldom.

As the study was anonymous, no ethical approval was required; nevertheless, the study protocol was evaluated by the regional ethics committee (ref. no. :2014/1011A).

2.2 | Statistical methods

IBM SPSS Statistics version 25, release 25.0.0.1. (SPSS Inc, Chicago, IL, USA) was used for statistical analyses. All *P*-values reported here are based on two-sided tests, with a significance level of 0.05. To test possible group differences, Pearson's chi-square tests or independent-samples *t* tests were performed. Variables tested in independent-samples t tests were age, QoL score, NDDIE score, AEP score, and AEP subscores. Independent variables tested for unintentional and intentional nonadherence in Pearson's chi-square tests were as follows: age (36 years or younger vs 37 years or older), gender, seizure type, seizure frequency (daily or weekly vs less frequently), monotherapy, different AEDs used in monotherapy, polytherapy (3 or more AEDs), NDDIE score > 14, and AEP score > 44.

We applied Hosmer's step-down procedure, which means that variables that were significant at the 0.25 level were included in the multivariate logistic regression model.[13] Odds ratios for factors associated with lack of adherence to the AED treatment plan agreed with the healthcare provider were estimated using bivariate and multivariate logistic regression analysis with 95% confidence intervals.

3 | RESULTS

A total of 466 of 513 patients (91%) agreed to participate in the study and completed the questionnaire, either partly or fully. Among these, 333 patients (72%) reported to have experienced seizures during the last 12 months despite the use of AEDs. Further analysis was done with these 333 patients. Demographic and clinical characteristics of the participants are summarized in Table 1.

Of the 321 patients who answered the question on unintentional nonadherence, 72 (22%) reported that they sometimes or often forgot to take their drugs as scheduled. Of the 325 patients who answered the question on intentional nonadherence, 61 (19%) reported that on some occasions they

TABLE 1 Demographic and clinical characteristics of the study participants (n = 333)

Characteristics	n (%)	Median (range); Mean (SD)
Age (y) (N = 331)		37 (17-72); 37.7 (13.00)
Female patients (N = 332)	188 (56.6)	
Male patients (N = 332)	144 (43.4)	
Age at first seizure (y) (N = 311)		15.0 (0-68); 18.1 (13.53)
Seizure types		
Tonic-clonic (N = 286)	198 (69.2)	
Seizure with loss of consciousness (N = 289)	198 (68.5)	
Seizure without loss of consciousness (N = 279)	220 (78.9)	
Seizure frequency (N = 333)		
Daily/weekly	210 (63.1)	
Monthly/yearly	123 (36.9)	
Number of AEDs in use (N = 333)		
1	97 (29.1)	
2	151 (45.3)	
3	69 (20.7)	
4	16 (4.8)	
NDDIE score (N = 315)		12 (6-24); 12.6 (4.11)
AEP score (N = 283)		44 (19-71); 42.8 (10.84)
AED used	Polytherapy (N = 333) n (%)	Monotherapy (N = 97) n (%)
Lamotrigine	132 (39.6)	35 (36.1)
Valproate	107 (32.1)	15 (15.5)
Levetiracetam	94 (28.2)	13 (13.4)
Oxcarbazepine	51 (15.3)	7 (7.2)
Lacosamide	42 (12.6)	1 (1)
Zonisamide	40 (12.0)	2 (2.1)
Carbamazepine	33 (9.9)	4 (4.1)
Topiramate	31 (9.3)	5 (5.2)
Eslicarbazepine	31 (9.3)	6 (6.2)
Clobazam	30 (9.0)	1 (1)
Perampanel	24 (7.2)	0
Clonazepam	13 (3.9)	5 (5.2)
Phenobarbital	7 (2.1)	1 (1.0)
Phenytoin	6 (1.8)	1 (1.0)
Vigabatrin	4 (1.2)	0
Ethosuximide	3 (0.9)	1 (1.0)
Gabapentin	2 (0.6)	0
Pregabalin	2 (0.6)	0
Brivaracetam	1 (0.3)	0
Diazepam	1 (0.3)	0
Sulthiame	1 (0.3)	0
Acetazolamide	1 (0.3)	0

N, Number of responses to each question.

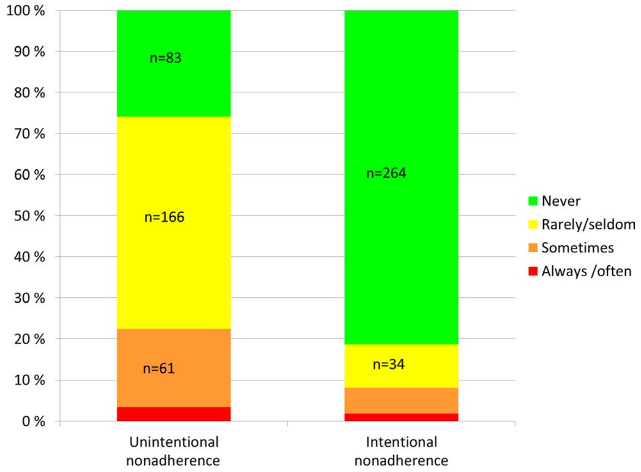

FIGURE 1 Results (%) of reported unintentional (n = 321) and intentional (n = 325) nonadherence

intentionally did not follow the AED treatment plan agreed upon with their physician (Figure 1). There were 36 patients who responded positively to both questions.

Of 22 different AEDs, the most commonly used drugs were lamotrigine, valproate, and levetiracetam, used as mono- or polytherapy. These three drugs were used by 65% of the patients in monotherapy.

Unintentional nonadherence was significantly correlated with young age (mean 32.7; SD 11.94) (mean difference 6.44; confidence interval [CI] 3.038-9.832; $P < .001$) and higher NDDIE score (mean difference 1.41; CI 0.289-2.530; $P = .014$). Intentional nonadherence was correlated only with young age (mean 33.7; SD 11.71; mean difference 5.17; CI 1.532-8.800; $P = .005$).

The following independent variables were significantly associated with unintentional nonadherence in logistic regression analysis: scoring 15 or higher in the NDDIE (odds ratio [OR] 2.03; CI 1.060-3.903; $P = .033$) and being younger than the median age (36 years or younger) (OR 2.309; CI 1.222-2.309; $P = .010$).

The only independent factor significantly associated with intentional nonadherence was being younger than the median age (OR 2.46; CI 1.252-4.808; $P = .009$). We found no association between both intentional or unintentional nonadherence and the following factors: gender, seizure type, seizure frequency (daily or weekly vs less frequently), monotherapy, different AEDs used in monotherapy, polytherapy (3 or more AEDs), NDDIE score >14, and AEP score >44.

There were no differences between men and women regarding nonadherence.

4 | DISCUSSION

The main result from this survey among Norwegian patients with refractory epilepsy was that approximately one in five rarely, sometimes, or often makes the conscious decision not to follow the AED treatment plan as agreed with their neurologist, but rather decides to take their AEDs differently than prescribed. Also, about one-fifth reported that they sometimes or often forgot to take their AEDs as scheduled.

Unintentional nonadherence was associated with young age and symptoms of depression, while intentional nonadherence was associated with young age.

Most publications on adherence to AED treatment do not differentiate between unintentional and intentional nonadherence. We believe this distinction is important when addressing measures to improve the treatment of this patient group.[12]

In previous studies, there are considerable variations regarding estimates of poor adherence to treatment in epilepsy populations. A recent review reported nonadherence in 26%-79% of patients.[4] Different study populations, different definitions of adherence, and different methods to measure nonadherence may account for the wide variability.

We found a correlation between nonadherence and young age and symptoms of depression. This is in line with other studies.[7,14,15] In contrast to other studies, we did not find a high score of adverse events[15,16] to be a risk factor for nonadherence, neither did we find male gender[4,12] to be a risk factor for intentional nonadherence. We did not find a correlation to either monotherapy or polytherapy. It has been shown that the number of AED doses per day twice or more can have a negative correlation with adherence[15,17]. But this is not necessarily dependent of the number of AED in use which could explain our findings.

In various studies on nonadherence, the rate of seizure-freedom in the respective populations either is not included[15] or around 30%.[11,16] Studies on nonadherence to treatment in refractory epilepsy are to our knowledge sparse. A study from the United States, defining refractory epilepsy as those currently using three or more AEDs, regardless of seizure rate, revealed a significant higher rate of adherence to treatment in these patients compared to patients using fewer AED.[18]

The ILAE task force defined drug-resistant epilepsy in 2010 as "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules".[19] Unfortunately, we did not have sufficient information on previously tried AEDs among our patients to apply this definition. We chose to define refractory epilepsy as having had seizures the last year despite the use of AEDs.

A previous open online survey of an epilepsy cohort consisting of 40% seizure-free patients disclosed that 40% reported unintentional and 30% reported intentional nonadherence to treatment, that is, a higher extent of nonadherence than in the present study.[12] In contrast to the previous study where 40% of respondents were seizure-free during the preceding 12 months, none of the patients in this were seizure-free. 63% had daily or weekly seizures, the rest monthly or seizures at least once during the last year.

The reasons why patients with refractory epilepsy are more adherent to treatment than those with more easy-to-treat epilepsy are not known. With earlier epilepsy onset (median debut at 15 vs 21 years old), regular AED intake may have become an established daily routine. Moreover, those with refractory epilepsy are usually followed more closely by an epileptologist and are probably provided with more thorough information on the necessity for carefully following the agreed AED treatment schedule. Also, fear of sudden unexpected death and more regular therapeutic drug monitoring might better adherence.

For clinicians, the results of this study underline the importance of keeping an eye on nonadherence and implement measures to improve adherence.

Clinical implications of this study point to the importance of acknowledging variable adherence as a factor contributing to variability and poor seizure control.

Further studies are needed to clarify in more detail the reasons for intentional nonadherence.

4.1 | Limitations of the study

As the majority of patients were using AED polytherapy, possible correlations between individual AEDs and nonadherence were difficult to detect. Another obvious source of error in studies on nonadherence is that patients might be reluctant to admit nonadherence, whether intentional or unintentional. Even if 96% and 98% of patients had answered the questions on adherence, they might have answered according to what they feel physicians would expect. As patients reported intentionally to take their antiepileptic medication differently than agreed upon with their physician, this could result in a lower or higher dosage, leading to a change in daily dosing regimen but not the total daily dosage.

While we did not recruit patients with learning disabilities, we cannot exclude that some of the patients participating could be living in a nursing home or other institution where there is some additional control on the administration of AEDs.

Ideally, we should have used the definition of drug-resistant epilepsy by the ILAE task force: "…failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules…".[18] For this, we would have needed information on previously used antiseizure medication ("appropriately chosen") and dosage, serum concentrations, and possible adverse events of actual and earlier used antiseizure medication ("tolerated, appropriately … used"). As the study is anonymous and based on information available from the questionnaires the respondents have filled in this information is not available. All patients included reported to have had at least one seizure during the last 12 months; due to the described lack of information, we do not know whether seizures could be due to nonadherence or inadequately dosing.

5 | CONCLUSIONS

The results from this study demonstrate that in a cohort of patients with refractory epilepsy, about one in five patients is nonadherent to their AED treatment regimen, either intentionally (rarely, sometimes, or often) or unintentionally (sometimes or often). Being of young age is the main risk factor. Minimizing nonadherence is important for improving seizure control and thereby reducing the risk of seizure-related complications in this patient group.

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CONFLICT OF INTEREST

Dr Henning has served as a paid consultant for Eisai, UCB, and LivaNova, outside the submitted work. Dr Lossius has served as a paid consultant for ESAI and UCB, outside the submitted work. The remaining authors have no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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