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Aspects of the influence of bioethical-medical and legislative factors on the quality of life of people with epilepsy

SUMMARY

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THANKS

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To conf. univ. dr. med. Ioana Mîndruță for instilling passion for epileptology,
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LIST OF ABBREVIATIONS

AVC — stroke
EEG — electroencephalogram
ILAE — International League Against Epilepsy
IRM — magnetic resonance imaging
MAE — antiepileptic medications
OMS — World Health Organization
QOLIE — Quality of life in epilepsy
QOLIE-31-P — Quality of Life in Epilepsy Questionnaire 31-P
SSQ — Seizure Severity Questionnaire
SNC — central nervous system
ST — total score
Video-EEG — video-electroencephalogram

ABSTRACT

Introduction: Epilepsy is a chronic neurological condition caused by recurrent seizures and is a public health problem that can have a significant impact on the patient's quality of life. Although there are numerous studies worldwide analyzing the quality of life of patients with epilepsy, in Romania there are insufficient data and no studies conducted in our country published in the international scientific literature in recent years. A better understanding of the quality of life of patients with epilepsy can lead to the identification and application of the most effective medical interventions to increase the quality of life of these patients.

Purpose: The PhD work aimed at three objectives by identifying the influence of socio-demographic and clinical factors on the quality of life of patients with epilepsy admitted to a hospital in Romania, evaluating over time the perception of a group of patients regarding quality of life and reporting the translation into Romanian and the cultural adaptation of the Seizure Severity Questionnaire - SSQ, an assessment tool that has never been used in our country, on a group of patients with epilepsy evaluated at a hospital in Romania.

Material and methods: The thesis comprises an analytical, observational, cohort study based on the QOLIE-31-P Quality of Life Questionnaire, a second analytical, cohort, longitudinal study based on the QOLIE-31-P questionnaire and a third analytical, observational, cohort study using the QOLIE-31-P questionnaire and the Romanian translated version of the SSQ questionnaire for cultural adaptation in Romanian patients with epilepsy. The studies received ethical approval from the Ethics Committee for Medical Scientific Research of the Transilvania University of Brasov and the Clinical Hospital of Psychiatry and Neurology Brasov.

Results: In the first study, according to the mean total QOLIE-31-P score most enrolled patients had an average quality of life. Patient age had a negative impact on quality of life domains and the older the patient age, the lower the quality of life. Scores were influenced by years of education and employment status, with sickness and old age pensioners having lower scores compared to those employed. In all domains except the effects of antiepileptic drugs, increased seizure frequency was a predictor of lower quality of life scores. Patients with uncontrolled seizures reported lower quality of life in terms of mood, daily activities, cognition, seizure-related worry, overall quality of life and total score. Because uncontrolled seizures impact patients' family, work and social lives, if doctors can reduce seizure frequency through appropriate assessment and treatment, they can improve the quality of life of patients with epilepsy. In the second study, at both the baseline and follow-up visit, higher seizure frequency was a predictor of lower total QOLIE-31-P score. At follow-up, the number of controlled seizure-free patients in the past year was higher, and good seizure control was associated with increased total QOLIE-31-P scores and improved perception of quality of life. At both assessments, patients on treatment with two or more antiepileptic drugs had worse perceptions of quality of life compared with those on monotherapy. The impact of treatment on quality of life may be correlated with the likelihood of adverse effects, confidence in treatment and compliance. Patients were assessed by video-EEG, and tracking the presence of epileptiform activity was studied as part of diagnostic and treatment management. The second study found that those with abnormal EEG signals during video-EEG monitoring had lower total QOLIE-31-P scores at baseline and final visit. The third study translated the SSQ from English into Romanian and

applied it to a heterogeneous sample of epilepsy patients. The SSQ total score was correlated with the QOLIE-31-P quality of life scores, with the gender of the patients and with clinical factors such as aura, seizure frequency or number of antiepileptic drugs. These results obtained may be useful in applying the SSQ in future larger research on more patients and in different areas of the country.

Discussion: Current progress in medicine and medical practice requires healthcare providers to adapt and keep abreast of the ethical issues they encounter in patients with epilepsy. Due to stigma and fear of having seizures, patients with epilepsy may face difficulties in employment, problems in accessing education and relating. Appropriate instruments such as the QOLIE-31-P and the SSQ allow objective assessment of the daily difficulties faced by patients with epilepsy based on their perceptions and allow identification of the psycho-social consequences of the condition. Absence of epileptic seizures is the main goal of epilepsy treatment, which ranges from the administration of antiepileptic drugs to surgery to remove the epileptic focus or vagal neurostimulation. However, for some patients with epilepsy, this is not possible and therefore understanding predictors of quality of life can improve clinical practice, treatment and support them in achieving their desired outcomes.

Conclusions: This research, through the results of the three studies, has shown that seizure frequency has an important impact on the quality of life of patients with epilepsy. Total QOLIE-31-P scores are lower in epilepsy patients with frequent seizures, uncontrolled disease, those using polytherapy and those with epileptiform abnormalities on interictal video-EEG recording. Seizure frequency was a significant inverse predictor of quality of life, and as epilepsy is a chronic condition requiring regular outpatient visits, clinicians should use tools to assess quality of life, identify patterns, and consider various clinical factors while trying to improve the prognosis of these patients. The impact of seizures traditionally studied in terms of frequency and manifestations can be better understood if analysed from the patient's perspective. Manifestations occurring before, during and after an epileptic seizure, such as the presence of a halo, involuntary movements, altered state of consciousness, confusion, affective disturbances, explored through the questions in this assessment tool, are relevant data for assessing the consequence of epilepsy on the patient's daily life. The Romanian version of the SSQ shows good reliability and adequate translation of the content and could be useful for measuring seizure severity in patients with epilepsy in Romania. The use of validated measurement tools for assessing quality of life of patients with epilepsy, such as the QOLIE-31-P questionnaire and the SSQ, should become routine practice, even though this may be difficult. Information collected in this way can adapt management and improve outcomes for these patients by looking at the influence of the condition and other modifiable factors in daily life.

The research results were disseminated through two ISI articles, one BDI article and in a national conference with international participation, as per the contractual terms of the 2016 registration year.

INTRODUCTION
Motivation for the choice of theme

Epilepsy is a neurological disorder characterised by a long-lasting predisposition of the brain to generate epileptic seizures and their presence has a major impact on quality of life. The concept of quality of life according to the World Health Organization is the individual's perception of his or her position in life in the context of the value system and culture in which he or she lives and its relationship to his or her goals, expectations, standards and concerns. (Saxena & Orley, 1997).

A better understanding of the quality of life of patients with epilepsy can lead to the identification and subsequent implementation of the most effective medical interventions to improve the quality of life of these patients.

From a medical practice perspective, in addition to the assessment, diagnosis and treatment of patients with epilepsy, I have been confronted with issues that have led me to research methods to assess the quality of life of these patients. There were numerous studies worldwide in the literature on the quality of life of people with epilepsy, but only two in Romania at the time of starting the research, which were not published in the international reference literature and none in Brasov county. Those existing in our country included a small number of patients, did not follow and did not deepen the influence of demographic factors and characteristics of the disease on quality of life. I also identified legislative ambiguities regarding the restriction of certain social rights such as the ability to drive a motor vehicle or professional reintegration.

External clinical evidence can inform but cannot replace personal clinical experience and so I wanted to explore these issues further by attempting to identify modifiable disease factors, ethnic, cultural, economic differences compared to other countries and their impact on the quality of life of patients with epilepsy. I also wanted to understand the opportunities and limitations of incorporating quality of life measurement tools into clinical practice.

My special interest and passion for epileptology originated in my neurology residency training, where, from conf.univ.dr.med. Ioana Mîndruță, I learned the first notions of video-electroencephalography (video-EEG) evaluation of patients with epilepsy and I participated with her and observed the first intracranial electrode implantation, long-term monitoring by video-EEG and epilepsy surgery in Romania. Subsequently, as a neurologist, I wanted that in Brasov people with epilepsy who come to the Clinical Hospital of Psychiatry and Neurology Brasov to benefit from diagnosis based on complete clinical, imaging and electrophysiological evaluations for an appropriate treatment, close to where they live. Also, if necessary, they can present these evaluations to centres in the country or abroad where they can benefit from advanced surgical treatment such as vagus nerve stimulator implantation or neurosurgical interventions to interrupt the epileptic focus. This was made possible by equipping the hospital with appropriate equipment, but sometimes perhaps unwise national and local decisions to block activity during the COVID-19 pandemic resulted in limiting epilepsy patients access to investigations and affecting their quality of life.

A significant number of people with epilepsy can effectively manage their condition, and the use of suitable treatment can enhance their medical and social outlook. On the other hand, individuals who have seizures that are not being effectively managed may experience challenges in finding and maintaining job, pursuing education, and forming personal connections. These

issues might arise as a result of social prejudice, stigma, and the dread associated with having seizures. (Asadi-Pooya et al., 2020).

CHAPTER 1

1.1. Ethics in medical practice
1.1.1. Principles

Health ethics faces a multitude of challenges in medicine, health care and scientific research. Ethical codes and their application have a long history since antiquity, and today both advances in medicine and medical practice are contributing at the same pace to the need for health professionals to strengthen their capacity to manage emerging ethical dilemmas effectively. They need to adapt and keep abreast of current ethical debates.

The four principles of bioethics are based on values such as respect for patient autonomy, doing good, doing no harm and justice (Taj & Khan, 2018) and were first mentioned together in 1979 as the Beauchamp and Childress principles (Beauchamp & Childless, 1991) with the aim of guiding clinicians in complex or uncertain situations.

There are four rules that complement these principles. Truthfulness, by communicating the truth while respecting patient autonomy and informed consent; respect for patient privacy and private information by not disclosing it; confidentiality by sharing private information strictly on a need-to-know basis; and fidelity by upholding the duty to care for patients without discrimination, no matter who they are or what they may have done (Benatar, 2006).

Confidential information provided by the patient should not be disclosed, and physicians should adopt a policy of not discussing specific patient details with family members in social gatherings (Weiss, 1982) or on social networks. Exceptions are in cases where the sharing of medical information by the treating physician to other physicians is necessary in the process of care and involves the patient's consent or in exceptional situations that may cause harm to others, such as infectious disease outbreaks, partner disclosure of HIV infection or genetic risks.

1.1.2. Ethical issues in patients with epilepsy

Insufficiently mentioned in the literature in patients with epilepsy, ethical principles have been used in some clinical settings such as guiding conversations with patients or their families about the risk of sudden death in epilepsy (Ronen, 2017) or counselling in epilepsy surgery (Rona, 2015). Adapting the recommendations, for patients with epilepsy, decisions should be made according to context, taking into account the patient's level of culture and training, regulations, as well as the relationship of patients and families with the healthcare team.

Epileptic seizures are unpredictable and their frequency varies from individual to individual, so it is essential that all those who support patients with epilepsy understand the particularities of each patient and how they want to be supported with their condition. A proper epilepsy management plan includes everything from assessing seizure type, to support needs, to emergency procedures, with the patient as an integral part of this plan and development process. (Bellon et al., 2014).

As ethical and clinical decisions are intertwined, trying to analyse them together should always be in the foreground and ethical values should never be in the background. Ethics is becoming part of a doctor's life and understanding how to manage this mix requires practice, skills and guidance. Better deliberation also requires clinical experience.

1.2. History of epilepsy and the development of antiepileptic therapies

1.2.1. History of epilepsy

The long history of epilepsy can be traced back to the first description of an epileptic seizure that appears in a text from 2000 BC, written in Akkadian, inscribed on a stone tablet from Mesopotamia (Labat R, 1951).

The term epilepsy comes from the Greek language and is derived from the verb epilambaneim, which means to contain, to suffer, to possess. In Ancient Greece, epilepsy was known as a sacred disease, a term that reflects ambiguity, as they considered epileptic seizures a form of demon attack or visions of people with epilepsy as being sent by the gods.

The modern view that the aetiology of epilepsy is physiological and not divine has its origins in the writings of what is considered the father of medicine, Hippocrates of Kos, dating from 400 BC. He argued against the widely held belief at the time that epilepsy had a spiritual cause and harshly criticised earlier doctors who attributed epilepsy to divine intervention, calling them quacks and magicians. Hippocrates was the first to attempt a scientific approach to the study and treatment of epilepsy and suggested brain dysfunction as a possible aetiology. (Magiorkinis et al., 2010).

Efforts in the post-Hippocratic era through the views of Galen or Aretaeus failed to make a contribution equal to that of Hippocrates, but they were perpetuated during the Middle Ages, and under the domination of the Church, religious beliefs about epilepsy continued to exist and slowed the progress of science. The Renaissance (1300-1600) opened a period of debate, and new findings expanded clinical knowledge. The observation of epileptic seizures as manifestations of newly discovered diseases such as syphilis, measles or chicken pox led to the concept of symptomatic epilepsy, where the term symptom was understood as a complication rather than a sign. (Patel & Moshé, 2020). Arguments between the divine and the physiological continued, however, until the 18th century Enlightenment, when the entire medical community in Europe largely agreed that divine intervention had nothing to do with epilepsy.

With the invention of electroencephalography (EEG) in 1924, the German psychiatrist Hans Berger was able to confirm that abnormal electrical activity in the brain was at the origin of epileptic seizures. (İnce et al., 2021). The development of EEG has led to significant progress in the understanding of epilepsy and accurate clinical descriptions.

1.2.2. Historical personalities whose lives were affected by epilepsy

The fact that epilepsy is not conditional on mental illness or developmental disorders is demonstrated throughout history by the many prominent figures who have suffered from the condition and who, despite the challenges of their condition, have achieved remarkable things and made significant contributions to society.

Although the Bible does not explicitly mention epilepsy, there are situations described that could be interpreted as in the case of Saul, king of Israel, whose manifestation in the Naioth prophecy to Samuel corresponds to an epileptic seizure (Williams & Le Roux, 2012) or St Peter whose vision on the road to Damascus suggests manifestations of a temporal lobe epileptic seizure (Landsborough, 1987).

The mythological hero Hercules served as the source of the divine connotation that epilepsy received in antiquity, many authors attributed his actions to seizures and called the condition Herculian disease. By associating epilepsy also with political and cultural leaders such as the philosopher Socrates, the poet Callimachus, the Persian king Cambyses II, Alexander the Great or the Roman emperor Caesar, it was considered a disease of geniuses (Orrego-Gonzalez et al., 2020).

The impact on society has been greatest when epilepsy has affected major political leaders. Napoleon I had both epileptic seizures that were the result of chronic uraemia due to gonorrhoea infection and psychogenic seizures related to the immense stress in his life (Hughes, 2003). The

disease also affected Soviet leader Vladimir Lenin, who also died after a 50-minute status epilepticus (Lerner et al., 2004).

Theodore Roosevelt, historian, Governor of New York City, although he suffered from epilepsy, visual impairment and asthma, was a respected man and became President of the United States at the age of 42. Richard Burton, at one time Hollywood's highest-paid actor, was plagued all his life by epilepsy, which later led to ethanol addiction and depression. (Hughes, 2005).

However, the lives of personalities who have suffered from this condition highlight the resilience of the human spirit in the face of health challenges. Their contributions in politics, literature, art and science demonstrate that epilepsy, though a formidable adversary, did not define or limit their potential. Instead, these examples serve as an inspiration and show how determination and creativity can overcome the limitations imposed by a medical condition, leaving their mark on history.

1.2.3. History of the development of antiepileptic therapies

Until the 19th century the treatment of epilepsy was based mostly on spiritual and supernatural beliefs. Hippocrates early recognition that epilepsy is a brain disorder was rejected for many centuries. It was not until the late 1700s that his view began to take root, and yet the treatment consisted of the administration of herbs or various empirical chemical preparations completely lacking any scientific evidence (Singh, 2002).

A chance observation was made by Charles Lacock, obstetrician to Queen Victoria of Great Britain, in 1857 (Eadie, 2012). He found that treatment with potassium bromide stopped epileptic seizures experienced by women with catamenial epilepsy, called hysterical epilepsy at the time, and evidence from British physician Samuel Wilks, a contemporary of Lacock, led to the introduction of potassium bromide as the first effective therapy for epileptic seizures.

German chemists working for Bayer synthesized 5-ethyl-5-phenyl barbituric acid or phenobarbital in 1911, which was marketed for the treatment of insomnia (Yasiry & Shorvon, 2012). With the use by Alfred Hauptmann in patients with *epilepsy* (Kumbier & Haack, 2002), phenobarbital was recognised as an effective and well-tolerated alternative to potassium bromide and has remained to date one of the main treatments in infants with epilepsy or in many patients in developing countries.

Phenytoin, although originally synthesised in 1908 by German chemist Heinrich Blitz, who studied its oxidative properties, was not synthesised further until 1920 when chemist Arthur Dox at the Park-Davis Laboratories in Michigan, USA, demonstrated its lack of sedative properties. It was not until 1938 that American researchers Tracy Putnam and Houston Meritt discovered the clinical efficacy of phenytoin (Anderson, 2009). It remained for several decades the main treatment for various forms of epilepsy, and the fosphenytoin derivative, synthesised in 1990, remains today the first-line treatment for status epilepticus.

The antiepileptic effects of carbamazepine were reported in 1963 and it was used as antiepileptic therapy initially in the UK from 1965, subsequently in Europe and later approved in 1974 in the United States (Magiorkinis et al., 2014).

Sodium valproate was originally synthesized in 1881 by Beverly Burton in the United States and used as an organic solvent. Antiepileptic properties were reported by Pierre Eymard of the Berthier Laboratories in Grenoble and it was launched as an antiepileptic drug in France in 1967, from 1970 in Europe and 1978 in the United States. (Magiorkinis et al., 2014; Shorvon, 2009). *The* first

benzodiazepine available for the treatment of epilepsy was chlordiazepoxide, launched in the UK in 1960 and followed by diazepam in 1963.

New antiepileptic drugs followed like vigabatrin in 1989, lamotrigine and oxcarbazepine in 1990, gabapentin and felbamate in 1993, topiramate in 1995, tiagabine in 1998, levetiracetam in 1999, zonisamide in 2000, pregabalin in 2004, stiripentol and rufinamide in 2007, lacosamide in 2008, eslicarbazepine in 2009, retigabine in 2010, perampanel in 2012, brivaracetam in 2016. (Shorvon, 2009). Although new molecules are constantly being developed, many patients continue to suffer from drug-resistant epilepsy. (Cioriceanu et al., 2020).

Epilepsy surgery was pioneered in 1886 by the English surgeon Victor Horsley, who operated on a patient with a skull fracture and Jacksonian epilepsy by removing scar tissue which resulted in the disappearance of seizures. (Schijns et al., 2015). Subsequent advances were due to studies conducted in the early 20th century by the German neurologist Hans Berger and the American neurologist Frederic Gibbs on the use of electroencephalography in the semiological characterization of epileptic seizures (Ali et al., 2016). In the mid-1950s stereoelectroencephalography using intracranial electrode placement was introduced by Jean Talairach and Jean Bancaud in France (Kahane et al., 2006), and electrocorticography with subdural electrodes was introduced by Wilder Penfield and Herbert Jasper in Montreal (Reif et al., 2016). These techniques were then taken up between the 1960s and 1970s mainly in Anglo-Saxon countries and marked the beginning of a new era of invasive epileptic seizure recordings by still using a combination of these different implantation techniques adapted to the complexity of each patient's condition.

Another important advance in the treatment of epilepsy was the development of the vagus nerve stimulation technique, approved in 1997 (Moshé et al., 2015). For patients experiencing significant adverse effects of antiepileptic drugs or those who are not eligible candidates for epilepsy surgery, this method could be a viable therapeutic approach.

Therapies, both medical and surgical, are not always perfect for the condition to be treated, and there is still the possibility of complications occurring and the goal of seizure freedom not being achieved. All this means that patients with epilepsy still face a combination of social and economic obstacles when integrating into society.

1.3.   Clinical aspects of epilepsy
1.3.1.   Definition, classification, etiology and diagnosis

According to the ILAE, epilepsy is defined as a disorder of the brain characterized by a sustained predisposition to generate epileptic seizures and the neurobiological, cognitive, psychological and social consequences of epilepsy (Fisher et al., 2014). It is a condition with multiple possible seizure types and syndromes, diverse aetiologies and variable prognoses. Advances in recent years in imaging, molecular biology and genetics have been able to improve our understanding of the pathophysiology of seizures and epilepsy. The Classification and Terminology Commission of the International League Against Epilepsy proposed substantial changes to the 1989 classification in 2010 and revised them in 2017 (Fisher, Cross, D'Souza, et al., 2017; Scheffer et al., 2017). The framework allows for three levels of diagnosis, namely seizure types, epilepsy types and epilepsy syndromes, depending on the availability of information and resources. Thus access to EEG, brain imaging or genetic studies may influence the maximum level of diagnosis, and in low-resource facilities the level may be limited to seizure type only.

The terminology of aetiological classification has also evolved over time. The latest International League Against Epilepsy (ILAE) classification of epilepsy in 2017 sets out six categories according to aetiology: genetic, structural, metabolic, autoimmune and unknown (Fisher, Cross, D'Souza, et al., 2017; Fisher, Cross, French, et al., 2017; Scheffer et al., 2017). The etiology of epilepsy should be considered at all three diagnostic levels and may be combined.

Formulation of a complete epilepsy diagnosis including disease certification, etiology, seizure semiology and degree of disability is performed by the neurologist based on these validated criteria of standard or specialized EEG evaluation, as video-EEG monitoring techniques and brain MRI imaging with HARNESS epilepsy protocol (Bajenaru, 2010; Bernasconi et al., 2019).

Correct diagnosis of epilepsy has essential implications for the patient's health, occupation and social interaction. EEG is essential for diagnosis and is a safe, non-invasive test. Video-EEG involves recording electrical activity of the brain by EEG coupled with a simultaneous audio-video recording that can be thoroughly analysed (Acharya et al., 2013). When there is uncertainty about the diagnosis of epilepsy, classification of seizure type or epilepsy syndrome, the ILAE recommends long-term video-EEG monitoring for seizure quantification and assessment of electrical characteristics (Velis et al., 2007). Paraclinical assessments are carried out according to each patient's particularities. The risk of recurrence and the need to initiate appropriate therapeutic measures require an accurate diagnosis based on clinical appearance, EEG or video-EEG, brain imaging by CT or MRI and it is recommended to evaluate a first unprovoked epileptic seizure in a specialised neurology service within two weeks of its occurrence. (Băjenaru, 2010).

Close communication between the patient, neurologist and family doctor helps to monitor the progress of epilepsy. The patient should receive accurate and thorough information about each phase of the disease, lifestyle and therapies administered.

1.3.2. General treatment principles

The management of patients with epilepsy involves three main objectives: seizure control, avoiding side effects of treatment and maintaining or restoring quality of life. The treatment of epilepsy includes treatment of seizures and status epilepticus, chronic treatment with antiepileptic drugs, surgical treatment and other therapeutic techniques. Knowledge of available drugs, their mechanisms of action, drug interactions and side effects is essential. Referral to a specialist neurologist when a diagnosis of epilepsy is suspected may be sufficient, but referral to a neurologist who is super-specialised in epilepsy may be necessary when there is doubt about the diagnosis or if the patient continues to have seizures.

About half of patients with newly diagnosed epilepsy may become seizure-free after the first antiepileptic drugs prescribed, but despite the availability of more than 25 antiepileptic drugs worldwide, current drugs are only effective in 66% of patients in high-income countries (Thijs et al., 2019). Antiepileptic drugs should be introduced slowly and doses should be gradually increased to the maximum tolerated dose, depending on symptoms or if seizures continue.

In 2010, the ILAE Therapeutic Strategies Committee defined treatment-resistant epilepsy as the failure to stop epileptic seizures despite drug treatment instituted after two therapeutic attempts with appropriately selected antiepileptic drugs used alone or in combination and at appropriate doses. (Cioriceanu et al., 2020; Kwan et al., 2009). In these cases all possibilities of treatment failure should be excluded and assurance that the diagnosis is correct should be ensured. Seizure control may require further investigation or referral to a specialised centre. If the diagnosis is confirmed, alternative non-pharmacological treatments including surgery or vagal neurostimulation should be considered.

Patients with pharmacoresistant focal epilepsy may benefit from disconnection or removal of the epileptic focus to achieve complete seizure control or at least to stop disabling seizures. In well-selected groups, the percentage of patients who are seizure-free after surgery can be as

high as 80%. (Ryvlin, Cross, et al., 2014). The benefits of successful surgery include good seizure control, increased quality of life, reduced risk of injury or premature death, ability to drive motor vehicles on the road, greater independence, and improved career options (Dewar & Pieters, 2015).

Neurostimulation techniques are palliative options for patients with pharmacoresistant epilepsy who are not considered candidates for focal resective epilepsy surgery (Skrehot et al., 2023)in case of failure or limited access. Vagus nerve stimulation is also approved in Romania for the adjunctive treatment of drug-resistant epilepsy in adults and children over 12 years of age. With this method, the cerebral cortex is stimulated in a controlled manner via the vagus nerve which is connected to an implanted generator. Vagal stimulation reduces the frequency of epileptic seizures by 50% or more in about a third of patients. (Boon et al., 2018), improves quality of *life* (Ryvlin, Gilliam, et al., 2014) and may reduce the risk of sudden death (Ryvlin et al., 2018).

Anti-epileptic drugs can control seizures in up to two-thirds of patients but do not alter long-term prognosis. Epilepsy surgery remains the most effective way to achieve long-term seizure elimination, but remains an option only for a few patients with drug-resistant epilepsy.

1.3.3. Particularities of the treatment of patients with epilepsy in Romania

In Romania there is no national register of epilepsy patients and according to the National Institute of Public Health the number of epilepsy patients in 2021 was 124,583 people. (Romanian Epilepsy Patients Association, 2022). But according to other estimates the number is now up to 500,000. (Romanian Ministry of Health, 2016)of which 100,000 are not registered with the National Health Insurance House because they prefer to purchase therapy on their own and hide their disease due to society's intolerance towards this category of patients. (Marica, 2018).

The number of specialist and primary care neurologists in Romania is 4.8 per 100,000 inhabitants, among the lowest in Central and Eastern Europe (Jędrzejczak et al., 2013). In order to acquire EEG interpretation skills, neurologists can attend courses dedicated to postgraduate training, but those wishing to specialize in epileptology can only access on their own courses organized and certified by various international scientific and professional societies ționale, in Romania there is no such certification.

Hospital epileptology departments exist in many European countries with comprehensive epilepsy programmes. In Romania, neurologists who do not have EEG skills or specialisation in epileptology, or lack the resources to fully investigate and treat patients with epilepsy, can refer them to a specialised centre, but these are often only found in certain hospitals in university centres.

The treatment protocol for patients with epilepsy in Romania is in accordance with the ILAE recommendations, aiming to control or at least reduce epileptic seizures, but the Guidelines for Diagnosis and Treatment in Neurology, which also include adult epilepsy (Bajenaru, 2010)In the last 15 years there has been an increase in therapeutic options with antiepileptic drugs, but their availability in Romania is limited or not supported by the compensation scheme.

Also, the access of Romanian patients with epilepsy to innovative therapies or the lack of fundamental therapies on the market, such as carbamazepine, have been repeatedly reported both by patients through the Romanian Epilepsy Patients' Association and by doctors. (Foarfeca, 2023; Păduraru, 2019). All these barriers have led to the need to adapt treatment standards at national level depending on the availability of therapies which is dependent on marketing policies, compensation or fluctuations in the supply chain.

In Romania, the epilepsy surgery program was launched with the first implantation of intracranial electrodes for stereo-electroencephalographic monitoring in 2012. (Boiangiu, 2012)through the efforts of a team composed of Dr. Ioana Mîndruță, a neurologist, Dr. Jean Ciurea, a neurosurgeon, Andrei Barborică, a physicist, together with collaborators from the University Emergency Hospital Bucharest, Bagdasar - Arseni Hospital Bucharest and the University of

Bucharest - Faculty of Physics. Due to scarce resources and limited experience, there are currently only three regional epilepsy centres accredited according to ILAE standards and financed by the state medical system, which integrate neurologists specialised in epileptology and neurosurgeons specialised in epilepsy surgery for adult patients at the University Emergency Hospital Bucharest and Bagdasar - Arseni Hospital Bucharest and children at the Clinical Hospital of Psychiatry Prof. Dr. Alexandru Obregia. (Romanian Ministry of Health, 2016).

This is a barrier to patients' access to treatment and could be countered by setting up more regional epilepsy centres. The situation is similar to other low- and middle-income countries (Mansouri et al., 2019).

The first vagus nerve stimulation device was fitted in Romania in 2009 (Romanian Epilepsy Patients Association, 2011). Currently, patients with epilepsy benefit from this therapy through the National Programme for the Diagnosis and Treatment of Drug Resistant Epilepsy, which is carried out in the three centres in Bucharest mentioned above. After implantation of the vagus nerve stimulation device, monitoring of the patients, adjustment and regulation of the parameters, checking the battery level, can be carried out in the territory by doctors who have the necessary knowledge and the tablet-remote control system that can be provided by the manufacturing company.

The health care provided to epilepsy patients in Romania is in line with that in Europe and faces similar problems such as insufficient use of epilepsy surgery, lack of comprehensive assessment, stigma and social problems, high costs of new antiepileptic drugs, lack of specialists and specialised epilepsy care or insufficient knowledge of the epilepsy profession, lack of equipment and allocation of financial resources. The lack of epidemiological data on patients with epilepsy is a problem in Romania and leads to difficulties in establishing with certainty specific deficiencies and delays in taking timely action. There is therefore a need for a register of patients with epilepsy in Romania, a review of the compensation and marketing policies for anti-epileptic drugs already approved at European level and not yet approved in Romania, and a harmonisation of the availability and indications of these drugs in all european countries.

1.4. Aspects and legislative implications of epilepsy diagnosis

People with epilepsy may face many obstacles in their daily lives related to work, driving, relationships and need medical guidance. These patients have the same rights as any employee and should be treated without discrimination.

The fact that a patient has a diagnosis of epilepsy does not mean that they cannot work. Doctors assessing patients with epilepsy for employment, both occupational physicians and neurologists, need to know the aetiology of the disease, the type and frequency of seizures, compliance with treatment and associated symptoms. Studies have shown that patients with epilepsy face social discrimination, have lower levels of education and finding employment can be difficult. (Chew et al., 2018).

According to Romanian legislation, epilepsy patients can be classified in a degree of disability that is associated with professional limitations, depending on the frequency of seizures. The right to work of people with disabilities is regulated in Romania by law no.76/2002 (Romanian Parliament, 2002) and Law no. 448/2006 updated in 2019 (Romanian Parliament, 2008). According to them, including patients with epilepsy, have the right to work according to their professional training and degree of disability. They can benefit from professional orientation provided by the state whereby

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following an assessment they can have access to information and choose the field that suits their skills and professional training, and employment can be made on the free labour market, in protected forms or at home.

Professional confidentiality remains one of the pillars of the doctor-patient relationship since the early days of medicine and is particularly important because without it, patients would not disclose essential information. Privacy and confidentiality are guaranteed in Romania by the Civil, Criminal and Medical Deontology Codes, and breaching them can be considered a crime. (Coca & Lazăr, 2015). However, a breach of doctor-patient confidentiality can and should occur in specific situations. Such legitimate situations in patients with epilepsy may be obtaining or withdrawing a car license, employment as drivers, or occupations that involve working at heights or with high sources of electrical voltage.

All European countries have restrictions on driving by people with epilepsy. Current legislation in most countries allows people diagnosed with epilepsy and who have controlled seizures to obtain a driving licence.

Given these issues, there are legal implications for patients with epilepsy and the doctor needs to know how to manage them and understand the medico-legal aspects. Prohibiting people with epilepsy from driving a motor vehicle on the road without proper screening results in significant limitations for patients with epilepsy in society and can make it difficult for them to travel to work, school or recreational activities, with a significant impact on quality of life. Since Romanian legislation does not distinguish between seizure types, but only between provoked, unprovoked and sleep-induced seizures, and although the law should be the basis for decisions, medical opinion tailored to each patient's particularities remains the most important part of the decision-making process.

1.5. Quality of life
1.5.1. General concepts

Life expectancy has increased due to improvements in medicine, public health, nutrition, income, education and migration. Thus, in addition to the treatment of age-related conditions, long-term care will increase, leading to higher life expectancy. A person's quality of life has been shown to be as important as life expectancy (Schmied et al., 2015).

According to the WHO, quality of life is an individual's perception of their position in life in the context of the culture and value system in which they live and in relation to their goals, expectations, standards and concerns. It presupposes a complete state of physical, mental and social well-being and the capacity to fulfil social roles and adapt to the changing environment, and not merely the absence of disease or infirmity. (World Health Organization, 1997). Quality of life is a multidimensional concept that depends on a variety of factors such as physical health (Rippe, 2018), mental and emotional well-being (Shahini et al., 2023), financial stability (Schinasi, 2005) and levels of spirituality, religion or personal beliefs (Borges et al., 2021).

Quality of life can be measured by patient self-assessment tools such as the naries, which can be specific and generic. This can provide valuable information on health status, psychosocial aspects and the effectiveness of therapeutic interventions. It can also determine the clinical and economic effectiveness of drugs, surgical interventions and their effects on patients' lives, and assess the legitimacy of certain costly medical procedures and cost-effectiveness in the health system. (Dziurowicz-Kozłowska, 2002).

Quality of life assessment can produce useful results in the context of improving the economic effects and functioning of the health system. The health system can generate high costs and there are no limits to the amounts that can be absorbed and even wasted. Thus it would be interesting to analyse the relationship between patients' quality of life and the health budget and to make accurate predictions about funding and its influence. Patient self-assessments of

quality of life are data that private insurance companies use to estimate the effects of disease on the cost of treatment (Pachalska et al., 2001) and their analysis could influence the management of the health system and help to save some money.

1.5.2. The evolution of instruments to assess the influence of epilepsy on quality of life

The literature indicates that there are three stages in studying the effects of epilepsy on cognitive, behavioural, social and physical functions. The first and earliest was characterised by the use of traditional forms of clinical assessment and available generic tests to study the general effects of epilepsy, the influence of specific clinical variables such as seizure type, age of onset or the consequences of treatment with antiepileptic drugs on patients' lives. The second phase was characterised by the development of epilepsy-specific measurement tools on cognitive ability, psychological state, psychosocial state and were designed to address clinical and research needs not provided by previous generic measurement tools. The third and most recent phase is characterised by the use of measurement models, techniques and tools developed from the field of health services research to formally assess contemporary definitions of quality of life in epilepsy.

These assessment methods varied in their coverage of different aspects, degree of use, complexity or source of information, from interview, self-assessment or data provided by carers. Thus, research assessment methods and procedures have been formally applied to epilepsy, modified for application in epilepsy or developed for epilepsy, and due to the growing interest in quality of life in epilepsy, a number of measurement tools have been developed and implemented.

Currently the most common scales are the generic European Quality of Life 5 Dimensions - EQ-5D and QOLIE-31. (Siebenbrodt et al., 2023). Despite its length, the QOLIE-31 accurately assesses quality of life compared to shorter assessments such as EQ-5D and QOLIE-10, especially in more severely affected patients (Willems et al., 2022). The EQ-5D, however, has the advantage of being easier to administer and consists of only five questions covering the domains of mobility, personal care, usual activities, pain/discomfort and anxiety/depression (Gottschalk et al., 2020).

QOLIE-31 can include multiple populations of people with epilepsy and address multiple social barriers. It is a questionnaire that includes 31 questions grouped into seven domains that assess health concepts such as mood, daily activities, energy/dizziness, cognition, seizure worry, medication effects, and general quality of life. These domains cover both general and epilepsy-specific quality of life over the past four weeks. The total QOLIE-31 score according to the scoring manual is obtained by the weighted average of the subscale scores, with values ranging from 0 to 100, with higher scores indicating better quality of life (Cramer et al., 1998). The QOLIE-31-P (Appendix 1) is the second, updated version, has minimal changes such as the names of some of the subscales and adds to each a new item, distress, defined as dissatisfaction for the respondent (Cramer & Van Hammée, 2003).

The two versions have been cross-translated from the English to the American version in a large number of languages, including Romanian. They have been validated on different populations and have become the most commonly used scales today in assessing quality of life of patients with epilepsy in medical literature and clinical trials.

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1.5.3. Particularities in quality of life research for patients with epilepsy

Epilepsy greatly affects quality of life and WHO ranks it as the second most burdensome neurological condition worldwide in terms of disability relative to years of life (Murray et al., 2012).

The quality of life of epilepsy patients in high-income countries is better than in low- and middle-income countries. Higher levels of poverty, limited access to health care and anti-epileptic drugs, shortage of specialised medical staff, stigma tisation, availability of drugs and labour market integration result in a worse quality of life for patients in low- and middle-income countries (Espinosa-Jovel et al., 2018).

The few studies on life expectancy show that it is reduced in patients with epilepsy, with the highest mortality rates among patients younger than 40, a group that in the general population has the lowest risk (Sander & Sillanpaa, 1997). Epilepsy has a known association with an increased risk of suicide, especially shortly after diagnosis (Christensen et al., 2007).

The consequences of epileptic seizures can include loss of employment, loss of the right to drive, impaired self-esteem and self-control, which is reflected in the quality of life profiles of patients who experience them. The burden of an epilepsy diagnosis affects patients, their families and carers. They may face stigma, public misunderstanding, lack of social support, social isolation, embarrassment, fear and discrimination, which affects the whole society (Jacoby et al., 2005). People with epilepsy are quick to adopt the assumption that epilepsy is a stigmatised condition and develop a particular perception characterised by a high degree of perceived stigma, leading to concealment of the diagnosis as a means of protecting themselves from discrimination (Mao et al., 2022).

The quality of life of patients with epilepsy depends on the effectiveness of antiepileptic drug therapy and the duration of the disease. Seizure frequency is one of the most important determinants of poor quality of life scores. Being seizure-free is a necessary but not sufficient condition for a better quality of life. However, in order to have a clear picture of the quality of life of patients with epilepsy, a better understanding of how it is influenced in different countries is needed due to the large number of cultural, ethnic and economic differences.

1.5.4. Trends in the study of the quality of life of Romanian patients with epilepsy

Studying the quality of life of patients with epilepsy in Romania is an unusual approach, although in recent decades efforts have been made worldwide to assess it and to study the impact of clinical, demographic, psychosocial factors and associated comorbidities. In our country studies are particularly limited, include a small group of patients, do not deepen all the factors and we have not identified any published in the international literature. The QOLIE-31-P questionnaire has been used in Romania in clinical studies (Zadeh et al., 2015).

The quality of life of patients with epilepsy should be of interest to doctors who care for them. Seizure control and antiepileptic drugs are modifiable parameters that can be considered to improve quality of life. Prescribing, changing a treatment, epilepsy surgery or implantation of vagus nerve stimulation devices should be carried out with the aim of achieving good seizure control with as few side effects as possible. Assessment of these issues could be achieved by regular quality of life investigations using simple, readily available and easy to interpret instruments.

1.6. Conclusions

Since ancient times, the diagnosis of epilepsy has been a challenge for both patients and doctors. Today, advances in medicine have led to the potentially curable disease in up to 70% of patients. Despite research efforts and available drug and surgical treatment options, the remaining patients remain drug-resistant.

Currently in Romania, epilepsy diagnostic and treatment guidelines are aligned with the ILAE recommendations and efforts are being made to improve them with new findings. Thus, patients with epilepsy in Romania benefit from traditional antiepileptic drugs, but measures need to be taken to allow faster market approval of new molecules and their compensation. The lack of a national register of patients diagnosed with epilepsy makes it difficult to estimate their real numbers, and the problems they face can only be brought to the attention of the population and decision-makers through patient associations and the neurologists who care for them. Periods of shortages of essential anti-epileptic drugs on the market in our country have led to signals from patients through the print and online media.

The stigma faced by patients with epilepsy is due to the low level of public awareness. Legislative ambiguity about the measures to be taken and the right to drive a motor vehicle in the case of patients with a first epileptic seizure or epilepsy diagnosis means that they tend to hide their illness or may expose doctors to situations with a medico-legal impact in the event of traffic accidents involving such patients.

Although research on the influence of clinical and demographic factors and the consequences of epilepsy on quality of life has a long history, demonstrated by numerous studies worldwide, and currently represents a new development in the field of epilepsy, none has been conducted in Romania in the last 12 years. The two studies identified in our country and carried out prior to this period included a small number of patients and did not follow and investigate all factors in depth.

International research evidence can only inform us on these issues and obviously cannot replace the lack of recent data and studies in our country. Thus, it is necessary to study the impact of clinical and socio-demographic factors on the quality of life of Romanian patients with epilepsy, to follow the evolution over time and to investigate the influence of epileptic seizure severity on quality of life.

A better understanding of the quality of life of patients with epilepsy can lead to the identification and application of the most effective medical interventions to maximise their quality of life and also the routine application of measurement tools in clinical practice. Comparison of data can identify ethnic, cultural, economic differences with other countries, provide useful information about the impact of epilepsy in different counties and stimulate research on these issues across the country for a broader perspective.

CHAPTER 2
Practical part

2.1.   Objectives and working hypotheses

The first study aimed to identify the influence of socio-demographic and clinical factors on the quality of life of people with epilepsy admitted to a Romanian hospital, using the QOLIE-31-P Quality of Life Questionnaire. The secondary objectives were to reflect on the opportunities and limitations of incorporating such a tool into clinical practice. The research hypotheses consisted in the assumption that there are differences influenced by socio-demographic and clinical factors regarding quality of life in a group of Romanian patients with epilepsy, that there are statistically significant correlations between the items of the applied measurement instrument and quality of life domains. Also that there are no differences between the predictors of quality of life of people with epilepsy in Romania compared to similar research conducted in other countries.

The second study had as main objective to assess over time the perception of a group of Romanian patients with epilepsy regarding quality of life, using the QOLIE-31-P questionnaire. The secondary objective was to deepen the relevance of patients' reassessment in their daily life by using this instrument, and the hypothesis of the study consisted in the assumption that a better control of seizures through a lower frequency of seizures improves the quality of life of PE.

The third study aimed to report on the translation and cultural adaptation of the Seizure Severity Questionnaire - SSQ, an assessment tool that has never been used in our country, on a group of patients with epilepsy evaluated at a hospital in Romania. The secondary objective was to assess the relationship between epileptic seizure severity and seizure frequency in patients diagnosed with epilepsy. The hypothesis of the study consisted in the assumption that there are statistical correlations between the SSQ total score and the QOLIE-31-P domain and total scores, and that this seizure severity measure may be relevant in application to Romanian patients with epilepsy alongside the QOLIE-31-P questionnaire.

2.2.   General methodology

The PhD thesis comprises an analytical, observational, cohort study based on the QOLIE-31-P questionnaire, a second analytical, cohort, longitudinal study based on the QOLIE-31-P questionnaire and a third analytical, observational, cohort study using the QOLIE-31-P questionnaire and the Romanian translated version of the SSQ questionnaire for cultural adaptation in Romanian patients with epilepsy.

The study period was February 2018 to August 2021 and digital video-EEG recording was performed to study the location of epileptiform activity in all participants.

For inclusion in the research all patients met the inclusion and exclusion criteria, signed consent forms for participation and for publication of results. The questionnaires administered were assigned numbers and together with the data collected were anonymised to achieve confidentiality.

2.3.   Influence of socio-demographic and clinical factors on the quality of life of Romanian people with epilepsy

2.3.1. Importance of the study

Epilepsy can be controlled in a relatively large percentage of patients (Kwan & Brodie, 2000)and appropriate therapy improves the social and medical prognosis of patients with epilepsy (Guekht et al., 2007). Patients with uncontrolled epileptic seizures may face difficulties in employment, problems in

education and relationships due to social discrimination, stigma and fear of having seizures (Asadi-Pooya et al., 2020).

Additionally, with a comprehensive clinical evaluation that considers a complete medical history, imaging studies, and electroencephalographic tests, it is necessary to conduct assessments to determine the subjective perception of quality of life in individuals with epilepsy. Acquiring and utilizing this information can aid in strategizing treatment, enhancing seizure management, reducing the adverse effects of antiepileptic medications, and enhancing general well-being (Baker, 2001).

Despite the existence of numerous global studies examining the quality of life of individuals with epilepsy, Romania lacks sufficient data and has not conducted any recent studies in our country that have been published in international scientific literature, utilizing quality of life assessment tools. Their utilization in regular clinical practice relies on the physician's resolve to allocate the requisite time for application and examination of the outcomes during the consultation or investigation.

2.3.2. Hypothesis and objectives of the study

Using the QOLIE-31-P questionnaire, the primary goal of this study is to determine how disease and demographic parameters affect the quality of life of people with epilepsy who are admitted to a Romanian hospital. The secondary aims seek to explore the potential opportunities and constraints of integrating this tool into medical practice.

The hypotheses of the research consist in the assumption that there are differences influenced by socio-demographic and clinical factors on quality of life in a group of Romanian patients with epilepsy, that there are statistically significant correlations between the items of the applied measurement instrument and the domains of quality of life. Also that there are no differences between the predictors of quality of life of patients with epilepsy in Romania compared to similar research conducted in other countries.

2.3.3. Material and methods

2.3.3.1. Study design

This analytical, observational, cohort, questionnaire-based study enrolled 91 patients, ranging in age from 18 to 79 years, who had a confirmed diagnosis of epilepsy based on the criteria established by the ILAE (Scheffer et al., 2017). These patients were admitted to the Clinical Hospital of Psychiatry and Neurology Brasov for examination using video-EEG. From February 2018 to August 2021, patients who consented to take part in the study were registered.

2.3.3.2. Inclusion and exclusion criteria

Only patients with progressing neurological or mental diseases, severe somatic pathology, intellectual disabilities, and difficulties in understanding research instruments were excluded. No further specific selection criteria were applied.

2.3.3.3. Research tool

Quality of Life in Epilepsy Questionnaire - QOLIE-31-P (Cramer & Van Hammée, 2003), w is a questionnaire designed for adults aged 18 years and older. It is an update of the of the Quality of Life in Epilepsy Questionnaire - QOLIE-31 version 1 (Cramer et al., 1998). The QOLIE-31-P is a

questionnaire that consists of 30 items related to various aspects of health. These items are divided into seven scales: emotional well-being (5 items), social functioning (5 items), energy/fatigue (4 items), cognitive functioning (6 items), seizure worry (5 items), medication effects (3 items), and general quality of life (2 items). Additionally, each scale includes a new item that asks about the level of distress experienced by the respondent in relation to the subject of that particular scale. The scoring methodology adheres to the guidelines outlined in the scoring manual for the QOLIE-31-P. The total and scale scores go from 0 to 100, where higher scores indicate a superior quality of life. The scoring technique initially transforms item responses into scores ranging from 0 to 100, where higher scores indicate a higher level of well-being. The QOLIE-31-P scale scores are calculated by multiplying the distress item of each converted item score and then taking the average. The overall score is determined by computing the mean of the weighted ratings from the seven scales.

Prior to beginning the study and application of this questionnaire, permission and copyright were sought from Joyce Cramer. These were obtained from the copyright holder, who submitted the QOLIE-31-P English version questionnaire used in this study. The questionnaire has been used before on patients with epilepsy in Romania and in clinical trials for antiepileptic drugs.

2.3.3.4.   Study procedure

Patients diagnosed with epilepsy who came for inquiry by video-EEG were identified based on the admission paperwork provided to the video-EEG unit. Following the confirmation of diagnosis through clinical examination, electrophysiological, and imaging tests, patients were invited to participate in the research and provided with a detailed explanation of its objective. The participants were given the chance to inquire about the research, and it was clarified that declining to participate would not result in any discomfort. Individuals who gave their consent willingly signed the necessary documents to participate in the research and allow the publication of the findings. Subsequently, the surveys were distributed, with the purpose of maintaining confidentiality by assigning numerical identifiers. A digital video-electroencephalogram (EEG) was conducted to investigate and analyze the epileptiform activity.

2.3.3.5.   Data collected

Data on socio-demographic factors including age, gender, residential setting, marital status, employment status, and level of education have been collected. Also included were the following clinical data regarding the diagnosis of epilepsy: age of onset of seizures, frequency of seizures, type of epilepsy after clinical onset, presence of aura, etiology, type of seizures, presence of seizures during sleep, number of antiepileptic drugs and date of last seizure.

2.3.3.6.   Statistical analysis

GraphPad Prism version 9.2.0 software was used to analyze the data. For categorical variables, absolute values and percentages were used, while other parameters were processed using statistical techniques for the variables, such as measuring mean scores and standard deviation (SD). Following seizure management, individuals with epilepsy were divided into two groups based on their most recent seizure: the controlled group, which had no seizures in the previous year, and the uncontrolled group, which had at least one seizure.

The Total QOLIE-31-P (ST) scores were categorized into three groups based on their mean scores: those who had scores ≥1 standard deviation from the mean were classified as having a high quality of life, those with scores within 1 standard deviation were classified as average, and those with scores ≤1 standard deviation were classified as having a low quality of life.

For the purpose to examine the relationships between socio-demographic and clinical characteristics and QOLIE-31-P ST scores and subscales, the independent samples t-test was

applied for quantitative variables involving two groups, while analysis of variance (ANOVA) was utilized for situations involving more than two groups. The Chi-2 test had been used for qualitative variables. The variables that were found to be statistically significant in the univariate analysis were included in a multiple linear regression model to examine their ability to predict QOLIE-31-P ST scores and subscales. A significance level of 0.05 for the p-value and a 95% confidence interval were established for all tests.

2.3.3.7. Ethical aspects

Prior to the start of the study, it received the approval with no. 1121/30.01.2018 from the manager of the Clinical Hospital of Psychiatry and Neurology Brasov and the approval with no. 1.1/21.05.2018 from the Ethics Committee of the Medical Scientific Research of the Transilvania University of Brasov.

2.3.4. Results

The mean total QOLIE-31-P scores of the participants were 64.89 (±14.72). The scores for the energy domain were 31.67 (±27.28), for mood 35.37 (±25.79), for the activities of daily living domain 43.32 (±32.17), for cognition 46.32 (±33.74), for the effect of antiepileptic drugs 46.83 (±34.06), for seizure worry 28.89 (±32.05), and for the general quality of life domain 37.91 (±25.54) in the energy domain. Among the patients, 23% (n=21) experienced a low quality of life, 49.5% (n=45) had a medium quality of life, and 27.5% (n=25) reported a high quality of life.

The socio-demographic data analysed were age, gender, residence, marital status, employment status and degree of education.

The mean age of epilepsy patients in this study was 43.04 years with an SD of 14.92 years. The minimum age was 18 years, while the maximum age was 79 years. By age group, between 18-44 years were 56.0% of patients and between 45-79 years were 44.0%. Comparing the two age groups, patients between 45-79 years had statistically significant lower total scores.

Patients aged 45 to 79 also had lower scores o on the domains of energy, mood, cognition, seizure worry and overall quality of life.

Of the total 91 patients with epilepsy, 57.1% (n=52) were female and 42.9% (n=39) male.

There was no significant correlation between the gender of epilepsy patients and the total QOLIE-31-P score.

Compared to men, women had lower mood scores.

The majority of epilepsy patients studied lived in urban areas, while 24.2% (N=22) lived in rural areas. There was no statistically significant correlation between participants' residence environment and total QOLIE-31-P score. We also did not find a correlation between residence environment and QOLIE-31-P domains.

62.6% (N=57) of the study participants were married, while 37.4% (N=34) were unmarried. There was no statistically significant correlation between marital status and total QOLIE-31-P score. There was also no statistically significant correlation between marital status and quality of life domains.

In terms of employment status, 45.1% (n=41) of participants were employed, 17.6% (n=16) were unemployed, 4.4% (n=4) were students, 9.9% (n=9) were retired due to illness and 23.1% (n=21) were old age pensioners. Epilepsy patients retired on sickness had the lowest total QOLIE-31-P score, denoting the lowest quality of life, compared to those with other employment status.

Being retired due to illness was associated with lower scores in the domains of mood, activities of daily living, cognition, seizure worry and overall quality of life.

In terms of educational level, 3.3% (n=3) have only 4 completed grades, 13.2% (n=12) have 8 grades, 18.7% (n=17) have completed vocational school, while 46.2% (n=42) have completed high school, and 18.7% (n=17) have a university degree. Patients with only 4 primary grades and those with 8 grades completed had the lowest total QOLIE-31-P scores compared to those with more years of education.

At the same time, scores in the general quality of life domain were lowest in patients with few years of education, 4 and 8 years respectively.

The clinical data of epilepsy analyzed were age of patients at seizure onset, seizure frequency, epileptiform activity recorded by video-EEG, number of antiepileptic drugs administered, type of epilepsy after seizure onset, etiology of the disease, presence of aura, seizure manifestations, presence of seizures during sleep and seizure control.

The age of onset of epileptic seizures in 30% (n=27) of patients was under 18 years, while in 70% (n=64) seizures started after 18 years. There was no correlation between age of onset of epileptic seizures and total quality of life score. We also found no correlations of age at seizure onset and QOLIE-31-P domains.

By seizure frequency, 15.4% (n=14) of the study participants had no seizures in the past year, 51.6% (n=47) had between 1 and 6 seizures per year, 26.4% (n=24) had 2 or ≥2 frequent seizures per month, and in 6.6% (n=6) seizure frequency was 1 per month. Patients with frequent seizures defined as 2 or ≥2 per month had the lowest total QOLIE-31-P score, followed by those with seizure frequency of 1/month, compared to those with more infrequent seizures of 1-6/year or those with no seizures in the past year.

Seizure frequency was correlated with almost all QOLIE-31-P domains, except the domain of antiepileptic drug effects. Study participants who had 2 or ≥2 seizures per month reported the lowest values in the domains of energy, mood, daily activities, cognition, and seizure-related worry.

Video-EEG recordings of brain electrical activity in patients with epilepsy in the study captured epileptiform abnormalities in 90.10% (n=82) of them, with 9.90% (n=9) having interictal recordings without changes. Epileptiform activity was predominantly in the right cerebral hemisphere in 33.0% (n=30), in the left in 24.2% (n=22) and 33.0% (n=30) had bilateral, generalized discharges. There were no statistically significant correlations between epileptiform activity and total QOLIE-31-P score. Patients without changes on the recorded video-EEG pathway had the highest mean score on the daily activity domain compared to those with recorded epileptiform abnormalities.

The majority of epilepsy patients studied, 56% (n=51) were on antiepileptic drugs alone, 28.6% (n=26) were on polytherapy and 15.4% (n=14) were not on treatment.

Patients who were not on antiepileptic drugs had significantly higher QOLIE-31-P total score values compared to the other categories. The lowest scores were recorded in those on polytherapy, signifying their poorer quality of life.

There were no statistically significant correlations between the number of antiepileptic drugs and QOLIE-31-P domains.

The majority of patients studied have a diagnosis of focal epilepsy and only 13.2% (n=12) generalized. We found no statistical correlations between epilepsy type and total QOLIE-31-P score. Correlations of statistical significance were also not found between epilepsy type and quality of life domains.

According to the ILAE classification, epilepsy was of structural etiology in 56.7% (n=48) of cases, unknown in 42.9% (n=39) and genetic in 4.4% (n=4) of cases. The etiology of epilepsy was not correlated with the domain score nor with the total score.

The majority of epilepsy patients in the study do not have aura preceding seizures, while 38.5% (n=35) of them reported the presence of aura at seizure onset. There were no statistically significant correlations between the presence or absence of aura at the onset of epileptic seizures and QOLIE-31-P or total domain scores.

In terms of seizure semiology, 85.7% (n=78) of patients had seizures with tonic-clonic limb contracture, and 14.3% (n=13) had no such manifestation during the events. The type of seizures after the presence or absence of tonic-clonic contractures did not influence the quality of life domains score nor the total score.

The presence of seizures during sleep was identified in 18.7% (n=17) of patients, compared to 81.3% (n=74) who did not have morphic seizures. The presence of sleep seizures was not correlated with the total QOLIE-31-P score. Patients with sleep seizures had higher mood scores compared to those without sleep seizures.

The majority of patients in the study, 90.1% (n=82) were uncontrolled in terms of epileptic seizures and only 9.9% (n=9) were seizure free in the last year. Patients with uncontrolled seizures had lower total QOLIE-31-P scores compared to those with controlled seizures and poorer quality of life.

Uncontrolled epileptic seizures predicted lower scores in the domains of mood, activities of daily living, cognition, seizure-related worry, and overall quality of life.

In multiple regression, the predictors cognition (t=3.743, p=0.0003) and MAE effects (t=3.481, p=0.0008) had the most significant influence on the total QOLIE-31-P score.

2.3.5. Discussions

In this study, the mean QOLIE-31-P ST for enrolled patients was lower than in UK studies (Ridsdale et al., 2017), Czech (Tlusta et al., 2009) or Greece (Piperidou et al., 2008)but higher than in research conducted in Bulgaria (Todorova, Velikova, & Tsekov, 2013)France (Picot et al., 2004), Germany (May et al., 2001), Spain (Villanueva et al., 2013) and Russia (Melikyan et al., 2012). It was also higher compared to European and *world* QOLIE-31 scores (Saadi et al., 2016), and the majority of enrolled patients had an average quality of life. The values of the scores may differ due to health conditions and demographic factors such as age (Edefonti et al., 2011), gender (Mehndiratta et al., 2015) or education level (Révész & Perju-Dumbravă, 2012), and higher scores could represent better information and awareness of the disease, social support and decreased stigma.

This research demonstrated that patient age has a negative impact on energy, mood, cognition, seizure-related worry, overall quality of life and total score, similar to correlations reported in other studies (Djibouti, 2003) and the older the patient's age, the lower the quality of life. There are also conflicting results reported that did not show significant correlations between age and total score (Shetty et al., 2011).

Female participants revealed notably lower scores in the mood domain, suggesting that both biological and psychological factors, such as personal life or motherhood, may have a greater influence than socio-economic ones. This finding aligns with previous study conducted in Romania. (Brusturean-Bota et al., 2013).

There is enough proof to support the notion that individuals diagnosed with epilepsy tend to have lower levels of education and income, and face more challenges in acquiring employment (Elliott et al., 2009). Education level is one of the important predictors of quality of life (Loring et al., 2004), and this study showed that overall quality of life and total quality of life scores were significantly

influenced by years of education. Compared to a study that included European countries in which employment rates altered all domains of quality of life (Herodes et al., 2001), in this study, statistical analysis showed that sickness and old age pensioners had lower scores in the domains of mood, activities of daily living, cognition, seizure worry, overall quality of life and total score compared to those employed. This may be influenced by poor economic status as these categories have low incomes compared to those in employment or other European citizens. (Bruzelius et al., 2017).

In all domains except the effects of antiepileptic drugs, increased seizure frequency was a predictor of lower quality of life scores. In addition, patients with uncontrolled seizures reported lower quality of life in terms of mood, daily activities, cognition, seizure-related worry, overall quality of life, and total score. Because uncontrolled seizures impact the patient's family, work and social life (Moran et al., 2004)if clinicians can reduce seizure frequency through appropriate assessment and treatment, they can improve the quality of life of patients with epilepsy. In addition to the goal of reducing seizure frequency, physicians must consider other factors of these patients' experiences.

The domain of antiepileptic drug effects had the least impact on QOLIE-31-P ST, although it was still considered a significant predictor. The majority of patients were receiving antiepileptic drug monotherapy, which decreases the probability of experiencing negative effects and enhances trust in the treatment. Adverse effects are linked to the usage of antiepileptic medicines and have been found to be connected with lower scores in quality of life in previous research (Jacoby & Baker, 2008).

This study enrolled patients diagnosed with epilepsy who underwent video-EEG evaluation to determine the location of epileptiform activity. There were no ambiguities regarding the diagnosis, type of seizure, or epileptic syndrome. However, there were no statistically significant associations found between epileptiform activity, seizure onset, etiology, presence of aura, seizure type, presence during sleep, domain scores, and the overall QOLIE-31-P. Previous PE quality of life studies that have provided these details have shown that seizure type is a predictor of quality of life. Both focal and generalized seizures have been shown to affect all domains of quality of life (Baranowski, 2018), although in another study seizure type was an insignificant predictor (Canuet et al., 2009).

Subsequent research should examine the quality of life of people with epilepsy and use information on the specific types of seizures in their examination to uncover possible factors that can predict outcomes.

The primary objective of treatment is to achieve freedom from seizures, however it may not be attainable for certain people. Gaining insight into factors that determine the quality of life may enhance clinical practice and treatment for patients, aiding them in attaining their intended results.

Depressive symptoms in patients with epilepsy have not been assessed using validated tools. This is because in clinical practice, we only document these symptoms when patients are suspected to have them and request interdisciplinary consultation from a psychologist.

The purpose of utilizing instruments to assess the quality of life in patients with epilepsy is to assist physicians in making informed decisions regarding the treatment and care of these individuals. The aim of this study was to assist physicians in identifying patients with low quality of life by categorizing the total QOLIE-31-P scores into low, medium, and high categories based on the mean scores. This categorization was done to facilitate the identification of factors contributing to low quality of life and to enable the implementation of interventions aimed at improving the quality of life for these patients.

Scoring the QOLIE-31-P questionnaire can be tough in regular practice due to its utilization of a weighted score that may provide difficulties in quick processing following its administration (Ogundare et al., 2021). In order to streamline this process, it is suggested that the questionnaire be

conducted following the patient's anamnesis, but before the preparation for video-EEG recording. Furthermore, the clinician can conveniently process the questionnaire data during the recording by utilizing an electronic template. After the investigation's interpretation is made public, the patient will be provided with suggestions tailored to their quality of life score. These recommendations may include psychological support for patients with low quality of life scores and indications of anxiety, as well as guidance on adjusting to alternative occupations or making treatment decisions.

By following this approach, the patient's waiting time can be minimized, the nurse's workload can be prevented from growing too much, and the findings of the video-EEG examination and QOLIE-31-P scores can be documented in the hospital's computer system for future evaluation and comparison. Furthermore, patients can enhance their level of engagement in the management of their disease and receive improved assistance through self-management programs. These programmes can support behavioural changes through strategies to improve relevant knowledge and skills, increase self-esteem and improve quality of life. (Yadegary et al., 2015).

2.3.6. Limitations

The main barrier encountered in this study was the limited availability of evaluations for epilepsy patients, which arose as a result of the onset of the COVID-19 epidemic. COVID-19, caused by the SARS-CoV2 virus, was initially identified in December 2019. On March 11, 2020, the WHO officially marked it an epidemic. Within a few months, the virus had rapidly spread around the globe (Shah et al., 2021). As of April 2020, the Brașov Psychiatry and Neurology Clinical Hospital where the study was conducted was included in the list of national support hospitals for the treatment of SARS-CoV2 infected patients, and the video-EEG monitoring unit, located on the second floor in one of the hospital wards, could not be moved which led to the blocking of its use when there were patients admitted in that ward.

Consequently, epileptic patients had a delay in their evaluations and were unable to seek treatment at other public hospitals due to the exclusive availability of the video-EEG unit in the city. A study conducted during the COVID-19 pandemic also demonstrated problems related to the availability of healthcare and perceived fears negatively impacting the lives of epilepsy patients (Strizović et al., 2021).

2.3.7. Conclusions

Currently, there is a lack of comprehensive research in our country about the quality of life experienced by those with epilepsy. Research findings indicate that the frequency of seizures significantly affects the quality of life for those with epilepsy.

The use of validated measurement tools to assess the quality of life of patients with epilepsy, such as the QOLIE-31-P questionnaire, should become routine practice, although this may be difficult.

Collecting data in this way enables adaptation of care strategies and enhances the results for these patients by examining the impact of the disease and other aspects that may be modified in their everyday lives.

Further research including individuals from many places around the country is necessary in order to acquire more accurate findings.

2.4. Evolution of the influence of clinical factors on the quality of life of Romanian people with epilepsy

2.4.1. Importance of the study

Epilepsy, a chronic neurological condition due to recurrent seizures, is a public health problem, affecting up to 2% of the global population and can have a significant impact on the patient's quality of life (Falco-Walter, 2020).

Quality of life is negatively correlated with seizure frequency in most studies (Baranowski, 2018; Strzelczyk et al., 2023; Tombini et al., 2021), including the one presented above (Cioriceanu et al., 2020). Numerous clinical characteristics identified in research have been found to significantly influence quality of life such as disease duration (Piperidou et al., 2008), age at seizure onset (Edefonti et al., 2011), type of seizures (Bujan Kovač, 2021) or number of antiepileptic drugs (Grinalds et al., 2023) but their determinant role varies between countries.

Although there are significant studies on the quality of life of people with epilepsy, longitudinal studies are limited in the global medical literature and altogether absent in Romania. To enhance research techniques and improve the management of patients with epilepsy, it is important to get insight into their perception of quality of life and investigate the factors that impact this view.

2.4.2. Hypothesis and objectives of the study

The primary objective of this study was to assess epilepsy patients' perceptions of quality of life in a Romanian hospital over time using the QOLIE-31-P questionnaire.

The secondary objective is to deepen the opportunity to reassess a group of patients in their daily life using this tool.

The hypothesis of the study is that better seizure control through lower seizure frequency improves the quality of life of people with epilepsy.

2.4.3. Material and methods

2.4.3.1. Study design

This analytical, cohort, longitudinal, questionnaire-based study comprises an initial assessment of 91 patients with epilepsy aged 18-79 years, who were evaluated by video-EEG at the Clinical Hospital of Psychiatry and Neurology Brasov between February 2018 and August 2021. Of the 91 patients we were able to retest and conduct a follow-up quality of life study in 35 of them.

2.4.3.2. Inclusion and exclusion criteria

Patients with a confirmed diagnosis of epilepsy according to ILAE criteria were included (Scheffer et al., 2017), no specific selection was made and only people with another progressive neurological condition, psychiatric condition, intellectual impairment or who had comprehension problems were excluded.

2.4.3.3. Research tool

The Quality of Life in Epilepsy Questionnaire - QOLIE-31-P was used. (Cramer & Van Hammée, 2003), an epilepsy-specific quality of life measure designed for use in adults aged 18 years and older. Before starting the study and applying the questionnaire, we sought permission from the copyright holder. Joyce Cramer provided and returned the English version that we used in this research. QOLIE-31-P has been used previously in Romania in clinical trials (Klein et al., 2015; Zadeh et al., 2015).

2.4.3.4. Study procedure

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Patients diagnosed with epilepsy based on clinical, electrophysiological, and imaging examinations, who went to the Clinical Hospital of Psychiatry and Neurology Brasov between February 2018 and August 2021 for video-EEG evaluation, were invited and informed about the research objective. The participants were have the chance to inquire about the research and were expressly informed that declining to take part would not result in any burden for them.

Out of the 91 patients who were first evaluated, we were able to retest 35 of them and carry out a further study on their quality of life. Patients who failed to reschedule their regular medical exams were contacted via phone call, and data collection was conducted at the video-EEG unit on the designated date from August 2020 to August 2021. The interval between assessments was determined by the availability of patients and the limitations imposed by the COVID-19 pandemic.

2.4.3.5.   Data collected

Socio-demographic information such as age, sex, last level of education, socio-professional category, residence, marital status was gathered. Clinical data on epilepsy included the age of onset of seizures, type of seizures, etiology, type of epilepsy after onset of seizures, presence of aura, frequency of seizures, presence of seizures in sleep and number of antiepileptic drugs and information on the location of epileptiform activity based on video-EEG recordings made of each participant.

The classification of epileptic seizures was made taking into account the frequency reported by the patient at baseline and final assessment and three groups were described: individuals experiencing one or more seizures per month, those having one to six seizures per year, and those who had not experienced any seizures in the last year. Based on the most recent seizure, the patients were categorized into two groups: those with uncontrolled epilepsy, who experienced at least one seizure in the past year, and those with controlled epilepsy, who did not have any seizures in the past year. During the follow-up visit, it was observed whether there was a disparity in seizure frequency as compared to the original evaluation.

2.4.3.6.   Statistical analysis

The statistical analysis was conducted using GraphPad Prism version 9.2.0. All test results were considered statistically significant with a p-value below 0.05. The confidence level of the interval is 95%. The analysis was conducted dynamically by comparing the results obtained at the initial and final visits, examining the progression of the perception of the quality of life of individuals with epilepsy and the correlation between the data from the QOLIE-31-P questionnaire, socio-demographic information, and epilepsy-related clinical characteristics.

2.4.3.7.   Ethical aspects

The research was approved by the management of the Clinical Hospital of Psychiatry and Neurology Brasov by opinion no. 1121/30.01.2018 and by the Ethics Commission of Medical Scientific Research of Transilvania University of Brasov by opinion 1.1/21.05.2018. Before enrolling in the research, patients provided informed permission, indicating their agreement to participate and allow the publishing of the study results.

2.4.4. Results

The first and subsequent evaluation included a cohort of 35 patients diagnosed with epilepsy. The mean (SD) interval between assessments was 23.46 (±7.54) months.

At baseline the mean (SD) age of the participants was 40.03 ±14.63 years, with a mean (SD) age at seizure onset of 28.57 (±18.72) years and had a mean (SD) duration of epilepsy of 11.46 (±12.90) years.

At the initial visit 65.7% of patients were aged 18-44 years and 34.3% over 45 years. At the final visit 54.4% were aged 18-44 and 45.7% over 45.

No statistically significant correlations were found between age and QOLIE-31-P total score at baseline and final assessments.

The study participants were 60% (n=21) women and 40% (n=14) men.

Gender was not correlated with total QOLIE-31-P score at baseline and final assessment.

80% of patients with epilepsy lived in urban areas and 20% in rural areas.

At the final assessment rural patients had a significantly higher mean total QOLIE31-P score than urban patients.

In terms of marital status, 54.3% of the participants were married and 45.7% were unmarried. Marital status was not correlated with total score at baseline and final visit.

48% of patients in the study had completed higher education. Education completed was not statistically correlated with the total QOLIE-31-P score.

In terms of professional status, 54.3% of patients were employed and 45.7% were from other categories (retired, students, unemployed). We did not find a statistically significant correlation between occupational status and change in total QOLIE-31-P scores at baseline and final visit.

The age of onset of epileptic seizures in the majority of patients was after the age of 18, with 34.3% having seizure onset in childhood and adolescence. Age of onset of epileptic seizures was not correlated with total QOLIE-31-P scores.

The seizure semiology in 91.4% of patients was with bilateral tonic-clonic limb contracture. Seizure type by presence or absence of tonic-clonic contractures was not correlated with total QOLIE-31-P scores at baseline and final visit.

82.9% of patients did not have sleep attacks, while 17.1% of patients had morpheic attacks. The presence or absence of sleep seizures did not influence the total QOLIE-31-P scores at the assessments.

Most of the patients studied, 94.3% had a diagnosis of focal epilepsy and 5.7% had generalized epilepsy. The type of epilepsy after onset was not correlated at baseline and final assessment with total quality of life scores.

The etiology of epilepsy was structural in 57.1% of the patients included in the study and 2.9% of genetic etiology. In 40% of cases, the aetiology of the condition was unknown despite MRI and electrophysiological imaging investigations. Epilepsy aetiology was not statistically correlated with total quality of life scores at any of the visits.

The presence of aura at the onset of epileptic seizures was identified in 45.7% of patients in the study, and in 54.3% seizures were not preceded by any sensation. At the final assessment, epilepsy patients without seizures preceded by aura had significantly higher mean total QOLIE-31-P scores compared to patients presenting seizures with aura.

Video-EEG recordings of brain electrical activity in patients in the study captured epileptiform abnormalities in 91.4% of them and only 8.6% had recordings without changes. Comparing the two groups at both baseline and final visits, patients with epileptiform activity detected by video-EEG recording had significantly lower total QOLIE-31-P scores.

At the final visit 60% of patients had not had any seizures in the last year and were in the controlled category, compared to the initial visit when only 14.3% were in this category.

Uncontrolled patients had lower total quality of life scores at both the baseline and final visit compared to the controlled group.

At the initial visit 34.3% of patients had frequent seizures of one or more per month, compared to 20% at the final visit. Comparing the two groups at both baseline and final assessment, patients with one or more seizures per month had significantly lower total QOLIE-31-P scores.

At the initial visit 45.77% of patients were on antiepileptic drugs alone and 40% were on polytherapy. 14.3% of patients were not taking antiepileptic drugs, a percentage that decreased at the final evaluation when only 5.8% continued not to take treatment against recommendations. Those with two or more antiepileptic drugs in treatment had statistically significantly lower total QOLIE-31-P scores at both assessments, with slightly increased values at the final assessment.

The mean QOLIE-31-P total score at the baseline visit (68.54 ±15.89) was lower compared to the mean QOLIE-31-P total score at the follow-up visit (74.15 ± 17.09).

Regarding domain scores, the cognitive domain had the greatest score (51.71±35.40) during the initial visit, while the seizure worry domain had the lowest mean score (32.43±31.28). The cognition domain had the greatest mean score of 66.39±32.92, whilst the energy domain had the lowest mean score of 45.24±31.58. The domain of medication effects had the most significant disparity in mean scores between the final and baseline assessment.

Comparing the groups at both the baseline and final visits, patients with epileptiform activity recorded by video-EEG, those with uncontrolled seizures, those with one or more seizures per month, and those on two or more antiepileptic drugs had significantly lower total QOLIE-31-P scores. After multiple linear regression, although at baseline the number of antiepileptic drugs (≥2)was associated with the total QOLIE-31-P score, only seizure frequency remained statistically significantly associated in both assessments and had the most significant influence on the total QOLIE-31-P score.

When comparing the groups at the baseline and final visits, patients who had epileptiform activity captured by video-EEG, those who had uncontrolled seizures, those who had one or more seizures per month, and those who were taking two or more antiepileptic drugs had significantly lower total QOLIE-31-P scores. Following multiple linear regression analysis, it was found that while the initial number of antiepileptic drugs (≥2) was linked to the total QOLIE-31-P score, only seizure frequency remained significantly associated in both evaluations and had the greatest impact on the total QOLIE-31-P score.

2.4.5. Discussions

Considering the unpredictable circumstances of the COVID-19 epidemic, this study was successful and it was observed that at the follow-up visit, the domain scores and total QOLIE-31-P assessed at baseline were higher. This suggests that, despite the negative impacts of the COVID-19 pandemic such as economic hardships and strain on the healthcare system, the patients in the study had a more positive perception compared to prior studies that examined the quality of life of epilepsy patients during the pandemic (Koh et al., 2021; Strizović et al., 2021).

There are few longitudinal studies in the medical literature before the pandemic, none conducted in Romania, and most are clinical trials with new antiepileptic drugs or with patients with temporal lobe epilepsy treated by epilepsy surgery.

At both the initial and follow-up visit, higher seizure frequency was a predictor of lower QOLIE-31-P total score, similar to other studies in which higher seizure frequency was a significant predictor of lower quality of life (Bujan Kovač, 2021; Piperidou et al., 2008; Strzelczyk et al., 2023; Tlusta et al., 2009).

At follow-up, the number of controlled seizure-free patients in the past year was higher, and good seizure control was associated with an increase in total QOLIE-31-P scores and improved perception. Studies investigating the evolving characteristics of quality of life perception in patients who changed antiepileptic drugs or had epilepsy surgery showed an improvement in the quality of life of these patients in whom seizure frequency decreased and especially in those who were seizure-free (Birbeck et al., 2002; Cramer et al., 2004; Lotfinia et al., 2019). The results of this study provide further evidence that efforts to reduce seizure frequency are important for improving quality of life.

At both assessments, patients in the study on two or more antiepileptic drugs had a worse perception of quality of life compared to those on monotherapy. In multivariate analysis, only at baseline assessment did the number of antiepileptic drugs administered remain significantly associated with the total QOLIE-31-P score These results are partly consistent with previous research describing the influence of polytherapy on quality of life (Dwivedi et al., 2022; Nagarathnam et al., 2017). Other studies found no correlation between number of antiepileptic drugs and quality of life (Guekht et al., 2007; Piazzini et al., 2007). The impact of treatment on quality of life may be correlated with the proba bility of side effects, treatment confidence and compliance. Future studies are needed to assess the impact on quality of life of the number of antiepileptic drugs used in patients with epilepsy in Romania.

The study evaluated patients using video-EEG to examine the occurrence of epileptiform activity as a component of diagnostic and therapy management. Our findings indicate that individuals that had abnormal EEG signals during video-EEG monitoring had poorer overall QOLIE-31-P ratings both at the beginning and end of the study.

We found no statistically significant association in baseline and final assessments between QOLIE-31-P total scores and age of seizure onset, presence of seizures in sleep, epilepsy type, etiology, seizure type or socio-demographic characteristics. These factors have already been described in different researches and cultures (Baranowski, 2018; Cioriceanu et al., 2022; Taylor et al., 2011), and further study of predictors of the QOLIE-31-P total score may improve clinical practice and support of patients with epilepsy.

2.4.6. Limitations

There were certain constraints in the study. During the COVID-19 pandemic, access to the Clinical Hospital of Psychiatry and Neurology Brasov was restricted for non-COVID patients. This, combined with the fear of patients with epilepsy to visit a healthcare facility and risk infection, resulted in a smaller number of participants in the study. As a consequence, statistical analysis was challenging. Another constraint is the study's exclusive focus on a single institution. However, this is counterbalanced by the meticulousness with which the study was done and the consistent use of rating criteria.

Because of the limited number of patients reassessed and the uncertain nature of the pandemic, we were unable to carry out a comprehensive assessment of the effects of limitations or SARS-CoV-2 infection on the quality of life of epilepsy patients. Consistent with previous research showing that stress levels are high in people with epilepsy (Sahin et al., 2021), the likelihood of coming into contact with infected patients and a potential diagnosis of COVID-19, could justify the refusal of some patients to present for reassessment. A global consensus on patients with epilepsy stated that they should refrain from seeking medical care in hospitals where there is a

potential for transmitting SARS-CoV-2. Instead, they should adhere to their treatment regimen at home and ensure consistent availability of antiepileptic medications. (French et al., 2020).

2.4.7. Conclusions

This follow-up study in real-life clinical practice in a Romanian public hospital showed that total QOLIE-31-P scores are lower in epilepsy patients with frequent seizures, uncontrolled disease, those using polytherapy and those with epileptiform abnormalities on the interictal video-EEG recording. The frequency of seizures was found to be a strong predictor of a lower quality of life. Since epilepsy is a long-term condition that requires regular visits to the outpatient clinic, clinicians should utilize assessment tools to evaluate the quality of life of patients. They should also take into account patterns and various clinical factors in order to enhance the prognosis of these individuals.

In order to obtain more accurate results, future research should aim to include a more extensive group of epilepsy patients from various regions of the country. This would enable comparisons to be made between different groups of patients while also taking into account the potential influence of psychological profiles.

2.5. Romanian translation and cultural adaptation of the Seizure Severity Questionnaire
2.5.1. Importance of the study

The main objective of epilepsy treatment is to reduce or completely control seizures. Studies have shown that increased frequency of epileptic seizures has been associated with poorer quality of life (Baranowski, 2018; Cioriceanu et al., 2023; Gonzalez-Martinez et al., 2022). The impact of seizures has traditionally been assessed by seizure frequency and seizure types, but these classifications do not take into account particular aspects such as seizure manifestations and after-effects, falls, changes in consciousness, or PE perception of seizure control.

These issues are important in patients in whom complete seizure remission cannot be achieved and reducing seizure severity can be a key factor in improving quality of life. However, validated and standardized seizure severity assessment tools are not available in Romanian and there are no studies conducted in Romania that highlight the reliability of using these tools.

The Seizure Severity Questionnaire (SSQ) was initiated in 1999 and underwent an initial validity and reliability assessment in 2002. (Cramer et al., 2002). Subsequently, the instrument has been increasingly used in clinical trials to assess seizure severity (Todorova, Velikova, Kaprelyan, et al., 2013).

2.5.2. Hypothesis and objectives of the study

The primary objective of this study was to report the translation and cultural adaptation of the SSQ on a group of patients with epilepsy evaluated at a hospital in Romania.

The secondary objective is to assess the relationship between seizure severity and seizure frequency in patients diagnosed with epilepsy.

The hypothesis of the study consists in the assumption that there are statistical correlations between the total SSQ score and the domain and total scores of the QOLIE-31-P, and that this seizure severity measure may be relevant in application to Romanian patients with epilepsy alongside the Quality of Life Assessment Questionnaire.

2.5.3. Material and methods

2.5.3.1.   Study design

This study was started with the permission of the author of the questionnaire, Joyce Cramer, who provided the original English version so that we could begin the process of translation into Romanian. The translation was carried out by the authorised translation agency Tradutex - Maltrev International and completed with a report of the translation process. Four translators were involved.

The aim was to achieve conceptual equivalence and cultural relevance of the translated notions and to ensure that the translated tool is understandable for Romanian patients. The final version was obtained for the Romanian population, with the same layout and images as the original men tului. A copy of the version together with the information with the fulfilment of the translation requirements was provided to Joyce Cramer for archiving and distribution to other researchers as needed.

This was followed by an analytical, observational, cohort study based on the SSQ Romanian version and the QOLIE-31-P, which included 67 patients aged 18-79 years with a confirmed diagnosis of epilepsy according to ILAE criteria. (Scheffer et al., 2017), conducted at the Clinical Hospital of Psychiatry and Neurology Brasov from February 2018 to August 2021.

2.5.3.2.   Inclusion and exclusion criteria

People who had epilepsy along with another progressive psychiatric or neurological disease, severe somatic pathology, intellectual disability, or trouble understanding parts of the research instruments were excluded from the study.

2.5.3.3.   Research tools

Two research instruments were used, the Quality of Life in Epilepsy Questionnaire - QOLIE-31-P and the Seizure Severity Questionnaire - SSQ. The former, the validated Romanian version, has already been described in the two previous studies in the paper.

The SSQ is designed as a self-report assessment instrument with 24 items and divides epileptic seizures into three phases: warning, ictal activity and seizure recovery. The recovery phase is subdivided into three components, namely cognitive, emotional and physical aspects of recovery, each of which is assessed in terms of frequency, severity and feeling of ill health. Global assessment of seizure severity is measured with the last two items.

The scoring algorithm version 3 was made available by the copyright holder with the English version and the total SSQ score ranges from 0 to 7, with higher scores indicating greater severity of seizures.

2.5.3.4.   Study procedure

Patients with good language skills, writing and comprehension skills and confirmed diagnosis of epilepsy based on clinical examination, electrophysiological and imaging examinations who presented for investigation by video-EEG were invited to participate in the study and their purpose and procedure were described. After being given the opportunity to ask questions about the research it was explained to them that a refusal to participate would not cause any inconvenience. Those who agreed, signed consent forms for participation and for publication of the results. The QOLIE-31-P questionnaire was initially administered and then the SSQ. Questionnaires were assigned numbers to achieve confidentiality. Digital video-EEG was performed and localization of epileptiform activity was studied.

2.5.3.5.   Data collected

Socio-demographic data collected were age, sex, residence, marital status, education, socio-professional status, and clinical data were duration of illness, frequency of epileptic seizures, etiology, presence of aura.

2.5.3.6.   Statistical analysis

The data were analysed using GraphPad Prism version 10.2.1 software using absolute values and percentages for categorical variables and statistical methods to process the variables by measuring mean scores and standard deviation (SD). Epileptic seizures were divided by frequency into one per month, two or more per month and between one and 6 per year.

The t-test was used to test for associations between the SSQ total score and the QOLIE-31-P total score and domains and between the SSQ total score and clinical characteristics. The level of statistical significance was established by a p-value <0.05 and a 95% confidence interval.

2.5.3.7.   Ethical aspects

The research had the approval no. 1121/30.01.2018 of the management of the Clinical Hospital of Psychiatry and Neurology Brasov and the approval no. 1.1/21.05.2018 of the Ethics Commission of the medical scientific research of Transilvania University of Brasov.

2.5.4. Results

Sixty-seven patients were eligible, of whom 56.7% (n=38) were female and 43.3% (n=29) were male, with a mean (SD) age of 44.07 (±15.06) years and a mean (SD) disease duration of 14.39 (±15.74) years.

The patients included in this sample had no difficulty in understanding, completing and completing the two questionnaires. The time taken to answer the questions was approximately 30 minutes.

In terms of residence, the majority of patients 74.6% (n=50) came from urban areas, while 25.4% (n=17) from rural areas.

By marital status, the majority of patients 59.7% (n=40) were married and 40.3% (n=27) were unmarried.

By socio-professional category 39% (n=26) of the study participants were employed, 5% (n=3) were students, 13% (n=9) were retired due to illness, 25% (n=17) were retired due to old age and 18% (n=12) were unemployed.

Patients with epilepsy who participated in the research had 46.3% (n=31) of them had completed high school, 4.5% (n=3) had completed 4 grades, 13.4% (n=9) had completed 8 grades and an equal proportion of 17.9% (n=12) had completed vocational school and higher education respectively.

All participants had a confirmed diagnosis of epilepsy, had had epileptic seizures in the last year. The majority of patients had epilepsy of structural aetiology, with seizure frequency between one and six per year and no aura at onset.

Of the study participants, women had lower mean total SSQ scores and less severe perceived seizures compared to men.

Those with aura at the onset of epileptic seizures had a higher mean total SSQ score with a more severe perception of seizures compared to those without aura.

By seizure frequency, epilepsy patients with rare seizures, between 1 and 6 per year, had the lowest mean total SSQ score compared to those with frequent seizures. Patients with 2 or more seizures per month had the highest mean total SSQ score.

By disease aetiology, no statistically significant correlation was identified with the total SSQ score of those with genetic epilepsy, but in those with epilepsy of structural aetiology the mean total SSQ score was higher compared to those with unknown aetiology of the condition.

According to the number of antiepileptic drugs, patients on monotherapy had a less severe perception of epileptic seizures compared to those on treatment with two or more antiepileptic drugs, the least severe perception of seizures was among those not on treatment.

The mean (±SD) total SSQ score was 3.114 (±1.477). All QOLIE-31-P quality of life domains correlated statistically significantly with the total SSQ score, as did the total QOLIE-31-P score.

2.5.5. Discussions

This study implemented English to Romanian translation of the SSQ and application to a heterogeneous sample of patients with epilepsy. Patients who completed the questionnaire in full had no problems in completing or understanding it.

The study showed that women had a better perception of seizure severity compared to men. This result is consistent with other research that has shown that men by nature of their occupation may be exposed to more risk factors such as head injuries or alcohol consumption (Hu et al., 2021).

Respondents who had epileptic seizures with aura had a more severe perception of seizure severity. Aura is a subjective ictal phenomenon that can encompass different sensations and is a clinical sign of a seizure that may occur before alteration of consciousness. It can often be recalled after a seizure. Studies investigating the influence of aura on seizure severity have produced conflicting results. Some studies suggest that the presence of an aura may increase the patient's perceived severity of seizures, possibly due to anxiety or fear associated with the aura experience. (Wolf et al., 2020). Other studies have shown no significant correlation between the presence of aura and seizure severity (Mula et al., 2006).

Epilepsy aetiology is a major prognostic factor for *seizure* recurrence (Roy et al., 2019). Focal epilepsies associated with structural brain abnormalities are less likely to enter remission compared to those occurring in patients with normal brain structures evidenced by imaging. This study supports higher seizure severity in patients with structural epilepsy similar to other research that has shown that patients with structural epilepsy were more likely to experience the worst outcome trajectory patterns compared to patients with other etiology (Choi et al., 2016).

This study shows a correlation of seizure severity with the number of antiepileptic drugs. Study participants on two or more antiepileptic drugs perceived seizure severity to be more severe than those on monotherapy or those not on any treatment, contrary to recommendations. However, this correlation may vary by individual and may not be direct. Patients on multiple antiepileptic drugs may experience more severe seizures due to treatment resistance or type of epilepsy. In other patients with epilepsy, the combination of antiepileptic drugs can effectively control the disease, leading to less severe or even no seizures. (Guery & Rheims, 2021; Kwan & Brodie, 2000). It is important for clinicians to rigorously assess each patient and tailor the treatment plan to achieve optimal seizure control and minimise side effects and possible drug interactions.

In this study, patients with rarer seizures perceived seizures less severely than those with frequent seizures. Previous studies have shown that epilepsy patients with frequent seizures experience a greater impact on quality of life compared to those with rare seizures and controlled condition (Birbeck et al., 2002), and those with frequent and severe seizures perceive significant impairment of physical health, emotional well-being and social relationships (Silva et al., 2006).

Results from this study may suggest that by reducing the frequency of seizures, perceptions of their severity may be improved.

The SSQ total score was correlated with the QOLIE-31-P quality of life scores, a questionnaire validated on the Romanian population and previously used in clinical trials. These results obtained on a smaller group of patients with epilepsy may be useful in the application of the SSQ in future larger research, on more patients and in different areas of the country.

The SSQ is a useful tool for assessing the severity of epileptic seizures from the patient's point of view and exploring the effects that occur before, during and after a seizure. A more realistic perception of the phenomena associated with seizures can enable patients to adapt their lifestyle to the type and severity of seizures. Quality of life is a concept that incorporates physical, psychological, social and economic aspects, and its assessment should come primarily from the patient, through tools provided by physicians or family in order to achieve a balance between the perceived state and the desired state. (Todorova, Velikova, Kaprelyan, et al., 2013). Appropriate instruments such as SSQ and QOLIE-31-P allow objective assessment of daily difficulties faced by patients with epilepsy based on their perception and allow identification of psycho-social consequences of this condition.

The SSQ was developed as a multidimensional assessment of seizures by the patient. Based on aspects reported by patients and their families that the recovery period after the seizure was the most problematic aspect, the SSQ includes questions covering cognitive, emotional and physical recovery after such events (Cramer et al., 2003).

The results of this study show that there is an association between seizure severity and quality of life. Patient-reported findings by SSQ and QOLIE-31-P scores could be important indicators for helping physicians and families to improve their perception of seizure severity and quality of life.

2.5.6. Conclusions

The impact of seizures, traditionally studied in terms of frequency and manifestations, can be better understood if analysed from the patient's perspective. Manifestations occurring before, during and after an epileptic seizure, such as the presence of a halo, involuntary movements, altered state of consciousness, confusion, affective disturbances, explored through the questions in this assessment tool, are relevant data for assessing the consequence of epilepsy on the patient's daily life.

The Romanian version of the SSQ shows good reliability and adequate translation of the content and could be useful for measuring seizure severity in patients with epilepsy in Romania.

CHAPTER 3
Final conclusions

By analysing the objectives and hypotheses of each of the three studies presented in the PhD thesis, I consider that they have been met and present the following general conclusions.

Study 1:
According to the average QOLIE-31-P ST most enrolled patients had an average quality of life.

Patient age has a negative impact on quality of life domains and the older the patient, the lower the quality of life.

Scores were influenced by years of study and employment status, with sickness and old age pensioners scoring lower than those in employment.

In all domains except the effects of antiepileptic drugs, increased seizure frequency was a predictor of lower quality of life scores.

Patients with uncontrolled seizures reported lower quality of life in terms of mood, daily activities, cognition, seizure-related worry, overall quality of life and total score. Because uncontrolled seizures impact patients' family, work, and social lives, if doctors can reduce seizure frequency through appropriate assessment and treatment, they can improve the quality of life of patients with epilepsy. In addition to the goal of reducing seizure frequency, physicians need to consider other factors of these patients' experiences.

In this study, people who had been diagnosed with epilepsy were included and evaluated via video-EEG. The location of epileptiform activity was also studied. There were no uncertainties in terms of diagnosis, seizure type or epileptic syndrome, but no statistically significant correlations between epileptiform activity, seizure onset, aetiology, presence of aura, seizure type, presence in sleep and domain scores and total QOLIE-31-P.

To date, there are insufficient studies in our country on the quality of life of people with epilepsy. This research has shown that seizure frequency has an important impact on the quality of life of patients with epilepsy.

Study 2:
At both the baseline and follow-up visit, higher seizure frequency was a predictor of lower total QOLIE-31-P score, similar to other international studies in which high seizure frequency was a significant predictor of lower quality of life.

At follow-up, the number of controlled, seizure-free patients in the past year was higher, and good seizure control was associated with an increase in total QOLIE-31-P scores and improved perception which provides further evidence that efforts to reduce seizure frequency are important for improving quality of life.

In both assessments, patients on two or more antiepileptic drugs had a worse perception of quality of life compared to those on monotherapy. The impact of treatment on quality of life may be correlated with the likelihood of adverse effects, confidence in treatment and compliance. Future studies are needed to assess the impact on quality of life of the number of antiepileptic drugs used in people with epilepsy in Romania.

The study involved evaluating patients using video-EEG to investigate the presence of epileptiform activity, which was analyzed as part of the diagnostic and therapeutic process. The results obtained indicate that individuals who exhibited abnormal EEG signals during video-EEG monitoring had lower total QOLIE-31-P scores at both baseline and final visits.

No significant correlation was observed in the initial and final evaluations between the total scores of QOLIE-31-P and factors such as age of seizure onset, occurrence of seizures during

sleep, type of epilepsy, etiology, seizure type, or socio-demographic parameters. These factors have been previously explored in various research studies and cultural contexts. Further investigation into the determinants of the QOLIE-31-P total score has the potential to enhance clinical practice and provide better care for patients with epilepsy.

Study 3:

The SSQ was translated from English into Romanian and applied to a heterogeneous sample of patients with epilepsy.

The total SSQ score correlated with QOLIE-31-P quality of life scores, patient gender, and clinical factors such as aura, seizure frequency, or number of antiepileptic drugs. These results obtained on a smaller group of patients with epilepsy may be useful in applying the SSQ in future larger research on more patients and in different parts of the country.

Appropriate instruments such as the SSQ and the QOLIE-31-P allow objective assessment of the daily difficulties faced by patients with epilepsy, based on their perception, and allow identification of the psycho-social consequences of the condition.

The results show the existence of an association between seizure severity and quality of life, and the findings reported by patients through the SSQ and QOLIE-31-P scores could be important indicators to support them by physicians and families to improve their perception of seizure severity and quality of life.

CHAPTER 4

4.1. Discussions

Current progress in medicine and medical practice requires healthcare providers to adapt and keep abreast of the ethical issues they encounter in patients with epilepsy. They may face difficulties in employment, problems in accessing education, relationships due to stigma and fear of having seizures.

Epilepsy is a neurological condition with a significant impact on patients' quality of life and can be controlled if patients receive a comprehensive evaluation by epileptology specialists, including a rigorous history, imaging investigations with a dedicated epilepsy protocol and electrophysiological investigations such as prolonged video-EEG.

The absence of epileptic seizures is the main goal of epilepsy treatment, which ranges from the administration of antiepileptic drugs to surgery to remove the epileptic focus or vagal neurostimulation. But for some patients with epilepsy this is not possible and therefore understanding predictors of quality of life can improve clinical practice, treatment and support them in achieving their desired outcomes.

Until this research in Romania there were no studies on the quality of life of people with epilepsy using QOLIE-31-P and SSQ. The Romanian version of the SSQ shows good reliability and adequate translation of the content and could be useful for measuring seizure severity in people with epilepsy in Romania.

These two measurement tools, widely used in the study of epilepsy patients' quality of life internationally, can help track patients, understand how they perceive quality of life and improve their management.

Their use in clinical practice depends on the physician's determination to apply and review the results during the consultation. Currently there is no national register of people diagnosed with epilepsy in our country and we do not know the exact number of patients. By routinely using quality of life assessment tools in conjunction with enrolling patients with epilepsy in a national register, we could help review health policies and identify the issues these patients face from accessing therapies, vocational integration or managing their ability to drive a motor vehicle.

Future studies should include a larger number of patients across the country to facilitate comparisons between different groups or patient populations and consider the influence of psychological profiles for more accurate results.

4.2. Original contributions

The study "Influence of socio-demographic and clinical factors on the quality of life of Romanian patients with epilepsy" is among the few studies conducted in Romania on the quality of life of patients with epilepsy and the only one in the last 20 years. Its results showed that seizure frequency was the most important factor impacting quality of life. Identifying these by using validated measurement tools for assessing quality of life of patients with epilepsy, such as the QOLIE-31-P questionnaire, should become routine practice, even though this may be difficult. Data acquired through this approach has the potential to enhance patient management and optimize outcomes by examining the impact of the disease and other factors that can be modified in everyday life.

The real-life study "Evolution of the influence of clinical factors on the quality of life of Romanian patients with epilepsy" showed that patients with frequent seizures, uncontrolled disease, those using polytherapy, those with epileptiform abnormalities on video-EEG interictal

recording have lower quality of life scores, and seizure frequency is a significant inverse predictor of quality of life score. As epilepsy is a chronic condition requiring regular outpatient visits, in an attempt to improve the prognosis of patients with epilepsy, the medical team should identify patterns and consider various clinical factors using quality of life assessment tools.

With the study "Romanian translation and cultural adaptation of the Seizure Severity Questionnaire (SSQ)", the translation from English into Romanian of the SSQ was carried out for the first time in our country, with prior permission of the copyright. The results of the application to Romanian patients with epilepsy showed an adequate translation of the content, a good reliability and a significant association of seizure severity with quality of life, but on a smaller group of participants in correlation with a larger study population. The data presented may be relevant for future use of this tool to measure the consequences of epileptic seizures on patients' daily lives and for larger studies.

4.3.   Future research directions

As future research directions I propose to implement a pilot program to routinely apply the QOLIE-31-P and SSQ questionnaires in the evaluation of patients with epilepsy at the Clinical Hospital of Psychiatry and Neurology Brasov. In this regard, I will propose the creation and submission for approval within the hospital of operational procedures.

This would allow each patient to receive recommendations based on quality of life and seizure severity scores and to be more actively involved in the management of the condition. The data obtained can be processed through an electronic template, entered into the hospital's computer programme and used for future comparisons.

By communicating the results of the three studies, together with medical societies and patient associations, we can draw the attention of decision-makers to the implementation of a national register of epilepsy patients and highlight the importance of using these quality of life research tools as a routine, not just clinical research. Also other particular aspects such as the stages of re-assessment for the revalidation of driving licence could be further analysed by additional information collected by these assessment tools together with a rigorous anamnesis.

Given the limited access of patients with epilepsy to medical services during the COVID-19 pandemic, I propose to carry out a research including a larger number of patients and to study together with psychologists and psychiatrists colleagues the evolution of quality of life over a period of time in these patients using both the two instruments and validated instruments to assess anxiety and depressive symptoms.

4.4.   Dissemination of results

In ISI journals:
Cioriceanu, I.-H., Constantin, D.-A., Marceanu, L. G., Anastasiu, C.-V., Serbanica, A. N., & Rogozea, L. (2022). Impact of Clinical and Socio-Demographic Factors on the Quality of Life in Romanian People with Epilepsy. Healthcare, 10(10), 1909. https://doi.org/10.3390/healthcare10101909
Cioriceanu, I.-H., Constantin, D.-A., Bobescu, E., Marceanu, L. G., & Rogozea, L. (2023). Influence of Clinical Factors on the Quality of Life in Romanian People with Epilepsy—A Follow-

Up Study in Real-Life Clinical Practice. Journal of Personalized Medicine, 13(5), 752. https://doi.org/10.3390/jpm13050752

In BDI journals:

Cioriceanu, I.-H., Constantin, D., & Rogozea, L. (2020). Impact of pharmacotherapy on life quality of patients with epilepsy Impactul terapiei farmacologice asupra calității vieții pacienților cu epilepsie. Jurnal Medical Brasovean, 1, 17–23. https://doi.org/10.31926/jmb.2020.1.5

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Conference communications:

Cioriceanu, I.-H (2023). Impact of clinical and socio-demographic factors on the quality of life of Romanian patients with epilepsy. *XXXI National Conference of the Romanian Society Against Epilepsy, 22-25 November 2023,* First Prize.

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DECLARAȚIE DE AUTENTICITATE

Subsemnații:

Ionuț – Horia Cioriceanu
(nume și prenume doctorand)

în calitate de

student - doctorand al IOSUD:

Universitatea Transilvania din Brașov
(denumire IOSUD)

autor al tezei de doctorat cu titlul: Aspecte   privind   influența   factorilor   bioetico-
medicali și legislativi asupra calității vieții pacienților cu epilepsie
(titlul tezei de doctorat)

și

prof.univ.dr. med. Liliana Marcela Rogozea
(nume si prenume conducator doctorat)

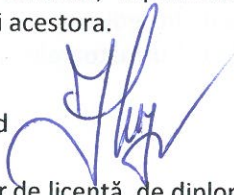în calitate de Conducător de doctorat al autorului tezei

la instituția

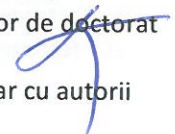**Universitatea Transilvania din Brașov**
(denumire institutie)

declarăm pe proprie răspundere că am luat la cunoștință de prevederile art.143 alin (4) si (5)* și art. 170** din Legea educației naționale nr.1/2011, ale art. 65, alin.5 – 7***, art. 66, alin (2)**** din Hotărârea Guvernului nr.681/2011, privind aprobarea Codului Studiilor universitare de doctorat, ale art. I alin. (5) și (7) ***** din Hotărârea nr. 134 privind modificarea Codului studiilor universitare de doctorat, aprobat prin HG nr. 681/2011 și ale Anexei nr. 2 (Soluționarea sesizărilor cu privire la nerespectarea standardelor de calitate sau de etică profesională, inclusiv cu privire la existența plagiatului, în cadrul unei teze de doctorat) din Ordinul MENCS nr. 3482/2016 privind aprobarea Regulamentului de organizare și funcționare a Consiliului Național de Atestare a Titlurilor, Diplomelor și Certificatelor Universitare (CNATDCU) și ne asumăm consecințele nerespectării acestora.

Semnătură   Semnătură
Student doctorand   Conducător de doctorat

*(4) indrumatorii lucrărilor de licență, de diplomă, de disertație, de doctorat răspund solidar cu autorii acestora de asigurarea originalității conținutului acestora
(5) este interzisă comercializarea de lucrări științifice în vederea facilitării falsificării de către cumpărător a calității de autor al unei lucrări de licență, de diplomă, de disertație sau de doctorat.
** (1) În cazul nerespectării standardelor de calitate sau de etică profesională, se aplică prevederile Hotărârii nr. 134 privind modificarea Codului studiilor universitare de doctorat, aprobat prin HG nr. 681/2011.
(2)Reacreditarea școlii doctorale se poate obține după cel puțin 5 ani de la pierderea acestei calități, numai în urma reluării procesului de acreditare, conform art. 158.
(3)Redobândirea calității de conducător de doctorat se poate obține după cel puțin 5 ani de la pierderea acestei calități, la propunerea IOSUD, pe baza unui raport de evaluare internă, ale cărui aprecieri sunt

validate printr-o evaluare externă efectuată de CNATDCU. Rezultatele pozitive ale acestor proceduri sunt condiții necesare pentru aprobare din partea Ministerului Educației, Cercetării, Tineretului și Sportului.

(4) Conducătorii de doctorat sunt evaluați o dată la 5 ani. Procedurile de evaluare sunt stabilite de Ministerul Educației, Cercetării, Tineretului și Sportului, la propunerea CNATDCU.

***(5)** teza de doctorat este o lucrare originală, fiind obligatorie mentionarea sursei pentru orice material preluat.

(6) studentul - doctorand este autorul tezei de doctorat și îşi asumă corectitudinea datelor şi informaţiilor prezentate în teză, precum şi a opiniilor şi demonstraţiilor exprimate în teză

(7) conducătorul de doctorat răspunde împreună cu autorul tezei de respectarea standardelor de calitate sau de etica profesională, inclusiv de asigurarea originalității conținutului, conform art. 170 din Legea nr. 1/2011.

**** protecția drepturilor de proprietate intelectuală asupra tezei de doctorat se asigură în conformitate cu prevederile legii.

*****(5) (6)** În cazul în care membrii CNATDCU din cadrul unei comisii de evaluare a unei teze de doctorat constată nerespectarea standardelor de etică profesională, inclusiv existența plagiatului, în cadrul tezei și/sau al activităților care au dus la realizarea acesteia, aceştia invalideaza teza de doctorat, comunică aceste constatări celorlalți membri ai comisiei de evaluare și sesizează Consiliul general CNATDCU pentru analiza responsabilității conducătorului de doctorat sau a şcolii doctorale și pentru aplicarea prevederilor art. 69 alin. (5).

(7) (3) În termenul prevăzut la alin. (2), Consiliul general al CNATDCU solicită IOSUD punctul de vedere care trebuie formulat în termen de maximum 30 de zile de la primirea solicitării. În situația în care IOSUD confirmă încălcarea standardelor de calitate sau de etică profesională, va transmite CNATDCU decizia privind propunerea de retragere a titlului, semnată de rector sau, după caz, de preşedintele Academiei Române, avizată din punct de vedere juridic de universitate sau, după caz, de Academia Română.

(4) În termenul prevăzut la alin. (2), Consiliul general al CNATDCU decide dacă au fost sau nu respectate standardele de calitate sau de etică profesională, inclusiv existența plagiatului, iar preşedintele CNATDCU transmite autorului sesizării, autorului tezei și IOSUD decizia Consiliului general al CNATDCU și motivarea acesteia. Aceştia au la dispoziție 10 zile pentru formularea unei contestații privitoare la procedură, iar Consiliul general al CNATDCU are la dispoziție 10 zile pentru formularea răspunsului la contestație.

(5) În cazul în care Consiliul general al CNATDCU decide că nu au fost respectate standardele de calitate sau de etică profesională, inclusiv în ceea ce privește plagiatul, preşedintele CNATDCU propune Ministerului Educației Naționale și Cercetării Ştiințifice una sau mai multe din următoarele măsuri:

a) retragerea calității de conducător de doctorat;
b) retragerea titlului de doctor;
c) retragerea acreditării şcolii doctorale.