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Review

Epilepsy beyond seizures: embracing a holistic perspective. Proceedings of the 2nd meeting (Episicily) of the epilepsy study group of the Italian Society of neurology

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ABSTRACT

The purpose of the second meeting of the Epilepsy Study Group of the Italian Society of Neurology, held in Sicily, Italy, and titled "Episicily" was on a new holistic approach to people with epilepsy. The most important points that the experts at the conference addressed and considered significant were the modern clinical approach of a physician dedicated to epilepsy that requests multidisciplinary collaboration and a dynamic vision throughout new diagnostic procedures. Then, the new antiseizures medications and their peculiarities, the role of neuroinflammation and finally the bidirectional relationship with sleep disorders.

1. Introduction

This paper summarises the second meeting of the Epilepsy Study Group of the Italian Society of Neurology, held in Sicily, Italy, and titled "Episicily," which addressed the concept of epilepsy beyond seizures, aiming to adopt a comprehensive perspective. The meeting took place in Giardini Naxos, Sicily, in March 2025, and included participants from several Italian regions, as well as two guests from the United Kingdom. The current conference focused on a new holistic approach to people with epilepsy.

The conference issue focused on patient-centred care, patient-oriented treatment, and tailored therapy designed around the specific features of each individual. In this setting, it is essential to consider comorbidities, multiple therapies, diagnostic tools, lifestyle, and the family and social context of the person. Always keeping in mind that many patients achieve an adequate seizure control thanks to the combination of different antiseizure medications (ASMS); however, the risk of becoming refractory to treatment increases with the number of drugs. In fact, in clinical practice, the choice of the first ASM is critical, as is the research of surgical biomarkers or the correct use of palliative procedures, such as vagal nerve stimulation.

Thus, it appears worthwhile to seek a modern epileptic algorithm that can facilitate a more precise diagnosis and treatment. Moreover, the present article is meant to serve as conference proceedings of the second Episicily, as it includes a series of summaries of the key presentations given in Giardini Naxos. They provide up-to-date information on clinical, electroencephalographic (EEG), genetic testing, neurophysiological tests, imaging features, and artificial intelligence applications in epilepsy. The second day of the conference focused more on treatment aspects, beginning with an examination of the role of neuroinflammation.

2. The modern epileptologist

It is now widely accepted that the management of epilepsy encompasses not only seizure control but also a complex, multifaceted endeavor that requires examining various aspects, necessitating a holistic approach [1]. Consequently, the modern epileptologist must integrate not only deep clinical expertise but also technological proficiency and cross-disciplinary collaboration to provide optimal care. This transformation is driven by an increasing recognition that epilepsy is not a singular condition but a spectrum of disorders with diverse etiologies, comorbidities, and sociopsychological impacts. The approach adopted by today's epileptologists encompasses diagnostic precision, individualised treatment strategies, psychosocial support, and optimisation of long-term outcomes. One of the central challenges lies in the accurate diagnosis and classification of epilepsy syndromes, which often require the synthesis of clinical semiology, neuroimaging findings, electrophysiological data, genetic testing, and patient history. This demands not only expertise in interpreting EEGS and MRI scans but also an understanding of emerging biomarkers and pathophysiological mechanisms.

Epilepsy often coexists with psychiatric disorders, cognitive impairments, and social stigma, necessitating an integrative model of care that includes psychiatrists, neuropsychologists, social workers, and specialised nursing staff [2].

The advent of artificial intelligence (AI) and machine learning has introduced a powerful dimension to this paradigm, with the potential to automate EEG interpretation, detect subtle patterns in neuroimaging, and personalise treatment options using large-scale data analytics [3]. However, the implementation of AI in clinical practice is accompanied by challenges related to data quality, algorithm transparency, regulatory compliance, and ethical considerations, especially regarding patient privacy and the explainability of machine-driven decisions. Modern epileptologists face the complex task of navigating this evolving landscape while maintaining the core responsibility of patient-centred care.

In addition to technical expertise, the holistic approach demands sensitivity to the patient's lived experience, particularly regarding the psychosocial dimensions of epilepsy. Chronic epilepsy can lead to unemployment, social isolation, anxiety, depression, and reduced quality of life [3]. Effective management must therefore extend beyond seizure suppression to address these broader impacts. This requires a multidisciplinary team capable of delivering comprehensive care plans, including cognitive-behavioral therapy, occupational rehabilitation, family counselling, and education about lifestyle modifications. Epileptologists must act as both clinical specialists and coordinators of care, navigating institutional structures and advocating for integrated service models that promote patient-centred care. The challenge is exacerbated in resource-limited settings, where access to specialised services and advanced diagnostics is constrained. Telemedicine, bolstered by AI-driven triage systems, has shown potential in bridging this gap, enabling remote consultations and decentralised management of epilepsy. However, disparities in digital literacy and infrastructure persist as significant barriers, underscoring the need for equitable deployment strategies of technology.

Training the next generation of epileptologists in this multifactorial environment poses its own set of challenges. Traditional fellowship programs must be redesigned to include exposure to AI applications, data interpretation, clinical genomics, health systems science, and patient-centred communication strategies. Mentorship and interdisciplinary exchanges are essential in developing a workforce that can effectively adopt the holistic model. Continuing professional development must also adapt, incorporating dynamic learning platforms and simulation-based training. The emphasis should be on cultivating adaptability, critical thinking, and collaborative skills alongside technical knowledge. Furthermore, ethical competence is essential, particularly as AI and personalised medicine introduce novel dilemmas around consent, data ownership, and therapeutic equity.

A holistic approach is not merely a philosophical stance but a practical necessity in managing the multifaceted realities of epilepsy. It demands multidisciplinary collaboration, lifelong learning, and a commitment to ethical, evidence-based practice. While AI and other emerging technologies offer powerful tools, their actual value will be realised only when embedded within a framework that prioritises humanistic care, equity, and clinical wisdom. As such, the epileptologist of the future is envisioned not just as a specialist in seizure disorders but as a dynamic leader at the intersection of neuroscience, technology, and compassionate medicine.

The development of a diagnostic algorithm for epilepsy remains a significant challenge due to the inherent complexity of the condition.

Epilepsy is characterized by substantial clinical pleiomorphism, regional variability in electroclinical patterns, and a diagnostic process that relies heavily on clinical intuition and historical data rather than purely objective measures. The multidimensional nature of epilepsy—encompassing diverse etiologies, genetic factors, and highly individualised treatment responses—further complicates the establishment of a standardised algorithm. Unlike other neurological disorders with more uniform biomarker profiles, epilepsy demands a nuanced and context-dependent approach, making it resistant to rigid algorithmic categorization [4].

Moreover, a historical examination of epilepsy reveals a gradual transformation in its conceptualisation. In the 19th century, epilepsy was largely regarded as a psychiatric disorder or an enigmatic condition beyond scientific understanding. The advent of EEG in the early 20th century marked a significant shift, reinforcing the physiological basis of epilepsy while stigma persisted. The late 20th century witnessed the emergence of epilepsy syndromes as a classification framework, alongside technological advancements such as neuroimaging and molecular genetics, which reshaped our understanding of its pathophysiology. The 21st century has further refined this model, recognising epilepsy as a dynamic condition influenced by genetic, neurobiological, and environmental factors [5].

Despite advancements in artificial intelligence (AI), epilepsy presents unique challenges that limit the straightforward application of AI-driven diagnostic tools. While AI can enhance EEG analysis and neuroimaging interpretation, it struggles to integrate the lived experience of individuals with epilepsy—personal histories, social contexts, and existential concerns—elements crucial to a comprehensive diagnosis. AI lacks relational intelligence and cannot replace clinician-patient interaction, which remains essential for epilepsy management. A balanced approach is needed, where AI supports but does not replace the human, multidimensional understanding of the disorder. Ethical considerations, such as data transparency and equitable access, must also be addressed to ensure that AI complements, rather than supplants, patient-centred care [6].

3. The role of the EEG, genetic, neurophysicology and imaging

EEG remains a cornerstone in the diagnosis and management of epilepsy. While the diagnosis fundamentally relies on a detailed clinical history of recurrent, unprovoked seizures, EEG provides indispensable support in confirming the epileptic nature of events, classifying seizure types, localizing the epileptogenic zone, informing prognosis, and guiding treatment decisions [7]. As neuroimaging, genetics, and molecular diagnostics continue to advance, the role of EEG is being actively re-evaluated, particularly with regard to its contribution to personalized treatment strategies.

The diagnostic utility of EEG is grounded in its capacity to directly record cerebral electrical activity. It is typically one of the first investigations performed after a suspected seizure and is especially useful in detecting interictal epileptiform discharges (IEDs), such as spikes and spike-and-wave complexes. While the sensitivity of a single routine EEG ranges from 29 % to 55 %, this yield increases significantly with repeated studies or activation procedures like hyperventilation, photic stimulation, and sleep deprivation [8]. Long-term video-EEG and ambulatory EEG further enhance the probability of capturing clinically relevant events, especially in diagnostically complex or refractory cases.

EEG plays a pivotal role in seizure classification, which is essential for therapeutic decision-making. Distinguishing focal from generalized epilepsies based on interictal and ictal EEG patterns is crucial for accurate ASM selection [7–11]. Moreover, EEG findings can aid in identifying specific epilepsy syndromes such as juvenile myoclonic epilepsy (JME), self-limiting focal epilepsies, or Lennox-Gastaut syndrome (LGS), each characterized by distinct electroclinical features, clinical trajectories, and therapeutic implications [12]. For example, the updated diagnostic criteria for LGS incorporate several EEG-based features [13]. In such cases, EEG-driven syndrome recognition expands the therapeutic armamentarium by supporting the use of targeted treatments such as cannabidiol and fenfluramine in drug-resistant LGS [14]. Syndrome recognition also informs the avoidance of potentially harmful ASMs. In patients with JME, for instance, accurate identification of the syndrome is critical to avoid medications such as selective sodium channel blockers, which may exacerbate seizures [15].

One of the key strengths of EEG lies in its ability to differentiate epileptic seizures from non-epileptic paroxysmal events. Disorders such as syncope, functional/dissociative seizure (FDS), migraine with aura (particularly with visual or sensory symptoms), movement disorders, and sleep disorders may mimic epilepsy. video-EEG is especially helpful in this differential diagnosis and avoiding unnecessary treatment escalation in patients with “pseudorefractory” epilepsy mimics or dual diagnoses [16]. The presence of epileptiform activity during or around the event supports the diagnosis of epileptic seizures. In contrast, its absence, particularly during or shortly after the episode, may point to an alternative diagnosis [7]. However, it is crucial to recognize that a normal EEG does not exclude epilepsy, especially if the epileptogenic focus is deep or in regions poorly sampled by scalp electrodes.

Moreover, EEG contributes significantly to presurgical planning. Although less sensitive than invasive techniques, scalp EEG—particularly during ictal events—can generate critical hypotheses about the epileptogenic zone [17]. Features such as ictal monomorphic theta activity in temporal lobe epilepsy have been associated with better surgical outcomes compared with ictal irregular delta patterns [18]. High-density EEG and source localization techniques increasingly complement neuroimaging in the presurgical setting [19]. These methods, in combination with structural and functional imaging, allow for accurate hypotheses regarding the seizure onset zone with high temporal resolution and can inform the placement of invasive electrodes and the extent of resective surgery.

EEG is also indispensable in the evaluation of status epilepticus (SE), particularly for detecting non-convulsive status epilepticus (NCSE), which may present with impaired responsiveness in the absence of overt motor symptoms [20]. In such cases, EEG allows for prompt diagnosis and therapeutic monitoring. Continuous EEG recording is frequently used in intensive care settings to detect subclinical seizures, evaluate treatment response, and assess prognosis in critically ill patients.

EEG provides valuable prognostic information [21]. In genetic generalized epilepsies, specific EEG markers—such as generalized paroxysmal fast activity or polyspike trains—have been associated with disease severity and treatment resistance [8]. Additionally, EEG proves valuable during ASM withdrawal: the presence of epileptiform discharges prior to withdrawal, as well as their emergence during the tapering process, may predict relapse, thereby informing safer tapering strategies [22–25].

Technological advancements are further enhancing the clinical impact of EEG. High-density electrode arrays improve spatial resolution, and computational EEG methods enable more refined analysis. Recent studies have shown that such methods can predict treatment response in drug-naïve patients and differentiate epilepsy from non-epileptic conditions, even when visual analysis of the EEG appears normal [26,27]. Additionally, machine learning algorithms have shown high accuracy in classifying epileptiform discharges [28], possibly helping particularly in settings where expert neurophysiologists are not available.

Despite its strengths, EEG has limitations. A normal EEG does not exclude epilepsy, particularly when the epileptogenic focus is deep or located in poorly sampled regions. Scalp EEG has limited spatial resolution, and artifacts or inter-observer variability may affect interpretation. These challenges underscore the importance of repeated recordings, optimized protocols, expert analysis, and advanced analytical tools. Integrating EEG data with neuroimaging, genomics, and clinical phenotyping is paving the way toward personalised epilepsy care, enabling earlier diagnosis, more targeted therapies, and improved patient outcomes [29].

In conclusion, EEG retains a central role in the comprehensive evaluation of epilepsy. Its unique ability to provide real-time insights into brain function ensures its continued relevance—not only for diagnosis but also for individualized treatment planning, prognostication, and the development of novel therapeutic strategies. The ongoing integration of EEG with cutting-edge technologies reaffirms its indispensable place in modern epileptology.

The application of next-generation sequencing (NGS) has profoundly transformed our understanding of the genetics of epilepsy [30]. To date, more than 900 epilepsy-associated genes have been catalogued in regularly updated diagnostic panels, and novel disease-causing genes continue to be discovered[31].

During the 2nd Episicily Conference, we explored the role of genetic testing in diagnosis, emphasising its value in the prompt identification of monogenic causes of epilepsy, which has significant repercussions in terms of prognosis and precision medicine [32,33].

Firstly, an overview of current genetic testing methodologies was presented, ranging from conventional karyotyping to whole-genome sequencing, highlighting the increasing availability and decreasing cost of next-generation sequencing (NGS) technologies. Indications for genetic testing were discussed, with particular reference to clinical features that predict a high likelihood of identifying a monogenic cause: a positive family history of epilepsy or convulsive seizures, seizure onset before 24 months of age, therapy-resistant epilepsy of unknown aetiology, and the presence of concomitant comorbidities such as intellectual disability [34].

Secondly, the profound impact of genetic findings on the classification of epilepsy syndromes was illustrated. The latest International League Against Epilepsy (ILAE) classifications for neonatal and infantile epileptic encephalopathies now incorporate gene-based nomenclature [35], as exemplified by KCNQ2-related developmental and epileptic encephalopathy [36] and GLUT1 deficiency syndrome [37].

Thirdly, the presentation addressed genotype–phenotype correlations and their variability. For instance, some examples related to single-nucleotide variants which may cause different phenotypes within the same family have been provided [38]. This further underscores the main theme of the conference – the importance of a holistic approach on epilepsies, with ongoing dialogue among geneticists, bioinformaticians, and clinicians.

Further, new emerging monogenic causes of epilepsy were discussed, including pathogenic intronic variants and long non-coding RNAs implicated in neurodevelopmental disorders [39].

The new findings on the implications of widespread background genomic features in classic monogenic disorders like Dravet syndrome were also discussed [40].

The challenges of variant interpretation in the NGS-era were emphasised, particularly the disproportion between the volume of detected variants and our capacity to classify them accurately, resulting in numerous variants of uncertain significance (VUS). Novel in silico tools such as AlphaMissense [41] or the SCN1A-prediction model that refine variant classification and interpretation were presented.

In conclusion, modern epileptologists can be optimistic: detailed phenotyping combined with timely genetic diagnosis paves the way for precision therapies and disease-modifying treatments. As genetic insights continue to expand, integrating genetic testing into routine clinical practice will be indispensable for optimising patient care and outcomes.

Over the years, the role of clinical neuropsychology in the diagnosis and management of epilepsy has become increasingly prominent. Neuropsychology evaluation doesn't merely consist of a static assessment of cognitive abilities, but rather integrates into a multidimensional framework that includes clinical course, therapeutic implications, and psychosocial well-being of people with epilepsy. According to the most recent recommendations of the Neuropsychology Task Force of the International League Against Epilepsy (ILAE) [42] neuropsychological assessment should be carried out by specialized professionals at every stage of the clinical pathway—from diagnosis to monitoring the cognitive side effects of antiseizure medications, and throughout the presurgical evaluation process. This type of assessment enables the early identification of deficits in memory, attention, language, executive functioning, and visuospatial processing, which are already evident in approximately 70 % of untreated patients.

In this framework, the International Classification of Cognitive Disorders in Epilepsy (IC-CoDE) represents an innovative procedure that, regardless of epilepsy syndrome, introduces a standardized taxonomy based on cognitive domain impairment. A recent study proposed a classification system grounded in cognitive phenotypes, distinguishing between: preserved or minimally impaired cognition, generalized cognitive impairment across all domains, and selective domain-specific deficits [43]. Furthermore, integrating IC-CoDE with neuroimaging, genetic data and environmental factors is expected to enable a deeper understanding of the underlying pathophysiology, encourage the development of approaches that focus on precision medicine.

One of the critical issues in neuropsychological evaluation of epilepsy involves the selection of the most appropriate instruments to address specific clinical questions. The routine neurocognitive tools employed must be sensitive, specific, and standardized, with the use of shared protocols. Screening instruments such as Montreal Cognitive Assessment (MoCA) or Mini Mental State Examination (MMSE) may guide the decision for additional neuropsychological evaluation. Actually, formal neuropsychological assessment remains the gold standard for diagnosing cognitive disorders associated with epilepsy. Specific cognitive domains may be further measured through tests selected due to their established psychometric properties and time-consuming.

As the literature suggests, there is a strong interaction between epilepsy, cognitive deficits and the presence of psychopathology. Indeed, about 45 % of people with epilepsy experience mood disorders, such as depression and anxiety [44]. These data reinforce the need for an integrated and expanded assessment, supported by validated tools or questionnaire.

The coexistence of psychopathology conditions may influence treatment adherence and disease course, highlighting the importance of a multidisciplinary intervention that includes a management of psychological and behavioural symptoms. Notably, Cognitive Behaviour Therapy has been shown to be effective in reducing seizures frequency and anxiety-depressive symptoms in individuals with epilepsy [45]. In addition, complementary approaches such as Mindfulness, Dialectical Behaviour Therapy and Acceptance and Commitment Therapy promote more stable emotional regulation and a global improvement of the quality of life.

In conclusion, the introduction of the IC-CoDE and the integration of psychological interventions represent a fundamental paradigm shift in epilepsy management, focused towards personalized, timely and multidimensional management.

Neuroradiological techniques, particularly Magnetic Resonance Imaging (MRI), play a pivotal role in the planning of epilepsy treatment—including surgical interventions—as well as in post-treatment evaluation. MRI has changed the ability of epileptologists to identify lesions even in patients considered to be "cryptogenic" [46,47]. Indeed, the modern epileptologist approaches persons with epilepsy looking at imaging together with electroclinical features. A critical aspect is the identification of the epileptogenic lesion, which is currently addressed using dedicated morphological MRI protocols that employ thin-slice volumetric sequences (MPRAGE and FLAIR) and appropriate scanning planes for the study of the temporal lobes and hippocampi [47,48]. There are several innovations in the field of MRI diagnostics of epilepsy with the possible application of T1 mapping sequences (MP2RAGE) and high-resolution Inversion Recovery in contrast between white and gray matter (EDGE – FLAWS), available on high and very high field magnets (3–9 Tesla) [48]. The diagnostic potential of MRI is significantly amplified by the introduction of artificial intelligence techniques in the clinical research field, both in the acquisition and interpretation phases.

This technique with these peculiar epileptic protocols has become fundamental in the management of refractory epilepsy because the identification of a clear-cut lesion on structural MRI is associated with a good seizure outcome after surgery.

Functional MRI techniques (resting-state and DTI) are useful in planning surgical treatment of epilepsy, especially in order to evaluate specific functions such as language lateralization, motor pattern, verbal and visual memory. The same techniques are also suitable for evaluating brain connectivity in patients with epilepsy, reduced along specific pathways that have the thalamus as a relay. Finally, in the context of treatment, MRI techniques can represent an alternative to surgery with the use of laser (MRIg-LITT) or Deep Brain Stimulation (DBS) in patients with drug-resistant epilepsy [47–49].

The integration of artificial intelligence (AI), particularly generative models, into medical diagnostics and prognostics is redefining the landscape of clinical neurology [50]. This presentation explores the application of AI in the diagnosis and prognosis of epilepsy, emphasizing the use of natural language processing (NLP) and generative AI tools such as ChatGPT. While generative AI demonstrates impressive performance in general medical reasoning [51]—surpassing medical students in standardized case assessments—its diagnostic accuracy in epilepsy remains limited, with relatively low sensitivity and high error rates [52–54] (diagnosed only 18.2 % of true epilepsy cases vs. 36.2 % by neurologists; sensitivity was 17.6 %, but specificity was 81.4 %). While promising, current generative models are not reliable for frontline diagnosis, but they may serve as educational or decision-support tools.

Current advances in AI applied to epilepsy diagnostics include the use of machine learning (ML) and deep learning (DL) models across multiple domains such as structural and diffusion MRI, electroencephalography (EEG), video-based seizure detection, and multimodal data for identifying subtle lesions like focal cortical dysplasia. These approaches show moderate to high diagnostic accuracy, sometimes rivaling expert human evaluators. In particular, the goal of AI in diagnosis is to help detect or classify the presence of epilepsy (and its subtypes) more accurately and often earlier than traditional methods. Several tools and data sources are used for applying AI methods in epileptic diagnosis:

A. *Neuroimaging data (Magnetic Resonance Imaging or Diffusion Tensor Imaging)*
B. ML and DL algorithms have been trained on structural and diffusion MRI data to distinguish between TLE-positive (TLE +) and healthy controls. Accuracy ranges from 66–74 %, which is considered moderate but clinically valuable [55]. Otherwise, when DL algorithms are applied on Focal Cortical Dysplasia (FCD) data significant findings are reported. Indeed, FCD often goes undetected in standard MRI. It has been demonstrated [56] that DL algorithms, using multimodal MRI data, can detect previously MRI-negative lesions with 93 % sensitivity and 89 % specificity. This empowers non-expert radiologists or clinicians to detect subtle lesions that might otherwise be missed.
C. *EEG Data*
D. To evaluate if AI models can be trained to interpret routine clinical electroencephalograms (EEGs) with accuracy equivalent to that of human experts, Tveit and colleagues have developed the SCORE-AI, a deep learning model able to interpret routine clinical EEGs with an AUC between 0.89 and 0.96. This study suggested that SCORE-AI could be applied in the clinical practice to enhance the speed and accuracy of EEG interpretation in busy or resource-limited clinical settings [28].
E. video-*Based Seizure Detection*
F. Rai et al., [57] evaluate the performance of a contactless, marker-free, video-based motor seizure detection system, to monitor epileptic patients at bed. This system achieves 95.2 % accuracy for tonic-clonic seizures, 86.7 % for automatisms, and 98 % for psychogenic non-epileptic seizures (PNES). This study demonstrates that AI-embedded video recording systems are valuable in remote monitoring or during video-EEG telemetry.

Prognostic modeling through neuroimaging [58] or omics data [59] further supports AI's potential in predicting treatment responses and seizure outcomes. However, variability in specificity and outcome prediction suggests that these tools are still complementary rather than standalone solutions. In the future, these methods will support personalized medicine by tailoring treatment to individual patients.

However, AI may help to stratify patients by risk, predict treatment response, and personalize care. This field of study highlights the presence of biological subtypes that can be extracted for neurobiological data. In a recent work, Jiang et al. [60] attempted to reclassify illness categories according on comparable pathobiology. Using cross-sectional MRI data from 296 patients with focal epilepsy originating from the temporal lobe (TLE) and 91 healthy controls, they demonstrated phenotypic heterogeneity in the pathophysiological course of TLE using a machine-learning approach. They distinguished between two phenotypes that are dominated by the hippocampus, with atrophy starting in either the left or right hippocampus; a third phenotype that is dominated by the cortex, with atrophy in the hippocampus occurring after the neocortex; and a fourth phenotype that does not have atrophy but has an enlarged amygdala. These subtypes help predict Response to antiseizure medications and Seizure outcomes post-treatment.

Overall, AI holds transformative potential for neurology, particularly in improving diagnostic yield, supporting non-expert clinicians, and enhancing precision medicine through predictive modeling. The future of AI in epilepsy may hinge on integrating wearable systems, biotyping strategies, and continuous learning frameworks to refine both diagnosis and prognosis [50].

4. Antiseizures medications and neuromodulation

The treatment of epilepsy has evolved significantly with the introduction of newer antiseizure medications (ASMs). However, older ASMs continue to play a crucial role in clinical practice. Nowadays, we can count more than 25 available ASMs to choose from which are often represented according to their year of introduction into the market. We may distinguish between older and newer generation or even among first, second and third generation drugs; however, at odds with other therapeutic areas, we cannot really highlight a specific advancement in the management of seizures [61]. For example, we clearly understand the advantages brought by newer drugs in the management of hypertension, diabetes mellitus or multiple sclerosis among others. In epilepsy, while we recognize advantages and disadvantages of each drug, they cannot be clustered by the time of market introduction.

Indeed, for a long time we have commented that newer drugs, despite their ability to reduce the number of people with drug resistant seizures, were better tolerated and had a reduced potential for drug-drug interactions (DDIs) while new mechanisms of action improved rational polytherapy; however, if we consider newer drugs such as cannabidiol or cenobamate, their potential for DDIs is as high as that of older ASMs [62].

The value and role of older ASMs is clearly highlighted and can be extrapolated by considering any list of recommended ASMs classified by seizure type or syndrome in which older drugs such as carbamazepine and valproic acid are always listed as suggested potential initial monotherapies [63]. Although we may consider that newer drugs could be initially considered, when analysing pattern prescriptions, we always find among the most prescribed drugs these with a longer market history [64].

Levetiracetam represents the most prescribed ASM and although it is considered a newer generation ASM it has already been on the market and used for more than 25 years.

When looking at the list of the most prescribed drugs in Italy, we find in the top 5 after levetiracetam, valproic acid, carbamazepine,

lamotrigine, oxcarbazepine and lacosamide; except the latter (commercialized about 17 years ago) all other represent old generation ASMs [65]. A similar pattern can be observed in other countries; undoubtedly, we are clearly observing a slow reduction over time in the use of carbamazepine and valproic acid [66]. The latter has been mainly affected by the warning and contraindication on its use in female patients of childbearing age. As an example, a study compared ASMs' prescriptions in Spain between 2013 and 2023 in patients with idiopathic generalized epilepsy and while valproic acid remains the most prescribed, its use in men is maintained while in women the use of levetiracetam, lamotrigine and brivaracetam has dramatically increased. More specifically, in men, a reduction of only about 4 % in the use of valproic acid can be observed between 2013 and 2023. While in women, valproic acid use goes from about 60 % to about 30 % with bitherapy and polytherapy proportionally increasing and levetiracetam and lamotrigine being each used in about 30 % of patients [65].

Older ASMs, including carbamazepine, valproic acid, phenytoin, and phenobarbital, but also levetiracetam, oxcarbazepine and lamotrigine have been the cornerstone of epilepsy treatment for many decades. Their efficacy in controlling various seizure types is well-established, and they remain valuable options, particularly in specific epilepsy syndromes and patient populations. The value of clinical experience in the choice of a drug is a major determinant.

The long-term use of older ASMs has provided a wealth of clinical data supporting their efficacy and safety. Clinicians have extensive experience with these drugs, allowing for optimized dosing and management of potential side effects. Nevertheless, if we consider focal epilepsy, there is no study demonstrating superiority of any drug over carbamazepine and network *meta*-analysis indicate that most drugs may be considered a valuable and effective initial treatment with retention rates being very similar among ASMs. Lacosamide appears to have a higher retention rate in comparison to carbamazepine and this may justify its recent increasing use [67]. Similarly, in generalized epilepsy, valproic acid remains the most effective treatment [68].

One major limitation in the use of newer drugs has been represented by marketing rules and the typical design of pre-authorization randomized clinical trials; newer drugs are always studied and then authorized as add-on therapies with limitations in their use in many countries. This implies a difficulty in the evaluation of the real efficacy of newer ASMs along with a longer time for clinician to gain experience in their use (above all as initial monotherapies). Furthermore, when comparing the efficacy of newer drugs, it is evident that both in randomized clinical trials and real-world studies, they appear very similar [69,70].

More recently, high hopes have been given to cenobamate with many articles claiming great efficacy which come both from pre-marketing studies and real-world experiences [71,72]. Indeed, cenobamate appears has a very effective and promising drug although not as much manageable as most of the newer drugs. Cenobamate requires a quite long titration but more importantly DDIs represent a relevant aspect of its clinical management being both of pharmacokinetic and pharmacodynamic nature. In other words, the current use of cenobamate as an add on often requires adjustment of the doses used for other ASMs and the appearance of side effects. Nevertheless, it has demonstrated a great efficacy in highly refractory patients with retention rates not different from other ASMs [73].

The current scenario for ASMs use is evidently based on clinical experience and therapy personalization according to seizure types, potential co-occurring disorders, but also gender and age among other factors. Despite the known disadvantages linked to the use of older drugs such as the occurrence of DDIs, side effects including blood dyscrasias, hepatotoxicity, metabolic alterations due to alterations in lipid metabolism or hormonal changes, sedation and cognitive impairment, their use remains prominent. Similarly, cenobamate appears a not easy-to-use drug but is undoubtedly considered a "game changer".

Therefore, the notorious risk/benefit ratio is eventually driving ASMs use with most of the patients starting on levetiracetam and then moving to one of the older ASMs or lacosamide while other valuable attempts with safer drugs may at least been tried in some patients. A relevant consideration when introducing a drug like carbamazepine must go to the future of the patient which will be almost certainly characterized by DDIs and side effects which may be avoided using one of the safer newer drugs.

In conclusion, older ASMs remain essential in the treatment of epilepsy due to their established efficacy, cost-effectiveness, and broad spectrum of action. While newer ASMs offer advantages in terms of tolerability and drug interactions, they may not always demonstrate superior efficacy. The fact that newer drugs are often used as add-on therapies makes it difficult to ascertain if they are as effective as older drugs. The choice of ASM should be individualized based on the patient's seizure type, epilepsy syndrome, comorbidities, and potential for drug interactions, and cost. A thorough understanding of the advantages and disadvantages of both older and newer ASMs is crucial for optimizing epilepsy management and improving patient outcomes while the major limitation in the use of newer ASMs is likely our personal experience.

Drug-resistant epilepsy (DRE) significantly affects quality of life and poses increased risks, including sudden unexpected death in epilepsy (SUDEP) [74]. For these patients, surgical resection of the epileptogenic zone (EZ) offers a potentially curative intervention. Recent advancements in surgical and VNS, biomarkers (objective, quantifiable indicators of disease presence or outcome), have emerged as vital tools to enhance preoperative evaluation and postoperative prognostication in DRE. Intracranial electroencephalography (iEEG) remains the gold standard for EZ localization in patients undergoing invasive monitoring. The use of quantitative EEG (qEEG) and network analysis of iEEG data offers deeper insights into epileptogenic networks rather than isolated foci. Key qEEG metrics include high-frequency oscillations (HFOs), particularly ripples (80–250 Hz) and fast ripples (>250 Hz), which are strongly associated with epileptogenicity [75]. Other measures include interictal epileptiform discharge (IED) rates, spectral power analysis, and functional connectivity indices.

Amongst qEEG measurement from iEEG, Epileptogenicity Index (EI) represent one of the most used. The EI is a quantitative tool that integrates the spectral and temporal features of iEEG signals to estimate the propensity of each brain region to generate seizures, supporting objective identification of the EZ. Increasingly, epilepsy is recognized not as a focal phenomenon alone but as a network disorder, where seizure generation and propagation involve complex interactions across distributed brain regions. This network perspective enhances the value of qEEG analyses in capturing both local and large-scale dynamics underlying epileptogenesis. However, iEEG has a limited spatial solution posing limits on the characterization of the whole-brain functional dynamics. In this light, high density EEG may represent a precious resource in order to characterize brain dynamics at the large scales. Recent findings showed that connectivity pattern of the epileptogenic regions, investigated at the source level throughout graph theory measures, may help to better delineate the identification of the epileptogenic zone [76,77]. Functional organization may also represent an important biomarker for the prognosis. Recent findings suggest that well-structured, internally cohesive networks with reduced external connectivity (i.e., lower inflow connectivity to the region containing the seizure onset zone and higher local efficiency and clustering coefficient) are predictive of successful seizure outcomes post-surgery [78]. Overall, qEEG and functional connectivity from invasive and non-invasive recordings hold promises from clinical application. However, a recent review emphasized the etereogenitiy in the methods limiting the generalizability in clinical practice of qEEG-derived connectivity measures, delineating futures strategies to promote clinical application of these advanced techniques [79].

A recent study suggests that diffusion MRI abnormalities reflect epileptogenic tissue and that their identification and surgical removal

can significantly improve seizure outcomes [80]. This supports the inclusion of dMRI-based abnormality mapping in pre-surgical planning, especially where standard imaging fails to provide clear targets. In this light, ultra-high-field 7 T MRI has revealed previously undetected cortical dysplasias, influencing surgical decision-making in over 50 % of reviewed cases [81].

Importantly the combination between structural and functional imaging may help in fMRI assesses brain activity by detecting changes associated with blood flow, while DTI maps white matter tracts. Combining these imaging modalities aids in identifying eloquent areas during surgery.

Labate et al. [82] showed that a valuable biomarker of refractoriness in MTLE was a significant reduction of fractional anisotropy (FA) along the white matter of the temporal lobes.

Morgan et al. [83] utilized MRI-based functional and structural whole-brain connectivity to generate a "network fingerprint"; representing the connectivity profile of patients who achieved seizure freedom following epilepsy surgery. This fingerprint was then compared to the connectivity profiles of 38 independent patients, under the hypothesis that greater similarity to the fingerprint would be indicative of a seizure-free outcome. Using receiver operating characteristic (ROC) analysis, the approach achieved 100 % sensitivity and 90 % specificity in distinguishing patients with poor outcomes (Engel class III–IV).

Molecular biomarkers, particularly microRNAs (miRNAs), are gaining interest due to their regulatory roles in neuroinflammation, apoptosis, and neurotransmission. Recent studies have highlighted specific miRNAs such as miR-654-3p and miR-328-3p for their prognostic value in surgical epilepsy outcomes [84].

Vagal Nerve Stimulation (VNS) is a neuromodulatory therapy that involves delivering electrical pulses to the left branch of vagus nerve, influencing brain activity to reduce seizure frequency [85]. It is hypothesized that desynchronization of the EEG is an important mechanism for antiepileptic effect [86]. The identification of factors predictive of VNS response is important for patient selection and stratification as well as tailored stimulation programming. However, there is a lack of reliable predictors of VNS response in clinical use. No individual marker demonstrated sufficient predictive power for individual patients, although several have been suggested, with some promising initial findings. Combining markers from under researched modalities such as T1-weighted MRI morphometrics (e.g., MRI) and functional (e.g., EEG) may provide better strategies for treatment optimization [87]. Some studies have evaluated the effect of VNS on functional connectivity using the phase lag index (PLI), showing a desynchronization in brain activity during and after VNS stimulation [88–93].

The integration of surgical biomarkers with VNS therapy offers a personalized approach to treating DRE. For patients with localized epileptogenic zones amenable to resective surgery, surgical biomarkers guide precise excision, potentially leading to seizure freedom. In contrast, for patients with multifocal or non-localizable seizures, VNS serves as a valuable adjunct or alternative treatment option. Combining these approaches allows clinicians to tailor interventions based on individual patient characteristics, optimizing outcomes.

Despite promising progress, challenges remain, including the need for standardization, validation in large cohorts, and clinical integration of emerging biomarkers. Nonetheless, the convergence of neurotechnology, molecular biology, and artificial intelligence heralds a new era in epilepsy surgery, moving toward more precise, effective, and individualized care possible.

5. The role of neuroinflammation: grey zones, gaps in knowledge and therapeutic implications

Neuroinflammation is the set of phenomena that leads, in the central nervous system (CNS), to the synthesis and release of inflammatory mediators, which may have CNS-specific effects.[92,93] Its relationship with drug-resistance is a promising field of investigation in epilepsy research, considering that this condition affects up to one third of epilepsy cases and determines a serious burden for patients and healthcare systems. [94] Hence, both clinical and basic research efforts point towards exploiting neuroinflammatory mediators and molecules as new therapeutic targets in difficult-to-treat epilepsies. [92].

However, this objective is not straightforward since the molecular, cellular and synaptic mechanisms that neuroinflammation can alter are diverse and potentially triggered by different stimuli.

In some cases, it is possible to pinpoint a genetic cause of the neuroinflammatory processes, such as in the case of the so-called "mTORpathies". [95,96] In these diseases, a genetically determined anomaly of the mTOR pathway, crucial for cell growth and proliferation, has been associated by a substantial number of studies with sustained neuroinflammatory responses. [97].

Furthermore, on the other hand, seizures and epilepsy have been linked to acquired dysregulation of the immune system itself, triggered by pathogens or tissue damages, [98]. These mechanisms can lead both to acute seizures and chronic epilepsies. [99].

Finally, it is now becoming clear that neuroinflammation is also perpetuated by recurrent seizures, which induce cytokine production, activation of downstream effectors and, possibly, alterations of astrocytic, glial and neuronal function. [100].

This *scenario* is extremely complex but, nonetheless, it is possible to highlight some common mediators, functional alterations and/or mechanisms that may constitute an important part of the link between epilepsy and neuroinflammation.

In particular, it looks like in epileptic conditions the resolving mechanisms are overburdened by the neuroinflammatory signals. [92] Experimental evidence supporting this statement came from different studies. For instance, pro-resolving lipidic mediators production is induced with significant delay, compared to pro-inflammatory molecules in the epileptic brain. [101] Moreover, pro-inflammatory cytokines apparently have the upper hand on the anti-inflammatory ones in terms of neurotransmission modulation. It has been shown that IL-1 a prototypic pro-inflammatory cytokine negatively modulates GABAergic function in temporal lobe epilepsy [102], focal cortical dysplasia [103] and gangliogliomas, where it also prevents GABA current potentiation mediated by the neuroprotective cytokine IL-10. [102] Finally, the levels of anti-inflammatory cytokines are generally downregulated in epileptic disorders. [104,105].

These findings can potentially lead to new therapeutic strategies. Indeed, the use of molecules blocking the action of pro-inflammatory mediators such as IL-1, IL-6 and CD20 is yielding promising results. [106] Future trials will likely shed light on the use of novel therapeutic agents blocking other key components of pro-inflammatory cascades, such as HMGB1 [107] and chemokines. [108].

Autoimmune encephalitis (AE) has recently emerged as a possible cause of seizures and epilepsy. Although considered rare —and likely underdiagnosed— it has rapidly become a focal point of research, as it represents a model for understanding the complex interplay between the central nervous system and the immune system. Moreover, AE-related seizure disorders pose a diagnostic challenge and question traditional paradigms in seizure management, highlighting the necessity of recognizing immune-mediated mechanisms underlying both ictogenesis and epileptogenesis. With such premises, it does not come as a surprise that the 'immune' etiology has been recognized as a distinct category in the latest classification proposal by the International League Against Epilepsy (ILAE) [109].

Seizures are a common and often prominent feature of AE —particularly in cases involving antibodies against leucine-rich glioma-inactivated 1 (LGI1), γ-aminobutyric acid A/B receptors ($GABA_{A/B}R$), and glutamic acid decarboxylase 65 (GAD65). Alongside altered mental status, psychiatric symptoms, and memory deficits, seizures are considered a key diagnostic criterion for AE [110].

In 2020, the ILAE Autoimmunity and Neuroinflammation Taskforce posed a conceptual milestone by distinguishing acute symptomatic

seizures (ASS) secondary to AE from autoimmune-associated epilepsy (AAE), defined as the persistence of seizures despite adequate immunotherapy (IT), and possibly related to both structural and immunological factors [111]. This statement has profound therapeutic implications, since ASS are primarily treated with IT, whereas AAE should be managed by using anti-seizure medications (ASM) only. Current literature shows that only a limited proportion of AE patients will eventually develop AAE, although variability in study designs and patient selection may affect these estimates. Diagnostic and treatment delay, severe initial presentation (e.g., status epilepticus), and the presence of intracellular antibodies, often associated with T cell-mediated cytotoxic response and irreversible neuronal injury, have been consistently linked with AAE, whereas the prognostic role of other factors (e.g. interictal epileptiform abnormalities, MRI findings) remains controversial [111,112].

Despite the conceptual and operational relevance of the above-mentioned definitions, their application in daily clinical practice can prove challenging, as the line between ASS and AAE is particularly blurred, highlighting the gaps in current knowledge about the pathophysiological underpinnings and long-term evolution of ASS and AAE [113].

First, there is no consensus on the temporal threshold separating ASS from AAE, nor validated biomarkers to confirm the presence or absence of ongoing autoimmune activity. Based on the "usual maximum period of time ASS can take to abate with treatment", a recent paper has proposed a 2-year cut-off to diagnose AAE in patients harbouring antibodies against neuronal surface antigens (NSAbs), and without evidence of ongoing inflammation (i.e. no MRI alterations, normal cerebrospinal fluid cell count, and decrease in autoantibody levels) [114,115]. This novel operational definition (yet to be tested in real-life practice) suggests that the progressive shift from immunological processes to structural damage might lead to AAE, and yet the rate and extent of such evolution might be extremely variable. Indeed, in some cases seizure remission has been achieved after more than 10 years [116], questioning the concept itself of 'acute' encephalitis, and suggesting the existence of prolonged 'active' immune-mediated mechanisms which might still benefit from IT escalation. Compounding this challenge is the documented underreporting of seizures in AE [117] and the frequent occurrence of subclinical seizures —only detectable through prolonged EEG monitoring- which limit the accuracy of long-term outcome assessment.

Another relevant concern regards the identification of relapses, which can manifest with subtle cognitive/behavioural changes or isolated seizure recurrence, often mimicking fluctuations seen in chronic epilepsy and making clinical decision-making extremely challenging. Similarly, some patients with new-onset seizures of immune origin might also present with a 'mild' phenotype, failing to meet the criteria for AE. These cases represent a particular diagnostic conundrum, and several studies so far have tried to identify distinctive semiological (e.g. pilomotor seizures, multimodal auras, sensitivity to hyperventilation) and EEG features (e.g. subclinical paroxysmal events, bilateral independent ictal patterns, ictal shifting) which might help clinicians suspect an underlying immune-mediated condition [118,119]. To aid in identifying autoimmune epilepsy in patients with focal seizures of unknown origin, scoring systems have been proposed. For instance, the Antibody Prevalence in Epilepsy and Encephalopathy (APE2) score [120] and the more sensitive Antibodies Contributing to Focal Epilepsy Signs and Symptoms (ACES) score [121] aim to guide clinicians in deciding when to screen for neural antibodies. While these tools have potential clinical utility, they rest on the assumption that neural autoantibodies serve as the primary biomarker for AE, thus excluding seronegative cases — a significant and still poorly characterized subgroup.

The complexity of this scenario underscores the need for reliable biomarkers to differentiate disease stages, identify relapses, and predict long-term outcomes. Neurofilament light chain (NfL) is a promising candidate, helping distinguish AE from psychiatric mimics [121] and correlating with disease severity. However, NfL levels may also rise in various neurological conditions and may be influenced by seizures themselves, which limits its specificity and leaves clinicians in want for accessible, specific biomarkers of active immune-mediated disease to guide patients' long-term follow-up and management.

In conclusion, although autoimmune seizure-disorders are relatively rare, their diagnostic and therapeutic implications are profound. Recognizing the fluid transition from ASS to AAE, employing structured diagnostic tools, and integrating biomarkers into routine care can guide more precise management, but further studies are warranted to fill the numerous gaps in knowledge and illuminate the *grey zones* between AE and AAE.

6. The bidirectional relationship between epilepsy, insomnia and sleep disorders

A converging body of work suggests that sleep and epilepsy present a strong bidirectional relationship. Several factors sustain it, such as the evidence that: 1) the vast majority of sleep-related seizures were followed by arousals or awakenings, 2) sleep fragmentation in drug-resistant epilepsy is associated with ictal and inter-ictal epileptic activity, 3) different sleep stages can modulate the interictal spiking with the higher number of spikes during the second cycling of Non-REM sleep and in particular in deep, slow-wave, sleep [122]. Although this evident relation between sleep and epileptic spiking, a few studies investigated the sleep macrostructure in people with epilepsy, either generalized or focal, and documented that in focal epilepsy there is a reduction of REM sleep quantity compared to that of healthy controls [123]. A recent polysomnographic study showed that sleep efficiency in reduced in treatment-naïve people with generalized or focal epilepsy, compared to healthy controls. This sleep dysregulation is featured by increased wakefulness after sleep onset, higher number of arousals, higher quantity of stage 2 of Non-REM sleep and a more frequent sleep stage shifting, particularly in focal epilepsy [124]. On the other hand, the importance of evaluating the sleep microstructure in people with epilepsy emerged due to the interdependent regulation of these two processes [125]. Rhythmicity of brain processes is a novel concept that could help understanding the periodicity of epileptiform discharges in sleep. Cyclic alternating patter (CAP) in sleep can be considered one of the main expression of brain rhythmicity in sleep. CAP is composed by A and B phases, and its rate can depict the stability of sleep; a higher CAP rate is indicative of an instable sleep and people with epilepsy can present an higher CAP rate than controls [126]. Phase A is in turn distributed in A1, A2 and A3 parts, and A1 is featured by synchronized EEG patterns while A2 and A3 present a progressive desynchronization of the EEG patterns. A more representative A1 phase than the other two is correlated with better cognitive performance [126]. The inclusion of cognition in the interplay between sleep and epilepsy depicts a multi-directional relationship among all these three components. Accordingly, interictal spiking during sleep is associated with a higher desynchronization of sleep that in turn is associated with poorer cognitive performance [125]. REM sleep microstructure is also impaired in people with epilepsy, with cortically generated sleep oscillations reduced even when epileptic activity is low [125]. Taking all this evidence into account, it appeared evident that desynchronization in sleep (such as what happens in REM sleep) tends to prevent spiking activity, while hyper-synchronization in sleep (such as what happens in deep, slow wave, sleep) tends to trigger spiking activity.

On this established relationship between sleep and epilepsy, the literature described the occurrence of sleep-related seizures (associated or triggered) and seizures occurring at awakening. Sleep-related seizures are those recently reviewed in the definition of sleep-related hypermotor epilepsy (SHE, previously known as nocturnal frontal lobe epilepsy), featured by seizures arising from sleep and manifest as complex motor behaviors or sustained dystonic posturing. For obtaining the diagnosis of SHE, video-EEG-polysomnography is mandatory, although this

expensive and time-consuming exam can be anticipated in advance by home-video recordings [127]. The disorders of arousals (DoA) are one of the main differential diagnosis of SHE. DoA are sleep parasomnias occurring in Non-REM sleep. The main difference between SHE and DoA is the more frequent occurrence in stage 2 of Non-REM sleep of the first and in stage 3 of Non-REM sleep of the second, although this difference is not diagnostic and the video-EEG-polysomnography is required for the correct interpretation of the sleep episodes [127].

Sleep disturbances are very common in people with epilepsy, and complaints of poor sleep, insomnia, and sleep-disordered breathing are the most frequent [128,129]. Considering the video-polysomnographic exams, bruxism, periodic limb movements and neck myoclonus can be a common finding that requires further investigations [130]. Very recently, circadian sleep-wake cycle disorders have been also described in people with epilepsy, who tend to present more commonly circadian sleep-wake cycle dysregulation and wake fragmentation due to napping [125]. Further supporting the importance of maintaining the regularity of the sleep-wake rhythm, an actigraphic-based study documented that fluctuations in bedtime and waketime is more informative than sleep duration for identifying seizure risk, opening the importance of controlling the rhythmicity of the sleep-wake cycle more than the total sleep time [131,132]. Therefore, maintaining a consistent sleep routine (bed and wake times) should be focused in the management of people with epilepsy more than the maximization of sleep duration [133].

In conclusion, optimizing night-time sleep and maintaining the vigilance during the day can help ensuring a regular sleep-wake cycle. Moreover, sleep disorders commonly presented by people with epilepsy should be recognized and treated as the regularity of sleep and the sleep-wake cycle can help in obtaining the seizure freedom. In agreement with this need, the antiseizure treatment strategies should be set on the importance of not affecting sleep and vigilance, by choosing drugs that can help in promoting sleep and maintaining daytime vigilance.

7. Take home messages and future perspectives

A simple Google search reveals how much attention and production of papers on medical humanities is growing. Our era is characterized by the expansion of the possibilities of biomedical research and intervention, but also by the urgent need to understand and to define these possibilities in cultural and social terms, to integrate them into daily life, both for the doctor and for the patient. This multidisciplinary approach must be able to connect the naturalistic understanding of the disease with the daily experience of those living with chronic diseases.

Those living with a chronic illness do not simply experience a biochemical or electrical imbalance, but face a reality that redefines their identity and perception of their body. Mind, body, thought, and perception are inseparable, and the term “holistic” is particularly pertinent to describe this integrated view. The adjective, appropriately recalled in the title of this conference, derives from the concept of holon, defined by Arthur Koestler [134] as a basic unit shared by biological and social systems. Like Janus, it is two-faced concept, which in the case of epilepsy is appropriate to recall, because it connects the naturalistic dimension of the disease and the phenomenological dimension of the experience of illness (and health).

Health and illness are interconnected experiences, which cannot be understood separately or only in naturalistic terms. It is essential to build a relational bridge between the two areas to improve the understanding of the experience of illness. The doctor must not see the patient only as a “biological dysfunction”, but as a person who lives the experience of the disease. This approach radically changes the training of the doctor, his role and his relationship with the patient.

William Gordon Lennox had already observed that people with epilepsy suffer more from the social consequences of the disease than from the disease itself, as evidenced by the stigma that often accompanies them. Recent studies, such as that of Alan W. C. Yuen [135], suggest that epilepsy should be considered as the sum of seizures and comorbidities caused by systemic dysfunction and that the complete management of epilepsy also includes the management of systemic dysfunction.

In the face of this acquired systemic medical dimension of the disease, however, there is no corresponding analogous attention and understanding aimed at restoring the complexity of the experience of living with epilepsy (illness). It should include the study of the psychodynamic and anthropological roots, in order to underly the different modes of reaction, especially collective, within the different cultural traditions (sickness).

Living with an illness is a transformative experience that changes the subject in a profound and lasting way, both from the point of view of knowledge (teaching new things through new experiences) and from a personal point of view (changing priorities and preferences according to new awareness). It is a condition that makes you see things in a different light that can prompt profound and creative changes with respect to the horizon of possibilities and the sense of trust [136].

As R. D. Laing observes the behavior of others is my experience, and vice versa. Social phenomenology deals with relating individual experiences, creating a field of “inter-experience” [137]. For those living with epilepsy, moments of loss of consciousness, seizures, create a desynchronization compared to the others, generating a dependence on their point of view. The person does not see himself during the seizure, and builds an image of himself that depends on the reactions of others, thus creating an experience full of meanings that feed the collective imagination on epilepsy.

Recovering the holistic dimension means that epilepsy does not only affect the person who experiences it, but also “others”, who contribute to it with their narrative and social imagination, shaping the *idea* of epilepsy, an alliance between biomedical sciences and social sciences and activists is needed to jointly address the issue of epilepsy, focusing on the interaction between individual and collective experiences.

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