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The clinical management and socioeconomic impact of epilepsy in Italy: current and future perspectives

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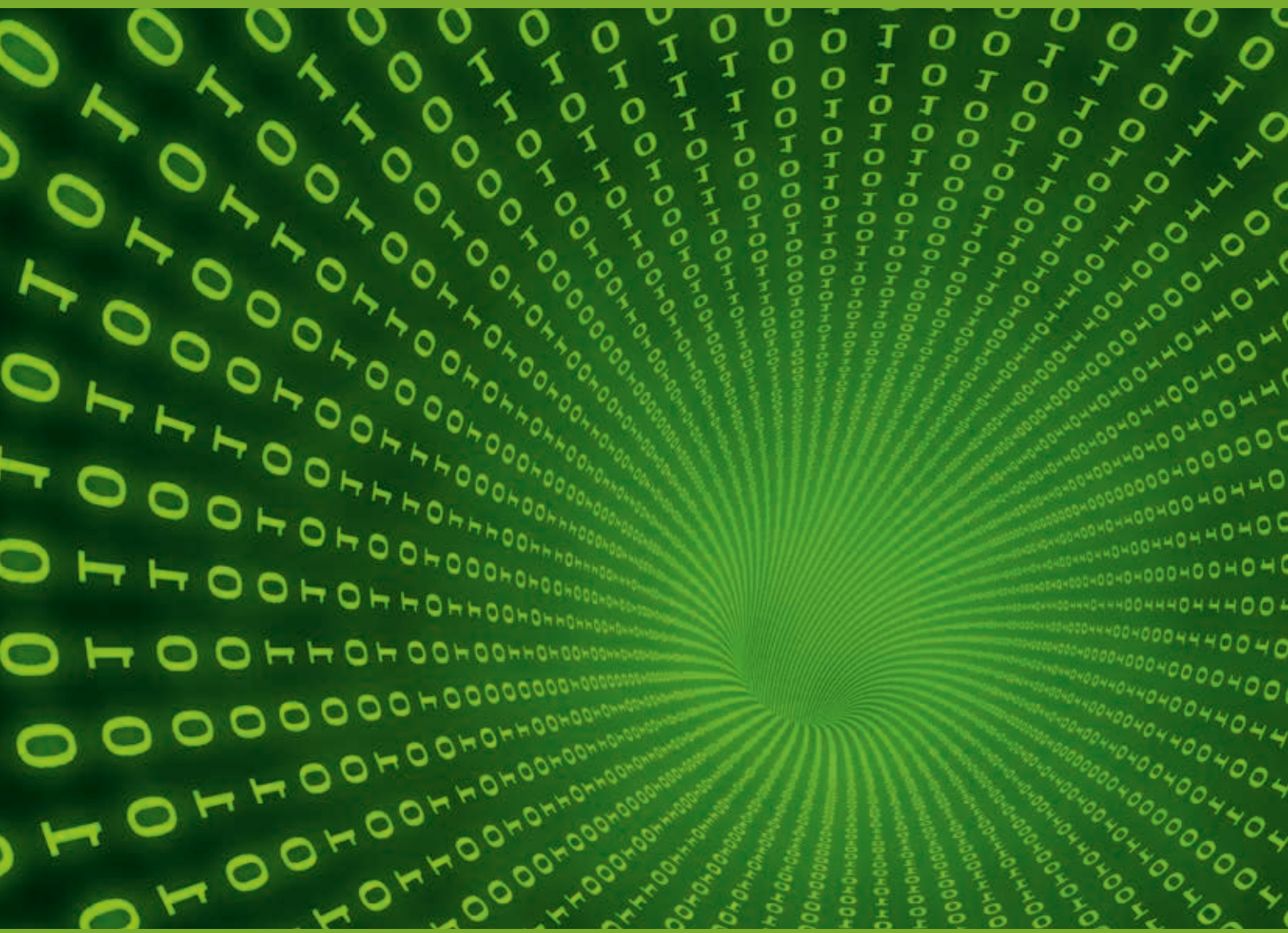

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EDITORIAL

The potential impact of PNNR on the management of patients with epilepsy

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In recent years, public health in Italy has changed significantly: scientific progress, continuously evolving research, the development of new technologies and innovative drugs have remarkably improved the quality and life expectancy of patients.

Inevitably, as in all sectors of economy, there still is the need to ensure a trade-off between innovation, sustainability and resource allocation.

In this scenario, some key health policy principles should be adhered to in planning medium- and long-term investments, and to allow for a rational allocation of resources, which must be in line with real needs. A critical element for building a 'mutually sustainable' system is to ensure, as far as possible, a solid and stable planning and financial framework.

The value of technologies, connected to the economic and social 'weight' of diseases, represents one of the most important elements in this scenario, especially if it refers to the concept of innovation. Epilepsy appears to fit within this context.

Epilepsy is a chronic condition affecting people worldwide. It is identified by recurring, uncontrolled phenomena called seizures, often leading to neurobiological, cognitive, psychological and social consequences. Seizures, usually of short duration (from a few seconds to a few minutes) are classified according to the awareness level of the patient (integral or impaired awareness) and to the presence of involuntary movements (motor and non-motor seizures). Based on their onset, we can identify focal or partial seizures (which arise in one cerebral hemisphere) and generalized seizures (involving both hemispheres) (1).

In Italy alone, there are over 500,000 people with active epilepsy and more than 36,000 new cases are expected every year. Epilepsy incidence appears to be higher in the first year of life, decreasing during adolescence, remaining low in adulthood and rising after the age of 75. People living with epilepsy experience reduced access to educational opportunities and barriers to enter certain occupations. Uncontrolled epilepsy is often associated with significant psychological dysfunction and impaired quality of life and carries the risk of premature death. Furthermore, stigma and discrimination still surround epilepsy across the world. The economic impact of epilepsy varies significantly depending on the disease duration and severity, response to treatment and the healthcare setting. Out-of-pocket costs and productivity losses inflict substantial burdens on households (2).

Epilepsy proves to be a condition which, if inadequately addressed in terms of organizational model and management approach to diagnosis and patient care, risks generating significant disabilities leading to remarkable economic and social impact (direct healthcare costs, direct non-healthcare costs, indirect and social costs).

It is necessary to allocate adequate investments aimed at improving disease management. Unfortunately, healthcare is generally, and erroneously, perceived as a cost. Only recently has the concept of healthcare cost been evolving in the concept of healthcare investment, despite some barriers still needing to be overcome.

Even if innovative, efficient technologies represent the main driver for improving health and attracting investments in healthcare, their return on investment is more in the long and medium term than in the short term. How is it possible, then, to foster innovative technologies? Which approach may allow decision-makers to match spending limits while ensuring access to effective innovative technologies (drugs, devices, prevention and vaccination campaigns)?

In major industrial countries, including Italy, health technology assessment (HTA) and economic evaluation are the most valuable tools to assess the real value of new technologies. However, it is not sufficient to demonstrate that a technology (health intervention, drug, etc.) is cost-effective: it is necessary to develop approaches based on HTA results, which allow to evaluate/calculate the willingness to pay of the system. In this respect, one of the most important organizational and managerial barriers in our health system is represented by the 'budget silos' approach, at the central, regional and local levels.

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The assessment of the impact of technologies, particularly drugs, takes into consideration their impact only within their sector (i.e. direct costs). This means that more complex technologies are deemed too expensive (as only their price is taken into consideration), without considering their impact on related expenses, such as loss of productivity (days of absence from work; loss of work), social costs sustained by the National Health System (NHS), for example, disability pensions or caregiver benefits, social spending and impact on employment. Applying the logic of silos, the focus has been on the expenditure for drugs without taking into consideration its possible positive effects in the comprehensive patient healthcare plan. The most impactful technologies would benefit from a broader perspective (from the point of view of both price and effectiveness), considering not only health expenditure (at general, regional and local levels) but also social and social security expenditures (direct and indirect costs). Many diseases have a dramatic impact of indirect and social costs which significantly influence the value of a given therapeutic option within an economic evaluation.

When we discuss disease costs, we often resort to the metaphor of the iceberg: the tip shows only direct costs; indirect costs, representing the most consistent part in most diseases or health interventions, are below the surface and therefore invisible.

An accurate estimate of all costs generated by an integrated care approach must therefore take into account all costs (3). With this in mind, when evaluating the use of certain technologies within a health programme (e.g. third-generation anti-seizure medication [ASM] epilepsy drugs), it is necessary to evaluate, along with the technology cost, the impact on indirect and social costs. In other words, it is necessary to evaluate the potential of technologies to reduce these cost items within a comprehensive healthcare plan, as well as their potential to improve efficacy and tolerability. Additionally, a cost assessment including indirect costs is a valid tool for efficient business and regional planning (4,5) and for a better allocation of resources.

However, we are currently experiencing significant inefficiencies between access regulations and actual access, especially for innovative drugs: budget impact, regional heterogeneity, clinical re-evaluation, etc., contribute to reimbursement delays and longer access times to drugs. It is not necessary, therefore, to reduce spending or to approve further cuts, but to identify those areas which allow for improved spending and, above all, to standardize organizational and management models.

The treatment of epilepsy should be managed by highly qualified clinicians, involved in specific contexts, taking into consideration the number of patients, the personnel required and the organizational complexity. On the Italian territory, reference centres with highly qualified personnel, defined on the basis of regional needs and the population, should be accessible to every person suffering from epilepsy. To avoid discrepancies in care and to overcome the 'health system regionalization', the central government should guarantee homogeneity in the qualification of centres dedicated to epilepsy, their medical personnel and the specific equipment (6).

To reach these goals, along with the remarkable effort of the Ministry of Health in securing important resources (increased resources for the health system, increase in pharmaceutical spending limits) the National Recovery and Resilience Plan (PNRR) could ensure a significant upgrade of the NHS, addressing the real needs of citizens. These assumptions are forcing both scholars and decision-makers to make an important evaluation. In my view, a once in a lifetime scenario for our NHS, and welfare as a whole, is taking shape. We see the real possibility of being able to plan a complete reorganization of our NHS and structure it to shape future challenges, with important benefits for the entire country's economic system. The PNRR represents – if well addressed – a unique opportunity for the future sustainability of the NHS. This option is identified not only by financing in itself but also by procedures which can facilitate important reforms in management and organizational models. This means innovative health technologies (drugs, devices, goods and services), new healthcare structures and the 'renovation' of a territory-based care model. With regard to health technologies (drugs and medical devices) we could finally see a rethinking of their role within the NHS and, above all, aligning resources to real needs (abolishing outdated limits and the silos approach). Health technologies are no longer considered a 'mere cost' but as the cornerstone of an investment strategy aimed at guaranteeing patients' timely access to novel and well-studied technologies, which ensure the improvement of patients' health (partial or even total recovery) as well as a significant reduction in costs in the medium- to long term, both direct and indirect (i.e. drugs and effective devices ensure a reduction in hospitalizations, in visits, in comorbidities and in a reduction of disabilities and inabilities).

In conclusion, the PNRR can represent the tool to guarantee sustainability to the NHS, but how resources will be allocated becomes crucial. There are two options available: a distribution of resources without controls or a targeted allocation based on 'robust' models, benefiting from HTA stakeholder involvement. Today more than ever, politics is called upon to make decisions that will determine the life of our country and the organizational, managerial and economic structure of our welfare system in years to come.

State intervention must be imperative both to respond to the critical situation today and also to avert future crises and to build the foundations which, in the long term, will guarantee the trade-off between innovation and sustainability, contributing to a bright future for our welfare system.

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REVIEW

Governance of the clinical pathway and management of the patient suffering from epilepsy and drug-resistant epilepsy

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ABSTRACT

Epilepsy is a diffuse chronic neurological disease affecting around 50 million people worldwide. The diagnostic criteria by the International League against Epilepsy must be fulfilled to diagnose the disease, which is characterized by brief and transient episodes of abnormal neuronal activity involving one or both hemispheres, depending on the epilepsy type. The diagnosis of epilepsy should be properly and timely made because patients suffering from the disease are affected not only by seizure recurrence but also by epilepsy-related psychiatric and/or cognitive comorbidities that may have a huge impact with severe professional and social implications. It is of vital importance to define a specific governance model that has to be virtuously applied into the different phases of the clinical pathway of the patients with epilepsy in order to guarantee them the best model of care possible.

Keywords: Anti-seizure medicines, Drug-resistant epilepsy, Epilepsy, Epilepsy management, First seizure clinic, People with epilepsy

Premises

Disease characteristics

Epilepsy (E) is a chronic neurological disease diagnosed according to the criteria by the International League against Epilepsy (ILAE) if one of the following conditions occurs: (1) At least two unprovoked (or reflex) seizures occurring >24 hours apart; (2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) Diagnosis of an E syndrome (1).

An epileptic seizure is a brief and transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity (1). Epileptic seizures can be classified as *acute symptomatic seizures* when they have a strict temporal association with a transient and acute brain insult, which can be of metabolic, toxic, structural, infectious or inflammatory origin (2), and as *unprovoked seizures* when an enduring cerebral predisposition to generate epileptic seizures can be identified (1). Therefore, both types of epileptic seizures can be defined considering the reversibility of the underlying responsible cause and the temporal relationship with the acute brain insult (1,2). For example, a cortical dysplasia or a brain tumour may permanently alter specific neuronal networks, predisposing a particular area of the brain to develop seizures; so, in these circumstances, it is right to talk about unprovoked seizures.

The classification of a remote epileptic seizure, which is symptomatic of E, can be made according to the onset of the abnormal neuronal activity, which can be *generalized* – if the abnormal electric discharge involves simultaneously both cerebral hemispheres from the beginning – or *focal* – if the discharge originates within a specific neuronal network limited to one hemisphere and may (or may not) rapidly engage the contralateral hemisphere (3). The clinical presentation of seizures can be characterized by impaired or unimpaired awareness/consciousness and presence or absence of more or less diffuse motor phenomena (3).

E is a medical condition in which epileptic seizures can be the main but not the only symptom (4). In fact, along with seizures, other signs or symptoms (neurological, psychiatric or involving other organs and apparatus) can be identified (4), as in the case of epileptic encephalopathies or developmental encephalopathies, which can be defined as electro-clinical

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syndromes with broad genetic spectrum in which E often combines with cognitive and behavioural alterations, electroencephalographic (EEG) abnormalities and other possible neurological or systemic manifestations (5).

The most recent classification of E elaborated by the ILAE has included the classificatory axes into the aetiologies of E, identifying six groups: structural, genetic, metabolic, infectious, immune and unknown (4). An aetiology does not rule out another one; in fact, a patient suffering from tuberous sclerosis carrying characteristic brain lesions and presenting with seizures has both structural and genetic aetiologies. The category 'unknown aetiology' indicates that we are not able to identify the exact cause of the disease, but this gap will hopefully be filled in the future through the improvement of the available diagnostic tools or the discovery of new ones (6). The neurodegenerative aetiology has not been nosologically defined as another possible aetiology of E yet. However, considering the increasing scientific evidence about the existence of a bidirectional relationship between E and neurocognitive disorders in the elderly (i.e. Alzheimer's disease), the involvement of neurodegenerative processes into epileptogenesis should be further analysed and studied (7-9). There is an age-dependent variability of the aetiology of E (10). Once the diagnosis of seizure or E has been made, the second step for the clinician should be the identification of the underlying aetiology. Recognizing the responsible cause is fundamental because it allows diagnostic as well as prognostic accuracy, other than the identification of the best therapeutic approach possible for that specific patient.

Anti-seizure medicines (ASMs) are a milestone in the treatment of E. Nevertheless, even with a large number of therapeutic alternatives, about 30% of people with E continue to have uncontrolled seizures despite different and rational pharmacological associations, belonging to the pharmacoresistant portion of people with E (11). ILAE defined drug resistance as 'failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom' and considered this a testable, working hypothesis to be refined with time (12). It is known that after the failure of two appropriate and adequately chosen ASMs the possibility to have a clinically successful response with another ASM drastically decreases (13).

From a therapeutic point of view, a part of people with focal types of E could undergo surgical treatment. Aim of E surgery is to obtain complete seizure control in the absence of neurological complications, trying to eliminate the potential cognitive, psychological and socio-professional consequences caused by seizure persistence and/or chronic anti-seizure therapy (14). Before surgical treatment, the patient should be thoroughly studied and the evaluation should be directed to the identification of the so-called epileptogenic zone, the part of the brain from which the abnormal neuronal discharge originates, which should be possibly removed without consequences. Pre-surgical evaluation requires specific equipment and qualified medical staff. In the last decades, E surgery has become a more concrete therapeutic option, and a safer and less invasive surgical approach is now possible thanks to advances in structural and functional neuroimaging and video EEG monitoring, along with the simplification of invasive electrode implantation and the availability of new neurosurgical tools such as neuronavigation, intraoperative echography, endoscopic techniques and new resective surgical approaches (thermocoagulation, laser ablation, etc.) (15).

Currently, patients who may benefit from surgical treatment of E (as long as the resection of the epileptogenic zone is possible and without sequelae) should have the following prerequisites:

- Drug-resistant E;
- Patients with controlled seizures thanks to ASMs, but suffering from unbearable treatment-related adverse effects;
- Patients without drug-resistant E presenting with structural brain lesions, such as brain tumours, which should be further studied because of their high risk of determining pharmacoresistant E (15).

The 'ideal' candidate is a person with focal E, a clearly identifiable epileptogenic zone located outside eloquent cortical areas (15).

In case of drug-resistant patients who cannot undergo or refuse surgical treatment of E, there are other 'palliative' therapeutic options available, between them neuromodulation (vagus nerve stimulation, deep brain stimulation, etc.) (16).

Recent biotechnological progress and the rapid spread of information about the biological basis of some forms of E led to the so-called 'precision medicine', which is an innovative approach to discovering and developing therapies which can give better clinical outcomes to patients, by integrating clinical and molecular information to understand the biological basis of disease (17). In this field some goals have been achieved, even though there is a long way to go yet. For example, it has been elucidated that some epileptic and neurodevelopmental encephalopathies are caused by genetically determined deficits of some molecular transporters, as in GLUT-1 deficiency (18), or by altered enzymatic functions, as in pyridoxin-dependent encephalopathies (19). The earlier a specific substitutive therapy is started, the better could be the outcome for the patient.

Psychosocial impact

Many decades have passed since the famous epileptologist William Gordon Lennox (1884-1960) said that the person with E suffers more for its social consequences than for the disease itself and, in an editorial often cited in the *British Medical Journal*, the neurologist Rajendra Kale wrote, 'The history of epilepsy can be summarised as 4.000 years of ignorance, superstition, and stigma followed by 100 years of knowledge, superstition, and stigma' (20). Even though significant progress has been made in the last few years about the understanding of biological and molecular basis of E and despite the availability of multiple therapeutic options, people with E continue to be victims of discrimination and stigma (21). The origins of stigma are deep and resistant and, in our opinion, trying to understand why they exist could help in the management of E.

Intuitively, the impairment of awareness/consciousness happening during an epileptic seizure can increase the risk of traumas, fractures, accidents, burns and drowning for the patient, and this could happen everywhere, at home, at school, in the street or in the workplace (22). The risk of these E-related risks has a burden on patients and caregivers, especially parents of children with E, leading to a progressive inactivity (i.e. physical inactivity), dependence and social isolation (23). When seizures are characterized by impaired awareness/consciousness but do not provoke violent falls to the ground, there is surely a lower risk of physical injuries for the person, but even so the patient does not have control of him/herself in relation to the environment, compromising educational, professional and social activities, such as driving. Limitations on driving can influence employment, social interactions and personal independence, representing one of the biggest issues for patients with E (24). That being said, the global situation of a patient with E includes not only seizure recurrence but also higher risk of anxiety, depression, suicide, cognitive impairment and systemic diseases, such as obesity (25). This complex clinical scenario leads to psychological consequences (impairment of self-esteem) and psychosocial implications (lower possibility of having a partner, low-grade educational goals, unemployment or unqualified jobs, low income and stigma) (25).

On the other hand, motor phenomena that often accompany seizures scare witnesses of these events, especially those not familiar with the disease, worsening the burden of the stigma over people with E.

E is a burdensome disease because of seizure recurrence, chronic anti-seizure treatment and E-related somatic and psychological consequences (26). Compared with other neurological disorders, in men and women, E has both the highest rates of standardized disability-adjusted life years (DALYs) – the measure combining the time lost for premature death and the time lived in suboptimal conditions or in a condition of disability related to a specific disease – followed by migraine and Alzheimer's disease. E accounts for >13 million DALYs (27).

Based on these considerations, in November 2020, the 73rd World Health Assembly (WHA) adopted a resolution to develop an intersectoral global action plan on E and other neurological diseases. The action plan aims to reduce and eliminate preventable deaths caused by E and other neurological disorders, to improve access to promotion, prevention, management and care services, decreasing stigma and discrimination and protecting the human rights of people with neurological disorders. This action plan promotes physical and mental health, prevention, early diagnosis, assistance, treatment and rehabilitation, along with social, economic and educational needs and necessity of inclusion for people with E or different neurological diseases and their family (28).

Epidemiology

E is one of the most frequent chronic diseases, affecting around 50 million people worldwide (29). Its prevalence in high-income countries accounts for 4-8/1,000 individuals (the highest values being the most reliable) and the annual incidence is about 50,000 cases per 100,000 individuals (30). The rate increases to 73-86 cases considering isolated seizures and 93-116 cases if provoked and acute symptomatic seizures are included (30). So, 500,000 people with active E are present in Italy and 36,000 new cases of E are expected every year. Incidence seems to be higher in the first year of life, decreases during adolescence, remains low in adulthood and increases again after 75 years (31). It has to be considered that the age-dependent distribution of E in the general population has significantly changed over the past century with a five-fold increase in the incidence of E in individuals ≥60 years in the last 40 years (32).

The patients' journey and unmet needs: governance hypothesis

If we consider the journey of a person suffering from E, some 'key' moments can be identified:

T0: when the first seizure occurs or the person recognizes seizure recurrence;
T1: when the patient becomes drug-resistant;
T2: the medical or surgical management of drug-resistant E.

T0: the diagnosis

Epileptic seizures are brief and transient episodes characterized by recurrence of signs/symptoms often resembling other paroxysmal events, so that the differential diagnosis can be challenging. The risk of misdiagnosis is still very high if we consider that about 20% of patients presenting to centres specialized in E surgery have an erroneous diagnosis or suffer from seizure recurrence due to wrong therapeutic management (33). This initial diagnostic mistake is the starting point of a diagnostic and therapeutic odyssey with increasing healthcare costs for the national sanitary system (34), other than E-related psychological and psychosocial consequences (26). This scenario is quite common because the initial diagnosis of E is often made by a clinician without specific education in E.

Hypothesis of virtuous governance (First Seizure Clinic)

When a suspected epileptic seizure occurs, people should seek medical attention according to the two principal following scenarios:

1. The person with the paroxysmal event/events is addressed by the general practitioner (GP) to a qualified E centre with an urgent request for a deferable neurological/epileptological consultation (within 7 days);
2. In the second case, the interested person is sent by the GP or voluntarily goes to the emergency services of the nearer hospital, where the physicians usually execute urgent blood tests (including haemachrome, hepatic and renal functions, electrolytes and coagulation tests) and a computed tomography scan of the brain in order to exclude acute metabolic disorders. After excluding acute conditions, the physician sends the patient to a specialized E centre with a request of deferable neurological/epileptological consultation within 7 days.

At the moment of the first epileptological consultation, if the suspect of seizure is confirmed by a highly trained epileptologist, an EEG with and without sleep deprivation and a magnetic resonance imaging (MRI) of the brain should be suggested according to the ILAE recommended protocol (HARNESS-MRI protocol) (35). This protocol, involving 3-Tesla-MRIs, would allow to identify even small cortical dysplasias or otherwise undetectable epileptogenic lesions. It is important to use this protocol to identify a potential epileptogenic structural alteration of the brain from the start to avoid useless future MRIs and to allow the best therapeutic approach for the patient who can also be properly informed about his/her prognosis (1).

If the suspect of seizure is not confirmed, other diagnostic options should be provided to the patient.

An approach like this would guarantee to the person the inalienable right of having a correct diagnosis in the least possible time, obtaining the best treatment possible as well.

T1: the diagnosis of pharmacoresistance

After the failure of the second appropriately chosen and adequately used ASM, according to ILAE guidelines, the patient is considered drug-resistant (12), even though this is a dynamic condition that can change over time even for the same person. As mentioned earlier, the chances of achieving seizure freedom drastically diminish with subsequent therapeutic approaches (13), so in this exact moment it is mandatory to revise the clinical history of the patient, taking into account the possibility of a surgical approach. E surgery, when possible, can give optimal outcomes with benefit for the patient and the healthcare system.

E surgery should be immediately considered in front of a patient with focal seizures, in the absence of cognitive or behavioural disabilities and with an epileptogenic zone located outside eloquent cortical regions (15).

In this way, the right to have the best therapeutic approach in the least time possible would be guaranteed to the patient, avoiding the psychological and social consequences of drug-resistant E (26).

Hypothesis of virtuous governance: to verify in the less time possible if the patient could be a candidate to surgical treatment of E.

T2a: the surgical management of drug-resistant E

Once the criteria for the inclusion of the patient in the pre-surgical evaluation are fulfilled, in the majority of cases, a video EEG is required. So, the presence of specific equipment and specialized medical and paramedical staff completely dedicated to the 'long-term monitoring' of EEG is essential for the structure where the patient has been sent.

In the case of positive outcomes after 'long-term' registration, the patient will be guided to hyper-specialized centres dedicated to E surgery.

The possibility of 'long-term monitoring' of EEG – and the subsequent E surgery as well – should be guaranteed to the patient, even though this is not an ubiquitous and homogeneous condition in Italy.

Hypothesis of virtuous governance: early access to E surgery increases the number of centres completely dedicated to increasing surgical treatment of E.

T2b: the medical management of drug-resistant E

This is the case of people with drug-resistant E who refuse or cannot/did not benefit from E surgery.

People with drug-resistant E and rare and complex epilepsies are burdened not only by seizure recurrence but also by different and multiple comorbidities, which require specific interventions and a multidisciplinary approach with the involvement of various medical figures as geneticists, psychologists, psychiatrists, gynaecologists and physiatrists. Moreover, chronic diseases and E in particular affect not only the single individual but also caregivers. Intellectual disability and behavioural alterations associated with E add an additional burden on caregivers' shoulders in terms of costs, responsibility of care, centralization of the family's attention and social isolation (36).

In our opinion, the most appropriate form of management in these cases is represented by the so-called 'complex and coordinated ambulatorial programmes', which are a group of medical services finalized to specific diagnostic and therapeutic goals, tailored to the patient and included in the regional list of ambulatorial specialties. These programmes take place in the morning, requiring about half a day, avoiding economic expenses to patient and caregivers and hospitalization, guaranteeing a better quality of life and a reduction of healthcare costs.

Also in these cases, only highly specialized centres with specific equipment and trained medical and paramedical personnel can adopt this kind of multidisciplinary programmes, where the cooperation between different specialists is a fundamental requirement.

The multidisciplinary approach in a selected setting dedicated to E and its comorbidities can improve the quality of care (i.e. with the access to new treatments in compassionate programmes or the simplification of complex and often useless polytherapies) and the quality of life for the patient and his/her family, reducing the number of hospitalizations or accesses to emergency settings.

In patients with drug-resistant E, 'palliative' and non-pharmacological approaches can be adopted, such as vagus nerve stimulation, which can reduce seizure frequency and intensity, improving the quality of life (16).

Hypothesis of virtuous governance: create highly specialized centres where trained and expert personnel could guarantee to the patient and his/her family a multidisciplinary approach, especially in case of rare and complex epilepsies.

Conclusions

The management of E should be given to clinicians with a certified and high competence in E working in specific settings considering the number of patients, the required personnel and the organizational complexity.

In the Italian territory, specific centres with highly qualified staff defined according to the regional needs and

numerosity of people should be accessible to every person with E. In order to avoid discrepancies in the care of people with E and to overcome the 'regionalization of the sanitary system', the central government should guarantee a homogeneous and equal presence of centres completely dedicated to E with uniformity in medical personnel and specific equipment.

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REVIEW

Socio-economic impact of epilepsy in Italy

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ABSTRACT

The World Health Assembly recognizes the growing economic and societal burden of neurological disorders, a leading cause of disability and the second cause of mortality in the world.
In this context we analysed the socio-economic impact of epilepsy in Italy with a specific focus on hospitalizations and costs related to disability pensions (DPs) and ordinary disability allowances.
In the case of epilepsy, between 2009 and 2015 we observed an alarming increasing trend for DPs (+26%), indicating that substantial expenses must be supported throughout the patients' lifetimes by both the social security system and the National Health Service (NHS) on top of the impact on caregivers.
We also analysed the hospital expenditure on epilepsy through the information available in the Hospital Discharge Cards between 2015 and 2018. Almost all admissions (76% ordinary hospitalizations, 24% day hospitals) were acute (95%), followed by rehabilitation (4%) and long-term care (1%).
The cost of acute and ordinary hospitalizations was by far the highest in 2018, the last year of analysis. This large expense due to hospitalizations could be reduced through the implementation of different organizational and management approaches. Our recommendation is that the policy maker should consider the best approach to ensure an early diagnosis for patients and provide early access to drugs and/or surgery. Finally, the adoption of new innovative treatments should improve effectiveness and, at the same time, reduce the expense of the NHS, of the social system as a whole, with a tangible improvement in patients' quality of life.

Keywords: Co-morbidities, Economic burden, Economic impact, Epilepsy

Epilepsy is a chronic brain disorder that affects people worldwide. It is characterized by the recurrence of phenomena called seizures, usually of short duration (seconds or a few minutes). Seizures may occur together with altered consciousness and/or involuntary movements affecting only one part of the body (partial motor seizure). Indeed, seizures can be of different types according to their complexity. More specifically, it is possible to distinguish between: partial seizures which can be more or less developed (simple or complex partial sensory seizures) or generalized seizures which involve the whole body, causing loss of consciousness and sometimes loss of sphincter control (1).

In order to ensure the proper attention that seizures deserve, the World Health Assembly (WHA), that is, the decision-making body of the World Health Organization (WHO), approved resolution WHA73.10 (12 Nov 2020) for '*Global action on epilepsy and other neurological disorders*.' The resolution strongly encourages member states to provide an 'integrated (multisector) response about epilepsy as well as other neurological disorders.'

This resolution is crucial for global neurology since it recognizes the growing economic and societal burden of neurological disorders, which are the leading cause of disability and the second cause of mortality all over the world.

Disability and mortality do not imply solely significant effects in terms of reduced health and increased costs for the National Health Service (NHS), but they produce effects also in terms of reduced quality of life (QoL), productivity loss (for both patient and caregiver), and costs borne by the society's security system (disability pensions [DPs] and ordinary disability allowances (ODAs)). Thus, there are not merely direct health care costs but also indirect costs.

According to international documents (WHO, WHA, and others), we strongly believe that it is crucial to analyse the socio-economic impact of epilepsy in Italy with a specific focus on hospital costs (hospitalizations), costs related to DPs, and ODAs. Following a systematic review of the literature (RSL), few studies have emerged concerning the economic impact of epilepsy in Italy. Of these, two refer to the costs for the treatment of drug-resistant epilepsy (2,3), another to the

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pharmacological treatment of epilepsy in children and adolescents (4), yet another estimated the direct costs for the treatment of refractory epilepsy (5), a latest study focused attention on the costs of co-morbidities and pharmaceutical expenditure (6). All these studies are also characterized, with the exception of the one on co-morbidities, by an important age of the data. Therefore, there is no current enhancement of the economic weight that weighs on the NHS in terms of hospitalizations but also an initial 'investigation' relating to the impact on the Italian social security system.

The main goal of this analysis, consequently, is to examine which costs, very recent, impact the most on the direct management of patients affected by epilepsy and to suggest new approaches to cope with these patients. We believe that it can be helpful to improve the effectiveness of health care intervention and the efficiency of the system (both NHS and social system).

The social security benefits analysis (DP and ODA) allows to understand the potential impact of increased disability due to epilepsy outside the 'classic' context (Silos budget approach) of the NHS. Indeed, the social security system, in case of injury or illness, recognizes the right for workers to be eligible for one of the mentioned benefits, depending on the degree of disability and whether they apply for it.

The ODA is designed for workers with a degree of disability of more than two-thirds (between 67% and 99%) whereas the DP is designed for workers recognized as totally disabled (100%).

Thus, an increase in DPs may be considered as a wake-up call for the decision maker because after the disease occurrence, a significant number of patients reach a level of full disability (100%). Such conditions no longer allow for recovery and permanently compromise all the patient's own activities, resulting in increased productivity loss.

Before focusing on epilepsy from the point of view of the social security system, we believe that it is useful considering the positioning of the nervous system and sense organ diseases within the social security benefits framework. Thus, a preliminary analysis was conducted at the macro level referring to the period 2009-2015. The findings reveal that this grouping of diseases is located among the disease groups with the greatest impact as far as the social security system is concerned.

Regarding the number of recipients of Ordinary Allowances, the Diseases of the Nervous System constitute the fifth largest pathological group (32,000 recipients on average each year) whereas DPs constitute the third largest pathological group (11,400 recipients on average each year), following cancer and mental disorders with a significant and worrying upward trend.

With respect to costs, diseases of the nervous system and sense organs have an average annual expenditure, for ODAs and DPs, of about € 413 million (€ 267 million for ODAs and € 146 million for DPs, accounting for a total of € 2.9 billion over the period (Fig. 1)).

In the case of epilepsy, an average of about 800 applications were filed each year; in 60% of cases these applications were unsuccessful, in 29% of cases disability was recognized, and in 11% of cases total disability was recognized.

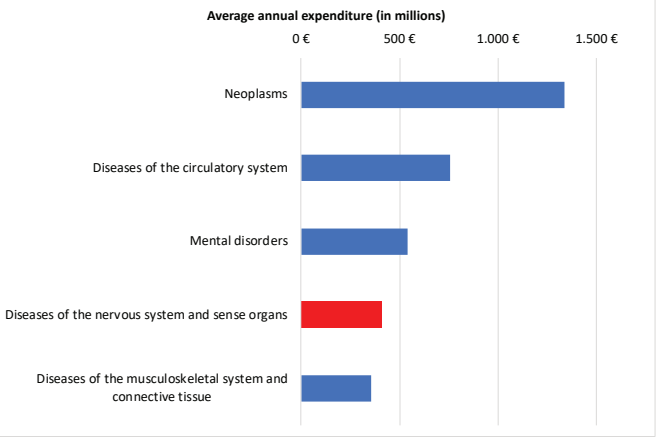

Fig. 1 - Average annual welfare spending (2009-2015).

In terms of beneficiaries, results reveal an average annual number of beneficiaries of 1,964 for ODAs and 620 for DPs (2,584 total). However, the most interesting and alarming finding is the trend recorded in the lifespan considered.

Indeed, between 2009 and 2015 (Fig. 2) it is possible to observe a decreasing trend for ODAs (−9%) unfortunately accompanied by an increasing trend for DPs (+26%). The findings should let us think, because an increase in DPs means an increase in the number of patients who, due to the disease, reach the highest level of disability (100%) with no possibility of recovery.

The trend in DPs is significantly alarming since it has an impact economically and socially. Indeed, substantial expanses must be supported throughout the patients' lifetimes by both the social security system and the NHS without forgetting the impact on caregivers (*out-of-pocket expenses and loss of productivity*).

The costs for services analysed amounted to € 171 million in the period considered (an increase of 16%). As regards DPs, an increase of +40% was recorded. Thus, also with respect to costs, it is fundamental to monitor the trend of DPs and think about models that could be implemented in order to control this worrisome growth related to disability.

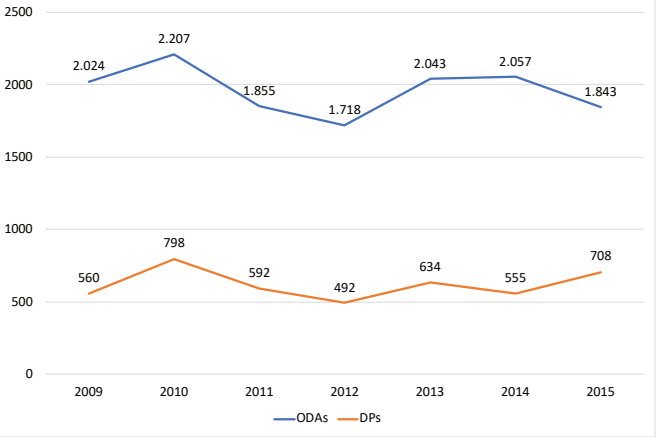

Fig. 2 - Estimated beneficiaries and trend (2009-2015).

Alongside the costs borne by the welfare system, with a specific reference to epilepsy, it is fundamental to analyse the economic burden at the hospital level. Indeed, international studies demonstrate that the greatest burden of epilepsy at the welfare level occurs precisely in hospitalizations. Hence, we analysed the hospital expenditure on epilepsy through the information available in the Hospital Discharge Cards (HDS). All the inpatient admissions with the principal diagnosis of epilepsy in the analysis period considered (2015-2018 – latest data available at the time of analysis) were selected, whereas for cost quantification, inpatient admissions were valued on the basis of the national fee schedule for hospital service remuneration.

The first finding that emerged from the analysis is one related to the distribution of admissions by both type of activity and regimen. With respect to the type of activity, it can be noticed (Figs. 3 and 4) that almost all admissions are acute (95%), followed by rehabilitation (4%) and long-term care (1%). Differently, the finding by hospitalization regimen infers that 76% are ordinary hospitalization, whereas the remaining 24% can be classified as day hospital.

The cost of acute and ordinary hospitalizations is undoubtedly the highest. Hence, reducing this cost item could be particularly important in terms of proper and efficient management of resources, especially considering that reductions in hospitalizations significantly improve the QoL of patients, generating a reduction in lost productivity.

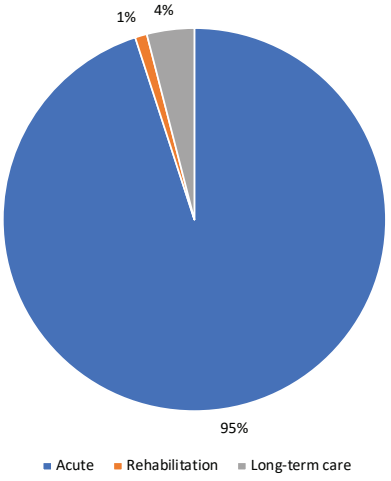

Fig. 3 - Distribution of total hospitalizations by type of activity.

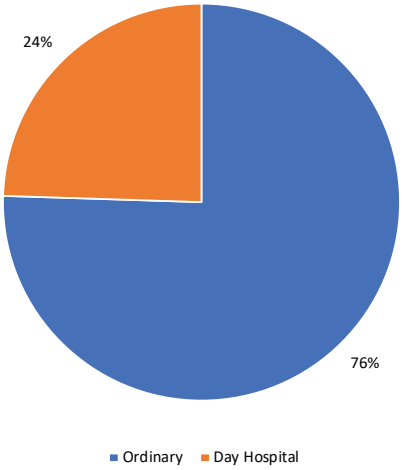

Fig. 4 - Distribution of total hospitalizations by inpatient regimen.

With specific reference to the total cost for hospitalization, the analysis reports a value of € 62 million in 2018 (the last year of analysis).

From the analysis of inherent hospitals and social security costs of epilepsy in Italy, it can be stated that the expense of hospitalizations should/could be reduced through the implementation of different organizational and management approaches. Furthermore, concerning epilepsy, we should bear in mind that, alongside the costs associated with hospitalization and those borne by the social security system, there are costs arising from co-morbidities which should be carefully analysed and considered.

If, then, we add to these costs those charged to pharmaceutical expenditure (more than € 300 million – OSMED Report), we can begin to better understand the magnitude of the problem both for the NHS and for the social system. But, the cost of co-morbidities must also be considered.

The co-morbidities of epilepsy can be identified as a meaningful burden for people affected by the disease, which should be carefully investigated to reduce not merely costs but also health consequences for patients. The number of co-morbid diseases tends to increase with age (7). The economic burden, in fact, varies considerably according to the severity of the disease (frequency of crises, co-morbidities). It is estimated that about 50% of adults with epilepsy have at least one other coexisting disease (8) and other studies report that the prevalence of some specific diseases is higher in people with epilepsy than in the general population (9). A recent analysis (6) calculated the costs due to co-morbidities. Specifically, patients with four or more co-morbidities show an average cost of approximately € 2,000, followed by those with two or three co-morbidities (approximately € 650). Patients who do not have co-morbidities are characterized by an average cost of € 380, highlighting once more how early management accompanied by effective treatments can not only improve patients' QoL but also be accompanied by an important cost reduction.

According to recent studies (10), screening programmes and guidelines should be developed in order to disseminate the knowledge gained by effective and meaningful clinical interventions. In this way, it might be possible to reduce the economic and social burden of the disease and ensure early patient care. Besides, the policy maker could adopt new innovative treatments to improve effectiveness and, at the same time, reduce the expense of the NHS, of the social system as a whole, with an evident improvement in patients' QoL.

However, it is fundamental to remind that through pharmaceutical treatments and surgery procedures we can control the disease 80% of the time with noteworthy positive implications on the social and health care system. Despite this awareness, reaching these results seems not to be straightforward, since they first require a change of perspective.

First and foremost, it is inevitable to think about the implementation of a different model in order to ensure an early diagnosis for patients and provide early access to drugs and/or surgery. Besides, there is the need to design homogeneous

and shared diagnostic pathways (diagnostic, therapeutic, and assistance pathways [PDTAs]) throughout the country so as to achieve equal access to treatment combined with vertical equity in the welfare pathway.

After all, we believe that resources offered by the National Recovery and Resilience Plan (Piano Nazionale di Ripresa e Resilienza, PNRR) can represent a valid opportunity to implement such care pathways and incentivize the adoption of community-based care wherever possible. In addition, it could ensure better QoL for both patients and *caregivers* with a meaningful reduction in social costs and *out-of-pocket* spending.

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REVIEW

New evidence in adjunctive treatment of focal-onset seizures in adults: a critical appraisal

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ABSTRACT

Anti-seizure medications (ASMs) represent the pillar of the treatment of epilepsy. The rate of drug-resistant epilepsy remained substantially unchanged over time and there is still the need for new and more effective treatment options. Brivaracetam, cenobamate, eslicarbazepine acetate, lacosamide and perampanel are 'third-generation' ASMs.

The aim of this article is to summarize the currently available evidence about the relative efficacy and tolerability of the 'third-generation' ASMs as adjunctive treatment of focal-onset seizures in adults.

So far, no randomized controlled study directly compared these ASMs, and their comparative efficacy and tolerability have been indirectly evaluated by one network meta-analysis. Sixteen trials were included in the network meta-analysis. The efficacy endpoints were the rates of seizure response and seizure freedom, defined as ≥ 50% and 100% reduction in baseline monthly seizure frequency. The tolerability endpoints were the rate of patients who developed any treatment emergent adverse events (TEAEs) and any TEAE leading to drug discontinuation. Cenobamate had the greatest likelihood of being the best option for the ≥ 50% and 100% seizure frequency reduction. Brivaracetam and lacosamide had the greatest likelihood to rank as the best-tolerated treatments for the occurrence of any TEAE and TEAE leading to discontinuation.

Although network meta-analyses are not substitutes of direct comparisons, they can provide valuable evidence about the hierarchy of interventions. Additional real-world data can be useful complement to characterize the clinical profile and therapeutic potentialities of third-generation ASMs.

Keywords: Anti-seizure medications, Epilepsy, Focal seizures

Background

Epilepsies are a group of neurological disorders characterized by recurrent, unprovoked seizures, which can be either focal or generalized. Focal-onset seizures are the most common type of seizures experienced by people with epilepsy, and they can be associated with impaired awareness. With approximately 70 million people affected worldwide, epilepsy accounts for a significant proportion of the global disease burden (1). The estimated proportion of the general population with active epilepsy, that is, continuing seizures or with the need for treatment at a given time, is between 4 and 10 per 1,000 people (2).

Epilepsy can have significant social impact and economic implications. People with epilepsy can experience reduced access to educational opportunities and barriers to enter some occupations. Uncontrolled epilepsy is often associated with significant psychological dysfunction and impaired quality of life and carries the risk of premature death (3,4). Further, stigma and discrimination still surround epilepsy in different countries across the world. The economic impact of epilepsy varies significantly depending on the disease duration and severity, response to treatment, and the health-care setting. Out-of-pocket costs and productivity losses create substantial burdens on households.

The treatment of epilepsy is mainly symptomatic, and anti-seizure medications (ASMs) represent the pillar. Most people with epilepsy can become seizure free with appropriate use of one or more ASMs. However, seizures are not controlled in more than one-third of the patients (5,6). Despite the increased availability of ASMs, the rate of drug-resistant epilepsy remained substantially unchanged over time and there is still the need for new and more effective treatment options (7). Over the last decade, five 'third-generation' ASMs, namely brivaracetam (BRV), cenobamate (CNB), eslicarbazepine

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acetate (ESL), lacosamide (LCM), and perampanel (PER), have been licensed for adjunctive treatment of focal-onset seizures in adult patients (8).

The aim of this article is to summarize the currently available evidence about the relative efficacy and tolerability of any of these 'third-generation' ASMs to one another as adjunctive treatments of focal-onset seizures in adults and suggest implications for clinical practice and future research.

The evidence from the literature

There are no randomized controlled studies that directly compared the 'third-generation' ASMs. So far, the comparative efficacy and tolerability of these drugs have been evaluated by one systematic review with network meta-analysis (9). Database and trial register including MEDLINE, the Cochrane Central Register of Controlled Trials, and the US National Institutes of Health Clinical Trials Registry were searched to identify randomized, double-blinded, controlled trials comparing add-on BRV, CNB, ESL, LCM, and PER versus any comparator in adult patients with focal epilepsy uncontrolled by one or more concomitant ASMs (9). Only trials with a maintenance period or a period of stable dose of 12 weeks or longer were considered (9).

The efficacy endpoints were the rates of seizure response and seizure freedom, defined as a ≥ 50% and 100% reduction in baseline monthly seizure frequency during the maintenance treatment period. When information over the maintenance phase was not available, the treatment period was considered (9). The 'pragmatic intent-to-treat' approach was used for defining the seizure freedom, whenever available. According to this approach, only patients who were seizure free and completed the entire study were considered as seizure free (10). This is a more conservative methodology to measure seizure freedom and it provides more reliable information about the actual treatment efficacy in comparison to the 'observation carried forward' strategy, which considers as being seizure free those patients who dropped out of a study and were free from seizures at the last available assessment (10).

The tolerability endpoints were the rate of patients who developed any treatment emergent adverse events (TEAEs) and any TEAE leading to drug discontinuation. For any drug, only licensed maintenance doses for adjunctive treatment were considered in accordance with the prescribing information. The daily doses were 50-200 mg for BRV, 200-400 mg for CNB, 800-1200 mg for ESL, 200-400 mg for LCM, and 4-12 mg for PER (11-15).

The comparative efficacy and safety of the included ASMs were estimated through network meta-analyses within a frequentist framework (16). The hierarchy of competing interventions was established through the surface under the cumulative ranking curve (SUCRA) and mean ranks.

The randomized, controlled trials included in the quantitative synthesis were sixteen (17-32): three for add-on BRV, one for add-on CNB, four for add-on ESL, four for add-on LCM, and four for add-on PER. The trials enrolled 6,753 participants: 4,507 were assigned to active treatments (BRV = 803, CNB = 221, ESL = 990, LCM = 1,104, and PER = 1,389) and 2,246 to placebo (9).

Efficacy

The rates of participants with ≥ 50% and 100% reduction in baseline monthly seizure frequency were provided by all the included trials. For the seizure freedom endpoint, the 'pragmatic intention-to-treat (ITT)' data were available in most studies; in three trials, the status at the time of treatment withdrawal was used to impute the freedom from seizure for the remainder of the study (21,24,32). The network meta-analyses showed that all ASMs were associated with higher rates of seizure response than placebo, and CNB was associated with a higher probability of ≥50% reduction in baseline seizure frequency than BRV, ESL, LCM, and PER (Fig. 1) (9). In the analysis of seizure freedom outcome, BRV, CNB, ESL, and PER were more efficacious than placebo, whereas there were no statistically significant differences between the ASMs (Fig. 2) (9). According to SUCRA, CNB had the greatest likelihood to rank as the best treatment option for both the seizure response and seizure freedom endpoints (Tab. I) (9).

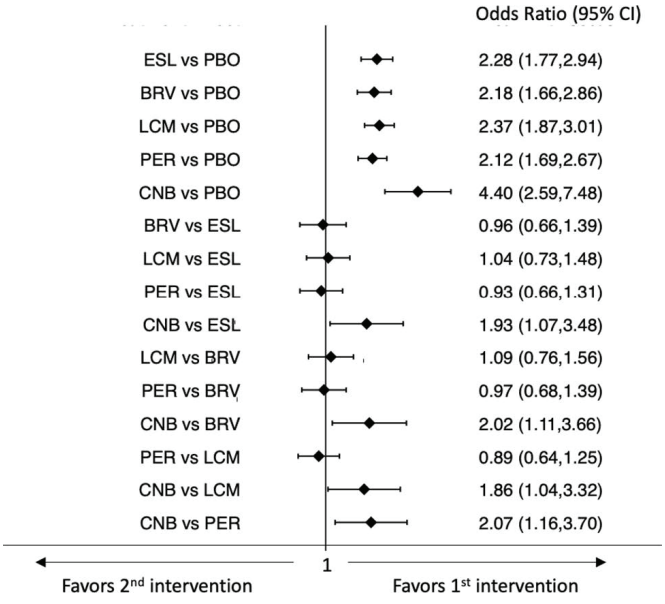

Fig. 1 - Interval plot for the seizure response outcome.

BRV = brivaracetam; CI = confidence interval; CNB = cenobamate; ESL = eslicarbazepine acetate; LCM = lacosamide; PBO = placebo; PER = perampanel.

Tolerability

The rates of participants who experienced at least one TEAE were available from all the included trials except two (26,27). The rates of participants who experienced at least one TEAE leading to discontinuation were available from all the included trials except one LCM study (27).

The network meta-analysis showed that all ASMs were associated with higher rates of participants who experienced at least one TEAE than placebo. Further, BRV and LCM were associated with a lower risk of the occurrence of TEAEs

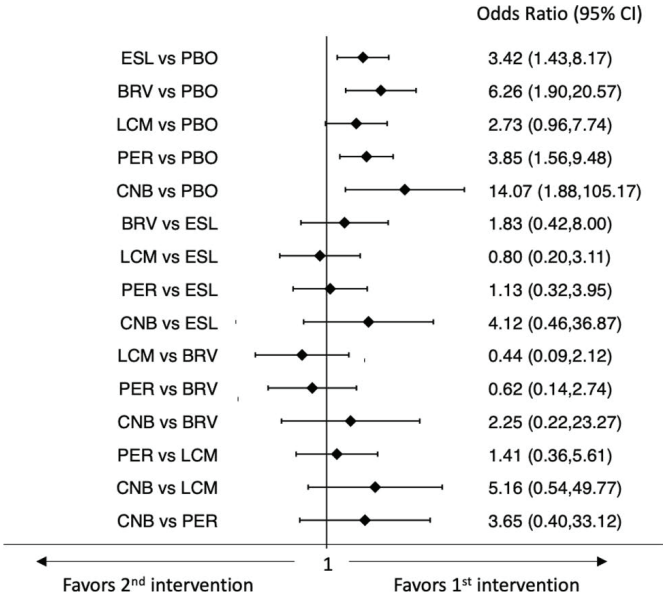

Fig. 2 - Interval plot for the seizure freedom outcome.

BRV = brivaracetam; CI = confidence interval; CNB = cenobamate; ESL = eslicarbazepine acetate; LCM = lacosamide; PBO = placebo; PER = perampanel.

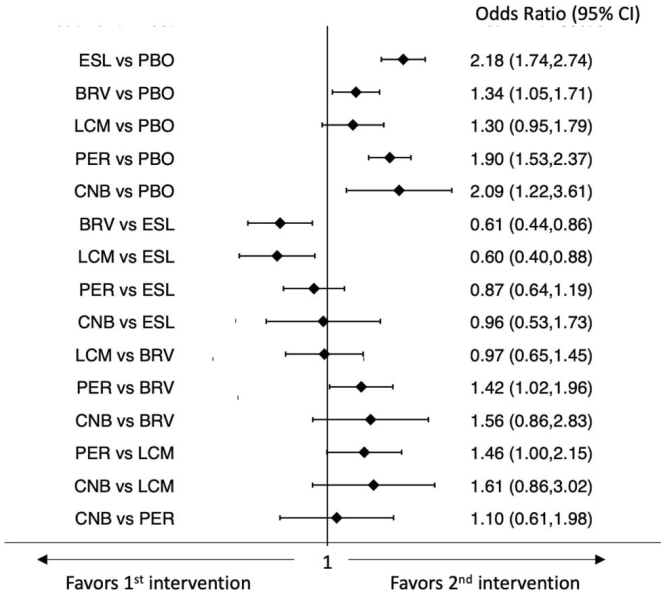

Fig. 3 - Interval plot for the occurrence of at least one treatment-emergent adverse event.

BRV = brivaracetam; CI = confidence interval; CNB = cenobamate; ESL = eslicarbazepine acetate; LCM = lacosamide; PBO = placebo; PER = perampanel.

TABLE I - Ranking according to the surface under the cumulative ranking curve and mean rank for the efficacy outcomes

Treatment	Surface under the cumulative ranking curve	Mean rank
Seizure response		
Brivaracetam	46.2	3.7
Cenobamate	99.0	1.1
Eslicarbazepine acetate	53.4	3.3
Lacosamide	60.8	3.0
Perampanel	40.7	4.0
Placebo	0.0	6.0
Seizure freedom		
Brivaracetam	72.4	2.4
Cenobamate	88.8	1.6
Eslicarbazepine acetate	47.2	3.6
Lacosamide	37.8	4.1
Perampanel	53.0	3.4
Placebo	0.8	6.0

Higher values of surface under the cumulative ranking curve correspond to higher probabilities of better efficacy.

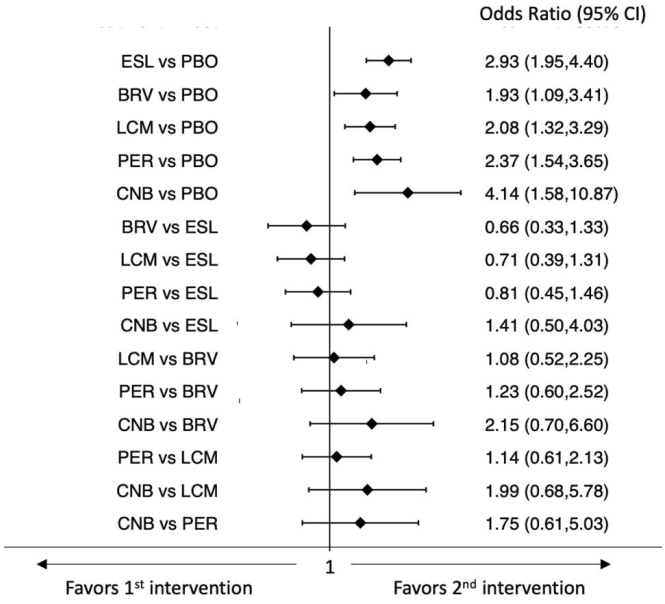

Fig. 4 - Interval plot for the occurrence of at least one treatment-emergent adverse event leading to discontinuation.

BRV = brivaracetam; CI = confidence interval; CNB = cenobamate; ESL = eslicarbazepine acetate; LCM = lacosamide; PBO = placebo; PER = perampanel.

compared to ESL; PER was associated with a higher risk of the occurrence of TEAEs compared to BRV (Fig. 3) (9). In the analysis of the rates of patients who experienced at least one TEAE leading to discontinuation, all ASMs were less tolerated than placebo, whereas there were no statistically significant differences between the ASMs (Fig. 4) (9). According to SUCRA, BRV and LCM had the greatest likelihood to rank as the best-tolerated treatments for both the endpoints of the occurrence of any TEAE and TEAE leading to discontinuation (Tab. II) (9).

TABLE II - Ranking according to the surface under the cumulative ranking curve and mean rank for the tolerability outcomes

Treatment	Surface under the cumulative ranking curve	Mean rank
At least one treatment-emergent adverse event		
Brivaracetam	67.0	2.6
Cenobamate	21.5	4.9
Eslicarbazepine acetate	12.8	5.4
Lacosamide	70.2	2.5
Perampanel	29.6	4.5
Placebo	98.8	1.1
At least one treatment-emergent adverse event leading to discontinuation		
Brivaracetam	62.3	2.9
Cenobamate	11.9	5.4
Eslicarbazepine acetate	24.8	4.8
Lacosamide	56.8	3.2
Perampanel	44.5	3.8
Placebo	99.7	1.0

Higher values of surface under the cumulative ranking curve correspond to higher probabilities of better tolerability.

Third-generation ASMs for focal seizures: comparative efficacy and safety

The currently available comparative analysis of the 'third-generation' ASMs suggested that CNB given as adjunctive treatment of focal-onset seizures in adult patients is associated with a higher rate of seizure response and a greater likelihood to rank best for seizure freedom outcome compared to add-on BRV, ESL, LCM, and PER (9).

Among the third-generation ASMs, CNB is the most recently approved for treating focal seizures, and these findings bring promise for people with epilepsy whose seizures are difficult to control.

The Food and Drug Administration in the USA approved CNB for the treatment of focal-onset seizures in adults in 2019 (33). The European Medicines Agency in the EU approved CNB for the adjunctive treatment of focal-onset seizures with or without secondary generalization in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least two anti-epileptic medicinal products in 2021 (12).

CNB is a novel tetrazole-derived carbamate compound with a unique dual complementary mechanism of action. It decreases excitatory currents by preferentially inhibiting the persistent component of the sodium current and enhancing the inactivated state of voltage-gated sodium channels (34). In addition, it enhances inhibitory currents by acting as a positive allosteric modulator of high-affinity γ-aminobutyric acid (GABA)A receptors at a non-benzodiazepine binding site (35). The unique dual mechanism of action of CNB suggests that it has the potential to both prevent seizure initiation and limit seizure spread (36).

The network meta-analysis suggested better tolerability of BRV and LCM against the other third-generation ASMs: these two compounds were associated with the greatest likelihood to be the best-tolerated options for both the endpoints of the occurrence of any TEAE and the occurrence of TEAEs leading to treatment withdrawal (9).

Among the considered ASMs, CNB ranked as the drug linked with the greatest probability of the occurrence of TEAEs. In this regard, the rapid uptitration of CNB by 100 mg for a week from the daily dosage of 200 mg to the daily dosage of 400 mg, and the impossibility to modify the concomitant therapeutic regimen during the trial might have played a role in the incidence of TEAEs. Importantly, drug–drug interactions may occur when CNB is administered. CNB can inhibit the cytochrome P450 (CYP) 2C19, and drugs like phenytoin and phenobarbital, which are metabolized, in part, by this isoenzyme may have their levels increased (37). Following multiple doses of adjunctive CNB, the plasma exposures of phenobarbital and phenytoin have been shown to increase by a mean of 37% and 84%, respectively (38). The elevation of drug levels may lead to increased risk of adverse events. The coadministration of clobazam with a CYP2C19 inhibitor has also been demonstrated to increase by two to six times the plasma levels of *N*-desmethylclobazam, which is the active metabolite of clobazam and is mainly metabolized by the CYP2C19 enzyme (39,40). Proactive reductions or dose alterations of concomitant ASMs should be considered according to the potential risk of drug–drug interactions to minimize the risk of treatment failure. In this regard, the effects of dose adjustments of concomitant ASMs have been explored in a post hoc analysis of a phase 3, multicenter, open-label study of adjunctive CNB for the treatment of uncontrolled focal seizures (38). Patients continuing CNB had greater mean reductions and percent changes of doses of concomitant ASMs from baseline compared to patients who discontinued the treatment. Doses of phenytoin, phenobarbital, clobazam, valproate, and LCM were decreased early, when patients were in the titration phase, while carbamazepine, oxcarbazepine, and eslicarbazepine had their doses decreased later, during the maintenance phase (38). Dose decreases were mostly due to the occurrence of adverse events related to the central nervous system, like somnolence, dizziness, and balance disorders. For example, phenytoin doses were reduced by a mean of 60.8% and phenobarbital doses by a mean of 40.0% in patients continuing CNB (38).

Direct head-to-head trials represent the most rigorous methodology to ascertain and compare the relative efficacy and tolerability of treatments. These studies, however, are costly and they are not required by regulatory authorities for ASM approval. It is unlikely that similar randomized controlled trials will be ever planned and conducted. In the absence of direct comparisons, network meta-analyses can use indirect evidence to estimate how ASMs measure up to each other and provide a hierarchy of competing interventions.

Importantly, the validity of the results of a network meta-analysis is strongly influenced by the degree of similarity and the methodological quality of the trials that

are included in the comparisons (41). The network meta-analysis comparing the third-generation ASMs adopted rigid inclusion criteria with the aim to reduce the source of heterogeneity across the trials and minimize as much as possible the influence of potential confounding variables on the estimates of treatment effect (9). All the studies included in the analyses were overall clinically and methodologically homogeneous and none was judged at high risk of bias. Despite their similarities, however, a certain degree of diversity may exist among the studies, even if not explicitly recognized by heterogeneity testing. Some differences in the design of the trials and the baseline characteristics of the study cohorts may have affected the findings. It is also worth noting that the low event rates and scarcity of patients achieving some of the endpoints were associated with wide confidence intervals and such imprecision in the estimates can limit the sensitivity to identify differences across the ASMs and influence the rankings of treatments (9). Importantly, all trials included in the network meta-analysis were sponsored by pharmaceutical companies, and evidence about the efficacy and tolerability of CNB is obtained from one single study (9).

Conclusion

Network meta-analyses cannot be considered as substitutes of direct comparisons. Nonetheless, under certain assumptions, they can provide valuable evidence about the hierarchy of interventions and offer guidance for clinical practice and decision-making (42-44).

The comparative analyses of data from randomized, placebo-controlled trials of third-generation ASMs suggested that CNB is associated with the highest probability to be the best treatment option for efficacy outcomes, and BRV and LCM are associated with the greatest probabilities of being the best-tolerated drugs (9). Additional data obtained in real-world practice can overcome the limits of the randomized, controlled trials and be a useful complement to better characterize the clinical profile and therapeutic potentialities of the third-generation ASMs for the treatment of focal seizures in adult patients.

Disclosures

Conflicts of interest: SL has received speaker's or consultancy fees from Angelini Pharma, Eisai, GW Pharmaceuticals, and UCB Pharma and has served on advisory boards for Angelini Pharma, Arvelle Therapeutics, BIAL, and GW Pharmaceuticals.

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