Tampere University

HIRE H HERSI

Response to Antiseizure Medications in Adult Epilepsy Patients

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ACADEMIC DISSERTATION
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Tampere University, Faculty of Medicine and Health Technology
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always rescued and comforted me when things went wrong. Also, to my children, some of whom have already followed in my footsteps.

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Abstract

Epilepsy is a heterogeneous condition that can affect individuals of different races, sexes, and ages. There are also multiple seizure types and epilepsy syndromes that can occur in individuals with epilepsy. The underlying causes of epilepsy can vary and include genetic factors, as well as various symptomatic causes such as brain injury, stroke, infections, tumors, and developmental disorders. Outcomes for individuals with epilepsy can vary widely depending on various clinical factors. The main aim in this dissertation was to study the effectiveness of antiseizure medications (ASMs) in patients with newly diagnosed epilepsy. The specific outcome assessed in this dissertation was seizure freedom. This objective involved analyzing data to determine how patient demographics and characteristics influence possibilities of obtaining seizure-freedom including factors such as ASM type and dosing.

The study cohort comprised of 459 patients, after thorough validation of epilepsy diagnosis. Oxcarbazepine (OXC) was the most used ASM, either as monotherapy or polytherapy, in 380 patients. Firstly, we evaluated interaction among the efficacy, tolerability, and overall effectiveness of the first ASM in patients 16 years or older with newly diagnosed epilepsy. At least one year seizure freedom was achieved in 73% of males and 60% of females with first ASM. The seizure freedom rate for focal epilepsy was 67%, with no significant difference observed between different ASMs. The study also found that patients with structural and unknownetiology had seizure freedom rates of 61.5% and 75.3%, respectively. Epileptiform activity on EEG in patients with focal epilepsy decreased the odds of achieving seizure freedom in adjusted logistic regression models.

The second study revealed that the overall seizure freedom rate with the first or subsequent ASMs was 88.0%, meaning that 404 out of 459 patients achieved seizure freedom. The rate of drug-resistant epilepsy (DRE), when defined as the failure of two ASMs for any reason, was 20.0%, and according to the International League Against Epilepsy (ILAE) definition of DRE, it was 16.3%. After failing the first ASM, 63.6% of patients (96/151) became seizure-free with subsequent ASMs and tried an average of 1.9 ASMs (range 1-5). Of the patients who achieved 1-year seizure freedom, 10.1% (41/404) were on polytherapy. The efficacy of the different ASMs

was largely similar, but ASMs that enhanced GABA-mediated inhibitory neurotransmission had the lowest seizure freedom rate. All patients with primary generalized epilepsy were seizure-free.

The third study demonstrated that the doses of ASMs associated with seizure freedom in patients with epilepsy receiving OXC were influenced by age, sex, and seizure type. The largest dose difference was observed between males aged ≤60 years and females aged >60 years, 1071 mg and 763 mg, respectively. The dosing strategy should be stratified according to the clinical factors recognized in our study. In older patients 600 mg of OXC would be the primary dosing target, which is only two thirds of the dosing strategy for patients under 60 years with much less potential for side-effects in the elderly patient group.

Finally, we investigated ASM doses required to achieve seizure-freedom and their correlation with the World Health Organization's (WHO) defined daily doses (DDDs). The mean prescribed doses (PDDs) and PDD/DDD ratio of the most used ASMs, i.e., OXC, Carbamazepine (CBZ), and Valproic acid (VPA), differed significantly between seizure-free and non-seizure-free status (992 mg and 0.99 vs 1132 mg and 1.13; 547 mg and 0.55 vs 659 mg and 0.66; and 953 mg and 0.64 vs 1260 mg and 0.84, respectively). The higher PDD/DDD ratio of OXC (0.99) than that of CBZ or VPA renders a generalized PDD/DDD comparison highly problematic. Furthermore, the study found that patients who failed an OXC dose of ≤ 900 mg had a higher likelihood of achieving seizure freedom compared to those who failed a higher dose of OXC.

Tiivistelmä

Epilepsia on heterogeeninen sairaus, joka voi vaikuttaa eri rotuihin, molempiin sukupuoliin ja eri ikäryhmiin. On useita kohtaustyyppejä ja epilepsiaoireyhtymiä, joita voi esiintyä epilepsiaa sairastavilla henkilöillä. Epilepsian taustalla olevat syyt voivat vaihdella ja sisältävät geneettisiä tekijöitä sekä erilaisia oireenmukaisia syitä, kuten aivovamma, aivohalvaus, keskushermostoinfektio, kallonsisäinen kasvain tai kehityshäiriö. Epilepsian ennuste voi vaihdella suuresti eri kliinisien tekijöiden mukaan. Tämän väitöskirjan päätavoitteena oli epilepsialääkkeiden tehon tutkiminen. Erityisenä päätapahtumana oli kohtauksettomuus. Väitöskirjassa analysoitiin, kuinka potilaiden demografiset tekijät, epilepsian kliiniset piirteet ja epilepsialääkkeiden eri vaikuttavat aineet ja annostukset vaikuttivat potilaanmahdollisuuksiin saavuttaa kohtauksettomuus.

Tutkimuskohorttiin kuului 459 potilasta epilepsiadiagnoosin perusteellisen validoinnin jälkeen. Tutkimuksen ensimmäisessä osassa tutkittiin ensimmäisen epilepsialääkkeen tehon, siedettävyyden ja kokonaistehokkuuden vuorovaikutusta 16-vuotiailla tai sitä vanhemmilla vastadiagnosoiduilla epilepsiapotilailla. 73 % miehistä ja 60 % naisista tulivat kohtauksettomiksi vähintään vuodeksi ensimmäisellä epilepsialääkkeellä. Paikallisalkuisen epilepsian kohtauksettomuusprosentti oli 67, eikä merkitsevää eroa havaittu okskarbatsepiini-, karbamatsepiini- ja valproaattiannoksilla välillä. Tutkimuksessa havaittiin myös, että potilailla, joilla oli rakenteellinentaituntematon etiologia, kohtauksettomuustodennäköisyys oli 61,5 % ja 75,3 %. Epileptiforminen aktiivisuus EEG:ssä paikallisalkuista epilepsiaa sairastavilla potilailla vähensi kohtausksettomuuden todennäköisyyttä mukautetuissa logistisissa regressiomalleissa.

Tutkimuksen toisessa osassa käsiteltiin kohtauksettomuuden todennäköisyyttä. Ensimmäisellä tai sitä seuraavilla epilepsialääkkeillä 404 potilaasta 459:stä (88,0 %) saavutti kohtauksettomuuden. Kun lääkeresistentti epilepsia määriteltiin kahden epilepsialääkkeen epäonnistumiseksi mistä tahansa syystä oli 20,0 % potilaista lääkeresistenttejä ja International LeagueAgainstEpilepsy (ILAE) määritelmän mukaan lääkeresistenttejä oli 16,3 %. Ensimmäisen epilepsialääkkeen epäonnistumisen jälkeen 63,6 % potilaista (96/151) tuli kohtauksettomiksi seuraavien epilepsialääkkeiden yhteydessä. Potilaille määrättiin keskimäärin 1,9

epilepsialääkettä (vaihteluväli 1-5). Potilaista, jotka saavuttivat 1 vuoden kohtausvapauden, vain 10,1 % (41/404) käytti polyterapiaa, eikä sillä ollut merkitystä oliko ensimmäinen epilepsialääke vaihdettu toiseen vai toinen lisätty ensimmäisen rinnalle. Eri epilepsialääkkeiden teho oli suurelta osin samanlainen, mutta lääkkeillä, jotka tehostivat GABA-välitteistä inhiboivaa neurotransmissiota, oli alhaisin kohtausvapausaste. Kaikki yleistynyttä epilepsiaa sairastavat potilaat tulivat kohtauksettomiksi.

Kolmannessa osatyössä arvioitiin epilepsialääkkeiden annosten eroavaisuutta suhteessa demografisiin ja epilepsiaan liittyviin tekijöihin. Tässä osatyössä havaittiin, että iällä, sukupuolella ja kohtaustyypillä oli vaikutusta siihen, millä okskarbatsepiiniannoksella kohtauksettomuus saavutettiin. Suurin ero annoksessa oli alle 60-vuotiailla miehillä (1071 mg) ja yli 60-vuotiailla naisilla (763 mg). Okskarbatsepiinin annostelussa pitäisi ottaa huomioon potilaan demografiset ja kliiniset piirteet oikeaa annoskokoa valittaessa. Iäkkäimmille potilaille 600 mg on tavoiteannos ja nuoremmille 900 mg. Iäkkäämpien potilaiden alhaisemmalla tavoiteannoksella vältytään potentiaalisesti lääkkeen sivuhaittavaikutuksilta.

Neljännessä osatyössä arvioitiin lääkeannosten merkitystä kohtauksettomuuden saavuttamisen kannalta. Potilaiden käyttämillä okskarbatsepiini, karbamatsepiini- ja valproaattiannoksilla oli merkittävä vaikutus epilepsiapotilaiden kohtauksettomuuden todennäköisyyteen. Erityisesti potilailla, jotka saavuttivat kohtausvapauden, oli pienempi keskimääräinen määrätty annos verrattuna potilaisiin, jotka eivät saavuttaneet kohtauksettomuutta. Lisäksi tutkimuksessa havaittiin, että potilailla, joilla ensimmäisenä lääkkeenä käytetty OXC-annos oli ≤ 900 mg ei tuottanut kohtauksettomuutta, oli suurempi todennäköisyys tulla kohtauksettomiksi verrattuna potilaisiin, jotka eivät tulleet kohtauksettomiksi suuremmalla OXC-annoksella.

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LIST OF ORIGINAL PUBLICATIONS

This dissertation based on the following publications, which referred in the text by Roman numerals I-IV. The articles are reprinted with the permission of their copyright holders.
The original publications will be referred to in the text by Roman numerals I-IV:

I. Hersi H, Saarinen JT, Raitanen J, Peltola J.Response to first antiseizure medication in patients diagnosed with epilepsy. Acta Neurol Scand. 2021 Jul; 144(1): 67-75

II. Hersi H, Saarinen JT, Raitanen J and Peltola J. Response to subsequent antiseizure medications after first antiseizure medication failure in newly diagnosed epilepsy. Front. Neurol.2022.13: 042168.doi:10.3389/fneur.2022.1042168

III. Hersi H, Peltola J, Raitanen J, Saarinen JT. Effect of clinical features on antiseizure medication doses in patients with newly diagnosed epilepsy. Front Neurol. 2023 Aug 7;14:1159339. doi: 10.3389/fneur.2023.1159339. PMID: 37609660; PMCID: PMC10440427.

IV. Hersi H, Raitanen J, Saarinen JT, Peltola J. Prescribed antiseizure medication doses and their relation to defined daily doses for achieving seizure freedom in newly diagnosed patients with epilepsy. Epilepsia Open. 2023 Sep;8(3):811-819. doi: 10.1002/epi4.12737. Epub 2023 Jul 8. PMID: 37010264; PMCID: PMC10472398.

AUTHOR'S CONTRIBUTION:

In Studies I, II, III, and IV, the author of this dissertation played a significant role in the research process. With guidance from the supervisors, the author actively participated in the study design, ensuring the research was methodologically sounds and aligned with the research objectives.

The author took the responsibility of collecting the data for the studies, meticulously gathering information from medical records, and ensuring the accuracy and completeness of the dataset. Throughout the data collection process, the author maintained a high level of attention to details and adhered to ethical guidelines.

To analyze the collected data effectively, the author collaborated with a statistician. Together, we utilized appropriate statistical methods to derive meaningful insights from the data. The author actively engaged in interpreting the results and drawing valid conclusions based on the statistical analysis with supervisors.

With the first draft of each study, the author took the lead in writing the manuscripts. The author meticulously organized the findings, ensuring clarity and coherence in presenting of the research outcomes. The author actively collaborated with supervisors, who provided valuable input and support, further strengthening the manuscripts.

The supervisors and data analyzer, their contribution was crucial in shaping the content and structure of the manuscripts. The dedication to achieving high standards in academic writing was evident throughout the manuscript preparation process.

Upon completion of the manuscripts, the author took the initiative to submit them to reputable journals for publication. The author navigated the submission process, ensuring that all necessary documentation and requirements were met. The author demonstrated his commitment to achieving publication goals by diligently addressing reviewers' comments and providing the final draft for publication with supervisor's help.

For all, the author's contributions in study design, data collection, analysis, manuscript writing, and publication demonstrates active involvement and dedication to the research process. His collaboration with supervisors, statistician, and along with his leadership in manuscript preparation, played a pivotal role in the successful completion and dissemination of the research findings.

ABBREVIATIONS:

AEs	Adverse events
ASM	Antiseizure medication
BZD	Benzodiazepine
CBZ	Carbamazepine
CD	Cortical dysplasia
CLZ	Clobazam
CI	Confidence interval
DBS	Deep brain stimulation
DDD	Defined daily dose
DRE	Drug resistance epilepsy
EEG	Electroencephalography
ESL	Eslicarbazepine acetate
FBTCS	Focal to bilateral tonic-clonic seizure
FIAS	Focal impaired awareness seizure
FAS	Focal awareness seizure
GBP	Gabapentin
GABA	Gamma-aminobutyric acid
GTCS	Generalised tonic-clonic seizures,
IEDs	Interictal epileptiform discharges
ILAE	International League against Epilepsy
LTG	Lamotrigine

LEV	Levetiracetam
MOA	Mechanism of action
MERRF	Multisystem mitochondrial syndrome characterized by progressive myoclonus and seizures.
MELAS	Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes
MTLE-HS	Mesial temporal lobe epilepsy with hippocampal sclerosis
NSF	No Seizure Freedom
OR	Odds ratio
OXC	Oxcarbazepine
PHT	Phenytoin
PDD	Prescribed daily dose.
IQR	Interquartile range
RNS	Responsive neurostimulation
SD	Standard deviation
TPM	Topiramate
VEEG	Video-recording EEG
VNS	Vagus nerve stimulation
VPA	Valproic acid
WHO	World Health Organisation

1 INTRODUCTION

Epilepsy is a common neurological condition characterized by a predisposition to seizure activity (Fisher et al, 2014). The condition is known to affect individuals regardless of age, ethnicity, and sex and is estimated to affect 3–4% of people during their lifetime (Beghi et al., 2019). While early diagnosis and management of epilepsy has contributed to a reduction in the burden of this condition in high-income nations, it remains an important source of negative health outcomes and deleterious effects on function (Xu et al., 2019). Indeed, epilepsy affects physical and psychological health, as well as vocational and social wellbeing (Beghi et al., 2019). It is estimated that epilepsy is the fourth leading cause of disability on a global level, illustrating the severity of the impact of the condition (Beghi et al., 2019). It is estimated that approximately 0.6% of the population of Nordic countries has active epilepsy (Syvertsen et al. 2015).

Following diagnosis of epilepsy, treatment is often based on the use of antiseizure medications (ASMs) (Abou-Khalil et al., 2019). The aim of any form of therapy is to eliminate seizure activity and facilitate a return to normal function, and ASMs have been associated with seizure freedom in around two-thirds of patients (Chen et al., 2018).

Drug-resistant epilepsy (DRE) and suboptimal therapeutic outcomes are two important factors that may lead to ineffective treatment and continued disability and poor health and wellbeing for the individual (Cheng & French et al., 2018). Furthermore, the side effects of ASMs may lead to drug discontinuation by patients and negative health effects (Cheng & French et al., 2018).

Where initial drug therapy may not lead to effective treatment, the decision to change agents or introduce combined therapy or polytherapy should be carefully considered (Verrotti et al., 2020). The aim of treatment is to achieve a seizure-free status for many patients, but this has the potential to lead to overtreatment and a high risk of adverse events associated with therapies (Liu et al., 2017).

Sequential drug therapy remains an area of interest in epilepsy management, although there is limited evidence or guidance supporting the use of specific agents in order,

including the relative efficacy of alternative therapies versus combined therapies in specific contexts (Perucca et al., 2018). As a general rule, rational polypharmacy is aimed to maximize efficacy and minimize side effects (Löscher et al., 2002). When combining antiseizure medications (ASMs), interactions can impact their effectiveness and tolerance. Some ASMs (like phenobarbital, phenytoin, and carbamazepine) increase drug metabolism, potentially reducing the effectiveness of co-administered drugs. Others (like valproate, felbamate, stiripentol, and cannabidiol) inhibit metabolism, increasing co-administered drug levels, which can lead to side effects and toxicity. These interactions are important to consider when prescribing and managing ASMs for epilepsy. Adjustments may be needed to optimize treatment(Zaccaraet al., 2014).

The following sections provide a detailed insight into the epidemiology, impact, diagnosis, and management of epilepsy according to current publications and practice standards. This examination provides a basis for highlighting gaps in the evidence base regarding the effectiveness of combination drug therapy and the relative efficacy of different agents when used as first, second-line or subsequent agents. The gaps in the evidence base are highlighted to support the research approach adopted to meet the needs of clinicians and patient subpopulations regarding epilepsy prescribing, treatment approaches, and optimization of a favorable risk-benefit profile in patients.

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2 REVIEW OF THE LITERATURE

2.1 Epilepsy

2.1.1 Definition of Epilepsy

An epileptic seizure, defined as a transient occurrence of symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al., 2005), can occur due to acute disease of the brain (e.g., acute symptomatic seizures due to cerebral hemorrhage) or systemic disorders (i.e., infection, metabolic disturbances) or as a symptom of a chronic disease, i.e., epilepsy.

According to the recent proposal of the International League against Epilepsy (ILAE), epilepsy is a brain disease with at least two unprovoked (or reflex) seizures, or one unprovoked (or reflex) seizure and a probability of at least 60% for further seizures to occur over the next ten years, or diagnosis of an epilepsy syndrome (Fisher et al., 2014).

Seizures can vary in severity, timing, and character but are generally brief episodes of involuntary movement that affect a part of the body (partial or focal) or the entire body (generalized) (Falco-Walter et al., 2018). Seizures may be linked to loss of consciousness and loss of control of bodily functions, including bowel or bladder control (Scheffer et al., 2016). The frequency of seizures and severity of seizures can vary dramatically between patients, but a single seizure alone is not necessarily predictive of a diagnosis of epilepsy (Perucca et al., 2018). Indeed, 10% of people have a seizure during their lifetime, and most do not experience recurrent unprovoked seizure activity (Maia et al., 2017; Perucca et al., 2018). While many conditions may be linked to the potential for seizures, epilepsy is characterized by a propensity for seizure activity related to specific etiological and pathological features that promote seizure activity in the brain, independent of other causes or diseases (Falco-Walter et al., 2018).

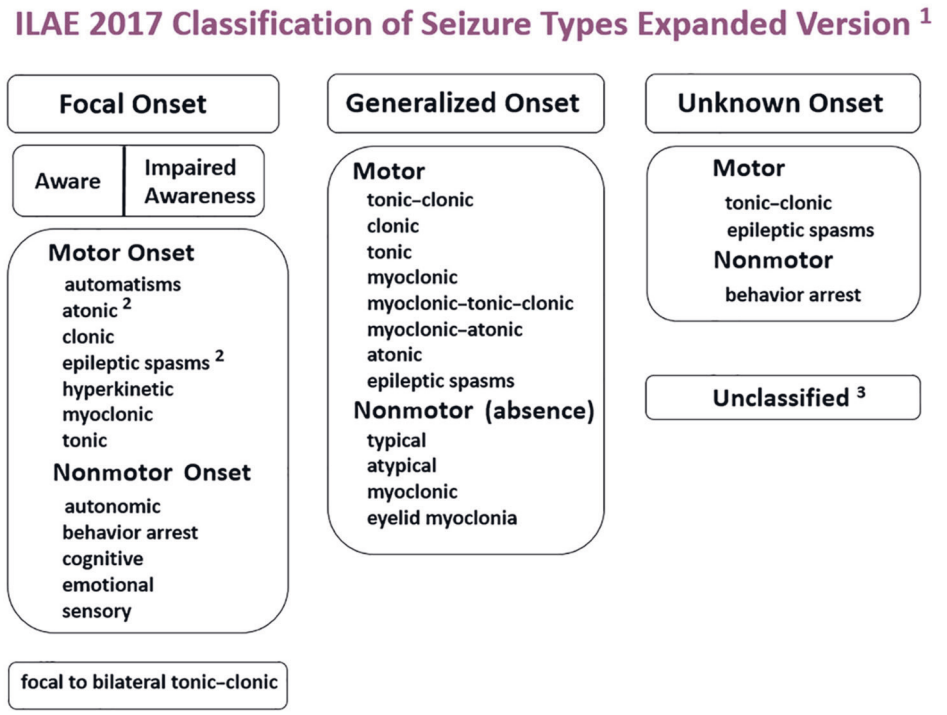
Seizure freedom is achieved when the patient does not experience any type of seizures for 12 months or there is three times the preintervention antiseizure interval, whichever is longer (Kwan et al. 2010). EEG, neuroimaging (e.g., magnetic

resonance imaging), and other tests may be performed to support the diagnosis, although many diagnoses are based on clinical features alone in practice (Bernasconi et al., 2019). The value of EEG assessment and neuroimaging rests with excluding other organic causes of epilepsy, as well as investigating the potential etiology of the specific epilepsy syndrome, including the presence of structural abnormalities that may precipitate seizure activity in the brain (Perucca et al., 2018).

2.1.2 Classification of seizures

A first-level diagnosis is achieved where the seizure type is identified and there may be limited resources to explore the diagnostic classification of the condition further (Scheffer et al., 2016; Fisher et al., 2017). Classification of seizure types and specific seizure syndromes has led to a diverse number of subcategories and epilepsy types, primarily divided according to focal, generalized, or unknown onset and then according to motor or non-motor symptoms and signs evidenced during seizure activities (Fisher et al., 2017) (Figure 1).

This classification can support the use of targeted therapies for the patient and may be sufficient to guide management and predict prognosis in some settings (Fisher et al., 2019). However, appreciation of the etiology of the condition is considered increasingly important in understanding the biology underlying seizures and the potential application of therapeutic interventions for the individual patient (Scheffer et al., 2016).



Epilepsia, Volume: 58, Issue: 4, Pages: 522-530, First published: 08 March 2017, DOI: (10.1111/epi.13670)

Figure 1: Classification of Seizure Types Expanded Version

The basic ILAE 2017 operational classification of seizure types.

By 2017, seizures were reclassified from "partial" vs. "generalized" to terms like "focal" and "generalized" with added descriptors (Fisher et al., 2017a, 2017b).

Fisher et al. (2017) outlines a revised classification of seizures as enclosed by ILAE. The revision by ILAE is premised on the fact that certain seizures can have either a generalized or focal onset. Further, the revision highlights unobserved seizures. More transparent names and seizure types that have remained missing in many epilepsy classifications are also highlighted. The classification outlined in (Fisher et al., 2017) is practical and based on 1981 and 2010 classifications. Some of the changes in the 2017 classification include changing partial into focal, using awareness as a classification for focal seizure, and eliminating the terms dyscognitive, secondary generalized, psychic, complex focal, and simple focal. The other changes in the 2017 classification include new focal seizure types, including emotional, cognitive, automatic, hyperkinetic, behavior arrest, and automatism, among other changes.

Focal to bilateral tonic-conic seizure (FBTCS) with EEG changes is a special seizure type and corresponds to the 1981 classification in which the phrase "partial onset with secondary generalization" was utilized. FBTCS with EEG changes and infers to a propagation pattern of seizure (Fisher et al., 2017). Essentially, FBTCS is not a unitary type of seizure but a propagation. Notwithstanding, it is an important proponent of seizures such that separate classification is necessary. The term bilateral is utilized to differentiate generalized onset seizure from focal –onset seizure.

According to Fisher et al. (2017) focal impaired awareness seizure (FIAS) was previously classified as complex partial seizure. For a patient experiencing seizure, impairment during any part of the seizure renders it FIAS with EEG. Commonly, focal impaired awareness seizure and focal awareness seizure have further classification including onset and non-motor onset symptoms. An example of such classification is the focal impaired awareness automatism seizure (Fisher et al., 2017). The proportion of patients with FIAS as their first seizure type was 36% in a study from Rochester Minnesota (Hauser et al., 1993).

Focal awareness seizure (FAS) with EEG changes and seizure freedom is premised on the 1981 classification and further the 2010 classification on seizures that impairment of consciousness and those where there is no impairment of the patient's consciousness. Now since consciousness is a complex phenomenon with various objective and subjective properties better classification was necessary (Fisher et al., 2017). The task force thus adopted a new classification. Thus, classification such as "focal aware seizure" and retained awareness" were adopted for clarity.

2.1.3 Classification of epilepsies

Already 1981 and 1989, the ILAE developed a classification system for epilepsy. It categorized epilepsies by factors like age, cause, seizure type, EEG patterns, neuroimaging, and coexisting conditions. Subsequent proposals, like those by (Berg et al., 2010), Berg & Scheffer et al., 2011), and (Engel et al., 2001), called for revisions.The proposed changes included replacing "idiopathic," "symptomatic," and "cryptogenic" with genetic, structural-metabolic, and unknown causes.Simplifying partial onset seizures as "focal seizures.

The (ILAE) updated epilepsy definitions and classifications to reflect contemporary understanding.The same year, epilepsy syndromes were comprehensively categorized by onset and etiology (Scheffer et al., 2017), underscoring the significance of precision medicine in treatment.

Strategies to classify epilepsy rest with determining the seizure type or etiology of the condition; ideally, both factors are used to understand the pathophysiology and treatment potential for both acute seizures and epilepsy syndromes. The (ILAE) task force (Scheffer et al., 2017) highlights four main epilepsy types that can be used to classify epilepsy: focal, generalized, generalized and focal, and unknown (Figure 2). The advantage of the ILAE strategy illustrated in Figure 2 is that diagnosis of epilepsy can be facilitated across multiple stages of the condition and based on the availability of information and resources in the local setting.

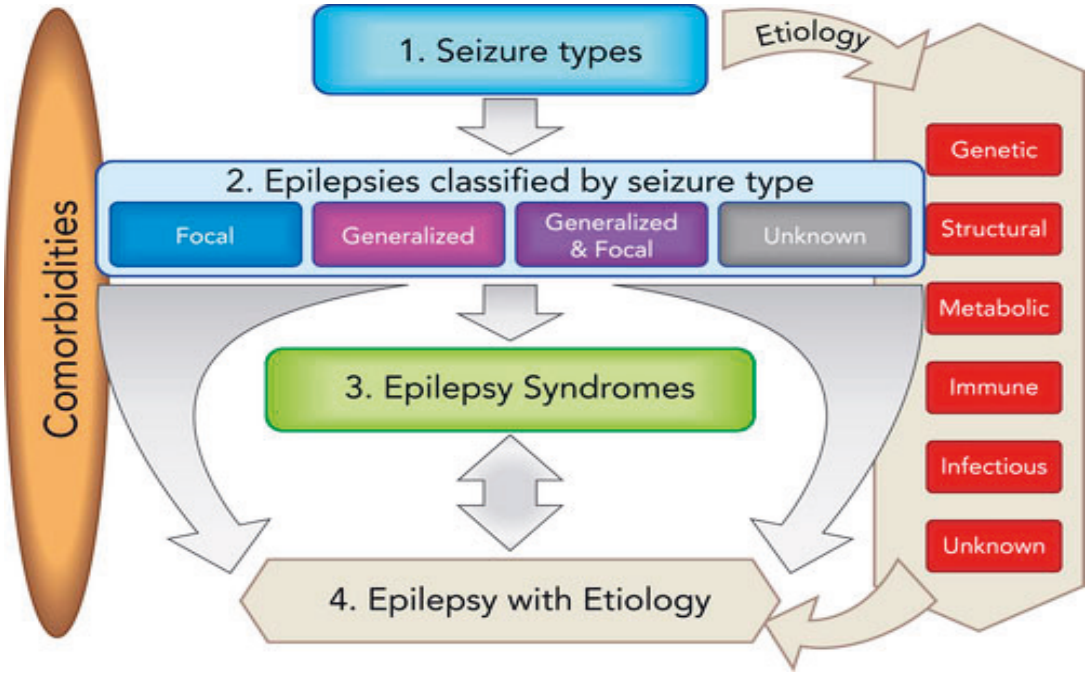


Figure 2. Classification of epilepsy by the International League Against Epilepsy. Adapted from Scheffer et al. (2017: 40).

The objective of (Scheffer et al., 2017) was to update the classification of epilepsy. The primary purpose of the reclassification was to help in epilepsy diagnosis, help improve the quality of epilepsy research, help fashion antiepileptic

therapies, and improve epilepsy communication. These new classifications are an adoption from comments from a public 2013 document that had been revised to include feedback from the international epilepsy community after several consultations. According to Scheffer et al. (2016), the classification is premised on three levels: seizure type, epilepsy type, and epilepsy syndrome. In seizure type, the assumption is that the patient has an epileptic seizure as outlined in the 2017 ILAE classification.

After diagnosing the seizure type, Scheffer et al. 2017) underline that it would be easier to diagnose the different types of epilepsy, including generalized epilepsy, combined generalized and focal epilepsy, focal epilepsy, and unknown epilepsy group.

A first-level diagnosis is achieved where the seizure type is identified and there may be limited resources to explore the diagnostic classification of the condition further (Scheffer et al., 2016; Fisher et al., 2017). Epilepsy classification highlights: Multiple seizure types in some epilepsy types. EEG and MRI differentiate focal vs. generalized epilepsy. Epilepsy syndrome diagnosis based on specific criteria like age, remission, triggers, prognosis, cognitive comorbidities.

An epilepsy syndrome is possible to diagnose; if specific seizure types, EEG, and the imaging findings occur, and it may display a typical age at onset and remission, seizure triggers, diurnal variations, even prognosis, and mental or cognitive comorbidities. Classification of epilepsy syndromes was based on the International League Against Epilepsy (ILAE) classification criteria (Scheffer et al., 2017). Focal epilepsy was diagnosed if semiology, imaging, and standard or LT-EEG indicated focal onset. Structural epilepsy was defined as seizures associated with epileptogenic brain lesions. Idiopathic/genetic generalized epilepsy (IGE) included syndromes characterized by typical EEG pattern and seizure types as well as an absence of significant brain lesions and neurological deficits.

The IGEs include four syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic–clonic seizures alone. Juvenile myoclonic epilepsy (JME) is a type of idiopathic generalized epilepsy that usually occurs during adolescence. The leading symptom is early-morning myoclonic seizures (MS) alone or combined with generalized tonic-clonic seizures (GTCS) or absence seizures (AS). (Janz D et al., 1985 &Ke M, 2019).

2.1.4 Epidemiology of Epilepsy

Epilepsy is the most common serious neurological condition on a global level (Beghi et al., 2019). A recent systematic literature review, including 167 articles across all WHO defined regions and income levels, found that the global prevalence of epilepsy was 1099 per 100,000 people, with a global incidence of 62 cases per 100,000 person-years (Vaughan et al., 2018). This equates to around 51.7 million active cases of epilepsy and 82.3 million diagnoses at any point in the lifetime on a global level (Vaughan et al., 2018).

Epilepsy prevalence varies based on factors such as the definition used and study design. Typically, it's reported to be in the range of 4 to 7 cases per 1000 individuals (Beghi&Hesdorfferet al., 2014). In Nordic countries, the prevalence is approximately 6 per 1000 (Syvertsen, Koht& Nakken et al., 2015).

Moreover, convulsive disorders are estimated to affect around 10% of the population, and approximately 3% of individuals will diagnosis epileptic seizures at some point in their lifetime (Hauser et al. 1996). These statistics underscore the significant impact of epilepsy-related conditions on a portion of the population, highlighting the importance of ongoing research and healthcare efforts in this field. While addressing inequalities in access to basic diagnostic and treatment services in low-and middle-income nations may overcome a large proportion of disability and mortality linked to epilepsy, there remains an important need to target therapy in high-income nations and to optimize treatment to prevent long-term disability and suboptimal outcomes (Beghi et al., 2019). Therefore, epilepsy is a global health challenge, despite differences in priorities according to national needs for treatment.

2.1.5 Sex and age-related variation both the incidence and prevalence

The incidence and prevalence of epilepsy vary significantly with age, exhibiting peaks in early childhood and later adulthood, a pattern underscored by numerous epidemiological studies (Hauser et al., 1993, Fiest et al., 2017).

The highest incidence rates were found in children under the age of 1 year and in individuals over the age of 75 year. Similarly, the prevalence of epilepsy also showed age-related variations, with higher rates observed in early childhood and older adulthood. These findings suggest that age plays a crucial role in the development and persistence of epilepsy, with distinct patterns observed across different age

groups. While females have a slightly higher incidence until age 5, males dominate thereafter, especially in senior years. When considering seizure type, generalized onset epilepsy shows its highest incidence in infancy, decreasing during childhood, and mildly rising in the elderly. However, partial seizure epilepsy maintains an incidence rate of about 20 until age 65, skyrocketing at age 75 and later (Hauser et al., 1993).

In the first year of life, the incidence rate of epilepsy is notably high for both sexes, followed by a sharp decline after 10 years of age, suggesting a pronounced contribution of genetic factors in early-onset epilepsy (Forsgren et al., 2005).

Epilepsy, a pervasive neurological disorder, manifests with age-related variations not only in incidence and prevalence but also in its causes. Research shows that the etiology of epilepsy can often remain unidentified, with the proportion of unknown causes ranging from 27% in 5–9-year-olds to a slightly higher 41% in the 10-19 age bracket (Dahl-Hansen et al., 2018).

Interestingly, the leading causes of epilepsy in the 5-9 age group are structural-metabolic epilepsies and perinatal insults, accounting for 46% of cases in this age bracket. In contrast, the youngest patients, those aged four and under, are mostly affected by disturbances in brain development, contributing to 23% of epilepsy cases (Dahl-Hansen et al., 2018). As age advances, different factors come into play. In those aged 60 and over, stroke becomes the most prevalent cause of epilepsy, responsible for 44% of the cases in this age group (Dahl-Hansen et al., 2018). These findings underscore the intricate interplay between age and epilepsy etiology.

The incidence and prevalence of epilepsy show age-related variations, indicating differences in the occurrence and persistence of the condition across different age groups. A seminal study by (Hauser et al 1993) examined the incidence of epilepsy and unprovoked seizures in Rochester, Minnesota, from 1935 to 1984. The study found that the incidence of epilepsy varied significantly with age, with higher rates observed in early childhood and older.

2.1.6 Burden of Epilepsy

While there is evidence that the global burden of epilepsy has decreased from 1990 to 2016 (6% decrease in age-standardized prevalence and 24.5% decrease in mortality rates), epilepsy remains a significant cause of disability and mortality worldwide (Beghi et al., 2019). The significance of epilepsy is linked to the potential for long-term disability, impaired function, and the risk of mortality linked to seizure

activity (Fiest et al., 2017). Seizure activity is linked to an increased risk of physical harm and injury, including bruising and fractures, as well as risks relating to occupational activities, such as driving or operating machinery (Scheffer et al., 2016).

Epilepsy has also been linked with psychological health problems, including an increased risk of anxiety and depression compared with the general population (Michaelis et al., 2018). This may reflect shared neurological pathways linking epilepsy and mental health conditions, as well as the impact of epilepsy and the chronic disease state on the wellbeing of the patient (Michaelis et al., 2018).

When physical and psychological health effects are combined, the risk of disability is significant in people with epilepsy, particularly when these conditions and impairments influence the potential to achieve occupational and social wellbeing (Steiger and Jokeit, et al., 2017). Optimizing management of epilepsy is a clear strategy for the prevention of avoidable morbidity and disability, with an estimated 70% of patients having the potential to be seizure-free based on current treatments (Institute of Medicine, 2012; Tian et al., 2018). In patients with DRE, there is a substantial burden, leading to comorbidities, psychological issues, reduced quality of life (QOL), increased mortality risk, and reduced life expectancy (Laxer et al., 2014).

Even seizure-free patients may experience depression, low self-esteem, and health-related concerns, affecting their QOL negatively (Hessen et al., 2008). Optimizing QOL becomes a crucial goal for those with drug-resistant epilepsy. Seizure frequency has a limited impact on QOL compared to mood and medication-related adverse events (AEs) (Birbeck et al., 2002). Long-term AEs should be carefully considered in exchange for short-term benefits (Roivainen et al., 2014). Achieving remission at the cost of unacceptable AEs can still result in poor QOL. Cognitive impairment, often overlooked, can be an AE of antiepileptic drugs (ASMs). Neuropsychological improvements post-withdrawal was observed, with a relative risk of seizure relapse (Lossius et al., 2008). Executive functions may also be impaired during ASM monotherapy (Hessen et al., 2009b). Early recognition of DRE is crucial to explore aggressive treatment options like surgery or neuromodulation, potentially mitigating these adverse consequences.

2.1.7 Acute symptomatic seizures

Acute symptomatic seizures are events closely associated in time with an acute central nervous system (CNS) insult, which can result from metabolic, toxic, structural, infectious, or inflammatory factors. Unprovoked seizures are those that

occur without an identifiable clinical condition or beyond the expected timeframe for acute symptomatic seizures. They differ from acute symptomatic seizures in terms of the risk of seizure recurrence and mortality across various underlying causes (Beghi et al., 2010)

Approximately 2–3% of patients in intensive care and even 8–11% of those in neurocritical care have acute symptomatic seizures (Vorderwülbecke et al., 2018) Overall in cerebrovascular disease, incidence ranges from 1.3% in ischemic stroke (Zöllneret al., 2020). To 4% in intracerebral or subarachnoid hemorrhage (Zöllneret al.,2020). Up to 34% in cerebral venous thrombosis (Lindgren et al.,2020)

It is common that the patient with a first seizure has had other events previously, which were not recognized as seizure, around 40%. Some may have had multiple seizures and even generalized motor seizures (Jackson et al., 2016). Some seizure types that may go unnoticed, like abdominal and psychic auras, myoclonic seizures in young patients after sleep deprivation, or absence seizures.

Over a 10-years period, individuals with first acute symptomatic seizures were 80% less likely to experience a second unprovoked seizure compared to individuals with first remote symptomatic seizure (Rizvi et al., 2017).

The risk of an acute symptomatic seizure patient representing an unprovoked second seizure is 33% after stroke, 13.4% after traumatic brain injury and 16.6% following CNS infection (Hesdorffer et al., 2009). A first acute symptomatic seizure does not allow clinicians to formulate a diagnosis of epilepsy.

Seizures are considered acute symptomatic if they occur within the first 7 days of cerebrovascular disease (Jennett et al., 1973; Camilo & Goldstein, 2004). Shortly after traumatic brain injury (TBI), including intracranial surgery (Jennett et al., 1973; Annegers et al., 1998). In cases of CNS infections, even beyond 7 days, with persistent clinical or laboratory findings (Annegers et al., 1988).

The main risk factors associated with the development of post-stroke epilepsy following an ischemic stroke include cortical involvement, hemorrhage, and early seizures (Ferlazzo et al., 2016). These factors are integrated into a validated clinical tool known as the SeLECT score, which helps predict the likelihood of late seizures or epilepsy after an ischemic stroke (Galovic et al., 2018).

Even in the absence of a definite stroke, cerebrovascular diseases such as leukoaraiosis are considered risk factors for the development of epilepsy, although the underlying mechanisms are less clear (Ferlazzo et al., 2016)

Seizures related to alcohol withdrawal typically occur within a window of 7 to 48 hours after the last drink. Seizures in the context of acute alcohol intoxication, often due to extremely high alcohol consumption, are likely linked to that exposure (Hillbom et al., 2003; Brathen et al., 2005). Additionally, acute symptomatic seizures can occur with the withdrawal of barbiturates and benzodiazepines.

In accordance with the current ILAE recommendations, seizures due to facilitating factors in patients with established epilepsy such as non-adherence to ASM or sleep deprivation were not considered as acute symptomatic (Beghi et al., 2010).

Misclassifying acute symptomatic seizures as unprovoked seizures is possible because the age distribution of incident seizures is similar, and acute symptomatic seizures are nearly as common as epilepsy (Loiseau et al., 1990; Hauser et al., 1991; Annegers et al., 1995). Etiologies and epileptogenic mechanisms are considered in detail in the following section.

2.2 Etiologies of epilepsies

The etiological factors that contribute to the onset of epilepsy in a patient are complex and incompletely understood (Beghi et al., 2020). The etiology of epilepsy remains an important appreciation in planning treatment and predicting the prognosis of the patient due to the potential therapeutic strategies and predicted course of disease based on underlying risk factors and pathology (Witt et al., 2019).

Broadly, categorization of the etiology of epilepsy has expanded from a model encompassing three categories (genetic, structural/metabolic, and unknown) to a model with six categories, reflecting expanding knowledge of the causes of epilepsy and the importance of refining causes to guide therapy as therapeutic advances emerge (Scheffer et al., 2017). The six categories include: genetic, structural, metabolic, immune, infectious, and unknown etiologies, as depicted in Figure 2.

2.2.1 Genetic causes of epilepsy

Genetic causes of epilepsy are often associated with epilepsy presenting in childhood or at a young age, reflecting the influence of specific genetic defects in determining a propensity for seizures (Perucca et al., 2020). Epilepsies with genetic causes are diverse, and often the specific genes responsible are still unknown. Genetic factors maybe influencing epilepsy's etiology, varying across age groups as shown by (Scheffer et al., 2017). They highlighted genes linked to childhood and adult-onset epilepsy, particularly prominent in syndromes like Dravet and genetic generalized epilepsies.

In contrast, acquired epilepsy linked to metabolic, structural, immune, or infectious causes is more common in adult populations and reflects specific processes that increase the risk of epilepsy, either with or without additional disease features and systemic illnesses (Beghi et al., 2015). While genetic risk factors are noted, incidents such as head trauma and cerebrovascular disease (e.g., stroke) can precipitate epilepsy in individuals without any predisposing risk factors, highlighting the importance of the integrity of brain tissue for preventing epileptogenic conditions (Perucca et al., 2018).

2.2.2 Structural causes of epilepsy

Structural cortex lesions can lead to seizures and epilepsy. Seizure characteristics are determined by lesion location, not the lesion type, diagnosis of structural lesions requires histopathological examination, tissue for examination is obtained from brain resections during epilepsy surgery or post-mortem, by the ILAE Commission on Diagnostic Methods specifies protocols for brain tissue examination in epilepsy surgery (Blümcke et al., 2016).

The most common causes of epilepsy affecting adults reflect trauma to the head, neurodegenerative or cerebrovascular diseases, malignancy, and specific conditions such as hippocampal sclerosis and cortical dysplasia (Walsh et al., 2017; Perucca et al., 2018). It has been estimated that almost one-quarter of epilepsy cases in adults may be preventable through reductions in exposure to trauma (particularly head trauma), highlighting how damage to brain tissues may be a key determinant in the potential for seizure development in previously healthy adults (Walsh et al., 2017).

Alzheimer's disease, malformations of cortical development and other neurodegenerative disorders are increasingly recognized as causes of epilepsy in adults, with significant implications for clinical management (Vossel et al., 2017). It appears as volume loss on T1-weighted sequences and as a hyperintense signal on T2/fluid-attenuated inversion recovery (FLAIR)-weighted sequences (Bernasconi et al., 2019). The development of hippocampal sclerosis is likely the result of a complex interplay between genetic factors and environmental insults, which can include factors such as prolonged febrile seizures, traumatic brain injury, and infectious causes (Walker et al., 2015).

The ILAE Commission on Diagnostic Methods has put forth a histopathological classification scheme, recognizing that hippocampal sclerosis is a heterogeneous disorder with distinct patterns of neuronal cell loss that are likely attributable to different underlying causes (Blümcke et al., 2013).

Common resected structural lesions for focal epilepsy treatment fall into six main disease categories: hippocampal sclerosis, brain tumors, vascular malformations, glial scarring (including stroke and traumatic brain injury), and brain inflammation (Blumcke et al., 2017).

Hippocampal sclerosis is characterized by neuronal cell loss in specific anatomical sectors of the hippocampal formation (Blümcke et al., 2013). The atrophy of the hippocampus is observable through MRI scans.

There is evidence to suggest that the location of brain injury, particularly in the temporal lobe, and the occurrence of early post-traumatic seizures are predictive factors for the development of post-traumatic epilepsy. Unfortunately, despite ongoing research, there is currently no effective prophylactic treatment available to prevent the onset of epilepsy after traumatic brain injury (Tubi et al., 2019).

2.2.3 Immune etiologies of epilepsy

Immune etiologies pertain to instances of epilepsy that arise directly from autoimmune-induced inflammation within the central nervous system. This inflammation manifests as distinct clinical attributes observed across pediatric and adult populations, as elucidated by (Scheffer et al., 2017).

Autoimmune diseases, though relatively rare in the brain due to immune privilege, have been associated with seizures. These diseases include systemic lupus erythematosus, sarcoidosis, coeliac disease, Behcet's, and Hashimoto's encephalopathy (Devinsky et al., 2013).

The mechanisms of these associations vary and may include vasculitis and metabolic disturbances. Autoimmune-associated seizures have also been reported in paraneoplastic syndromes. Moreover, there is a growing number of autoantibodies specifically linked to seizures, directed against either cell surface or intracellular antigens. These antibodies have varying associations with tumors, such as ovarian cancer being associated with NMDA receptor antibodies, small cell lung cancer with AMPA receptor and GABA(B) receptor antibodies. Lancaster et al. (2011) described pathogenic autoantibodies in Ophelia syndrome that target the metabotropic glutamate receptor 5 (mGluR5) and cause a decrease in mGluR5 density on neurons and Hodgkin lymphoma with mGluR5 antibodies.Additionally, anti-AMPA-GluR3 antibodies, anti-NMDA-NR1 antibodies, anti-NMDA-NR2A/B antibodies, anti-mGluR1 antibodies, and anti-mGluR5 antibodies have been found in subpopulations of patients with epilepsy, encephalitis, and cerebellar ataxia. These antibodies are associated with various autoimmune neurological and neuropsychiatric disorders, each with their specific clinical manifestations and implications (Spatola et al., 2018).

2.2.4 Infectious causes of epilepsy

Cerebral infections caused by bacteria, viruses, fungi, and parasites are among the most common reasons for seizures and epilepsy worldwide, with a particularly high prevalence in developing countries. These infections can trigger seizures through various mechanisms, including direct damage to brain tissue, the production of toxins by the infectious organism, and the induction of inflammation. It's important to note that seizures represent an independent risk factor for mortality in patients with cerebral infections. For instance, in cases of bacterial meningitis, individuals with associated seizures faced a staggering ~18-fold higher risk of death (Hussein et al., 2000).

Infectious causes of seizures are often medical emergencies, and it is crucial to promptly address both the infectious agent and the seizures themselves. In Sub-Saharan Africa, infections account for epilepsy in as many as 26% of patients (Preux et al., 2005). Infectious causes of seizures and epilepsy are significant medical concerns and require prompt treatment. The type of virus and the occurrence of early seizures play crucial roles in determining the risk of epilepsy.

Sporadic viral encephalitis is commonly caused by herpes simplex virus (HSV) type 1, with other important causes including HSV type 2, cytomegalovirus, varicella zoster, and enteroviruses. Endemic encephalitis often results from arthropod-borne viruses like Japanese B encephalitis, West Nile virus, and Nipah virus (Michael et al. 2012).

Infectious causes of epilepsy have complex implications for treatment due to potential drug interactions. For instance, enzyme-inducing antiseizure medications can lower the serum levels of antiretroviral and anti-helminthic drugs. Rifampicin and meropenem can reduce serum levels of certain antiseizure medications.

2.2.5 Metabolic causes of seizures and epilepsy

Metabolic causes of seizures and epilepsy can be either acquired or genetic. Acquired metabolic causes can result from organ failure (e.g., liver, kidney, or pancreas), nutritional deficiencies, autoimmune conditions (e.g., type I diabetes mellitus, autoimmune cerebral folate deficiency), or exposure to exogenous drugs and toxins (Angel et al., 2011). Many of these conditions lead to acute seizures, often accompanied by acute encephalopathy, rather than epilepsy unless they cause permanent brain damage, which can occur in cases like hypoglycemia or hyperammonemia. Among exogenous toxins, alcohol is a common cause of seizures in young adults, and its consumption is associated with the development of epilepsy in a dose-dependent manner (Samokhvalov et al., 2010). The underlying mechanisms may not be directly related to alcohol but rather comorbidities such as traumatic brain injury and cerebrovascular disease (Samokhvalov et al., 2010).

Mitochondrial disorders are frequently associated with seizures and epilepsy as part of their phenotype (Rahman et al., 2013). These disorders are often multisystem conditions, with typical presentations such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) and myoclonic epilepsy with ragged red fibers (MERRF) syndromes. Mutations in the mitochondrial DNA polymerase gamma gene (POLG1) are typically associated with Alpers syndrome, characterized by psychomotor regression, seizures, and liver disease, but they can also manifest with other phenotypes. Status epilepticus in these conditions often leads to cognitive and neurological deterioration. Importantly, the use of sodium valproate in these conditions can result in fatal hepatotoxicity (Milone et al., 2010).

2.2.6 Unknown etiology of epilepsy

Unknown etiology of epilepsy reflects a situation where there is no underlying cause identified, either reflecting a lack of clarity regarding genetic or structural causes (the most common causes of epilepsy) or lack of investigation into such causes (Manford et al., 2017).

One of the challenges in determining the cause or risk factors for epilepsy development is that many patients do not follow the typical model for chronic disease development, whereby a clear genetic risk is then linked to environmental risk factors that trigger the condition in a vulnerable individual (Perucca et al., 2020).

2.3 Epileptogenesis

Epileptogenesis is a term used to define the development or extension of tissue that can generate spontaneous seizures and may occur during the time of injury or tissue damage or in the aftermath of the initial insult, whereby molecular and cellular changes in the brain lead to profound changes in neurological function that can precipitate seizures (Pitkanen et al., 2015).

The process of epileptogenesis is considered dynamic in nature, whereby changes in neurotransmission, excitability of affected neurons, and architectural changes in brain tissue occur, predisposing individuals to spontaneous seizure activity (Scheffer et al., 2016). Identification of the region affected by this insult can be vital in guiding targeted interventions, such as surgery, but there remain key challenges in targeting specific brain regions with pharmacological agents (Balestrini &Sisodiya et al., 2018).

Modifying the development of epileptic foci and seizure-producing regions of the brain can be important in preventing epilepsy in the future, but there is little research supporting strategies to modulate this risk or prevent epileptogenesis (Kobylarek et al., 2019). Accordingly, therapeutic approaches are aimed to either remove the affected region, disrupt erroneous signaling activity, or modify neuron excitability to prevent seizure activity from developing in specific circumstances (Radzik et al., 2015).

2.4 Prognosis

The relapse patterns of epilepsy can be classified as early relapse, late relapse, and seizure-free (Park et al., 2020). In addition, outcomes can be categorized into 4 patterns: A) early and sustained seizure freedom; B) delayed but sustained seizure freedom; C) fluctuation between periods of seizure freedom and relapse; and D) seizure freedom never attained (Brodie et al., 2012). However, prognostic factors for achieving remission with the second or subsequent ASM regimens have been less explored. According to a recent study, seizure freedom with the second ASM was more probable in men and patients >45 years, and patients with generalized TCS or FBTCS before initiation of the first ASM were more likely to respond to the second ASM (Bonnett, et al 2014).

The development of DRE was associated with the following factors: symptomatic etiology of epilepsy, epileptiform abnormality in EEG, number of anti-seizure medications and seizure frequency of ≥1 /month at first arrival ($P < 0.001$). For symptomatic epilepsy, patients with meningitis/encephalitis ($P = 0.007$) were more likely to develop DRE than these with other causes (Yang, H. et al., 2021). About one in four MTLE-HS patients (24.7%) experienced a seizure-free period lasting more than a year. A challenging prognosis and drug resistance were linked to starting seizures at a younger age ($p=0.002$), having a prolonged history of epilepsy ($p=0.018$), using multiple current anti-epileptic drugs (ASMs) ($p<0.001$), and undergoing several ASM treatments ($p<0.001$) as reported by Pohlen MS and colleagues in 2017 (Pohlen et al., 2017).

The risk of premature death is three times higher in people with epilepsy compared to the general population (WHO, 2019). Sudden unexpected death in epilepsy (SUDEP) is themost common cause of epilepsy-related death in children and adults. The most important risk factor for SUDEP is the presence and frequency of generalized tonic-clonic seizures (Whitney et al, 2019). Optimal therapy may reduce the risk of premature death and seizure-related mortality directly, as well as impacting on wider health outcomes and risks (Fiest et al., 2017). However, optimal treatment relies on timely and accurate diagnosis and classification of the condition to guide interventions, as considered in the following section.

The annual incidence of SUDEP in individuals with epilepsy ranges from 0.33 to 1.35 per 1000 (Thurman et al., 2017). Among the factors influencing premature death in epilepsy, etiology stands out as the most significant prognostic factor. The standardized mortality ratio (SMR), which compares the observed number of deaths in the epilepsy population to the expected number in the general population after standardization, is approximately 2.3 for epilepsy (Thurman et al., 2017).

The mortality rate in individuals with epilepsy compared to the general population varies depending on the underlying etiology. Notably, it is reported as 1.6 in genetic epilepsy and 4.3 in structural epilepsy (Cockerell et al., 1997).

Furthermore, the influence of age on achieving remission in epilepsy is generally considered to be relatively small (Cockerell et al. 1997). Other factors and individual variations play a more significant role in determining the prognosis of epilepsy.

The epilepsy syndromes, the prognosis can vary significantly from poor to excellent, with approximately two-thirds of patients experiencing a favorable long-term outcome (Beghi, Giussani & Sander et al., 2015). Seizure relapse occurs in a range of 23% to 71% of individuals following the first unprovoked seizure (Beghi et al., 2003).

Epilepsy patients can be classified into four prognostic groups based on a classification proposed by Sander.: 1. Excellent prognosis (about 20–30%): These patients have a high likelihood of spontaneous remission. Examples include benign focal epilepsies, benign myoclonic epilepsy in infancy, and reflex epilepsies. 2. Good prognosis (about 30–40%). Patients in this group have easy pharmacological control and the possibility of spontaneous remission. Childhood absence epilepsy and some focal epilepsies fall into this category. 3. Uncertain prognosis (about 10–20%): Patients in this group may respond to drugs but tend to relapse after treatment withdrawal. Examples include juvenile myoclonic epilepsy and most focal epilepsies, whether symptomatic or cryptogenic. 4. Poor prognosis (about 20%): This group includes patients in whom seizures tend to recur despite intensive treatment. It encompasses epilepsies associated with congenital neurological defects, progressive neurological disorders, and some symptomatic or cryptogenic partial epilepsies (Kwan &Sander et al., 2004)

This classification remains relevant even with the advancements in diagnostic techniques and the introduction of new antiepileptic drugs. It helps in assessing the expected course of the disease and guiding treatment decisions for epilepsy patients.

In conclusion, discussing the prognosis of epilepsy for an individual patient is complex and requires a detailed understanding of the specific epilepsy syndrome they have. Epilepsy is not a single, uniform condition but rather a group of disorders with diverse etiologies, clinical presentations, and disease courses. For instance, while genetic epilepsies often have a more favorable prognosis, it's essential to recognize that this group encompasses conditions like absence syndromes that tend to spontaneously resolve over time, as well as severe conditions like Dravet syndrome.

Dravet syndrome is a rare and lifelong form of epilepsy associated with cognitive impairment and a significantly higher risk of sudden unexpected death in epilepsy (SUDEP) compared to other childhood-onset epilepsies (Skluzacek et al. 2011). Given the wide range of disease courses, prognosis should always be evaluated in the context of a comprehensive assessment of the individual patient's condition.

2.5 EEG patterns

Electroencephalogram (EEG) remains a fundamental diagnostic tool in epilepsy, enabling classification of seizure types and informing prognosis (Rajendran & Sridhar et al., 2020). Yet, while EEG's sensitivity varies from 29–55% in standard application and up to 80% when optimized, its specificity is high with minimal false positive rates (Benbadis et al., 2020; Goenka et al., 2018). This balance of sensitivity and specificity enables the detection of interictal epileptiform discharges (IEDs), which can confirm epilepsy diagnosis in patients with a first unprovoked seizure (Benbadis et al., 2020). However, it's important to interpret IEDs in the context of history and examination findings.

Additionally, EEG serves a prognostic role and guides medication withdrawal. The presence of IEDs before medication withdrawal is a strong predictor of seizure relapse (Lamberink et al., 2017). Video-EEG (VEEG) is increasingly used to capture nuanced seizure patterns, while machine-learning pattern recognition systems show promise for epilepsy diagnosis, though further validation is needed (Benbadis et al., 2020; Chen et al., 2020). Nevertheless, the classic three-tiered EEG analysis (normal, abnormal, epileptiform) remains a reliable method for predicting diagnosis and likelihood of seizure recurrence. Focal slow wave activity on an EEG suggests localized brain abnormalities. The pattern of slowing can vary from intermittent to persistent, with persistent slowing often indicating more severe underlying cerebral dysfunction. Abnormal EEGs containing IEDs help classify seizures and identify epilepsy syndromes. Generalized spike-and-wave (GSW) patterns on EEG are the hallmark of generalized (genetic) epilepsies (GGE), with discharges within bursts characteristically repeating at 3 Hz or faster. The presence of slow (<3 Hz) spike-and-waves (SSW) is typical of an epileptic encephalopathy, such as Lennox-Gastaut syndrome (LGS). Focal anterior temporal spikes are often associated with mesial temporal lobe epilepsy (TLE). However, only some intracranial IEDs can be detected by standard scalp EEG recordings in PWE, limiting representation of underlying cortical epileptiform activity (Ray et al.,2007).

2.6 Treatment

By defnition, antiseizure medications (ASMs) prevent or suppress the generation, propagation, and severity of epileptic seizures. The term "antiseizure medication" has replaced the old term "anticonvulsant drugs" because epilepsy therapies suppress not only convulsive but also nonconvulsive seizures (Browne et al., 1978, &Shorvon et al., 2020)

Furthermore, the term "antiseizure medication" more and more replaces the term "antiepileptic drug" because such drugs provide symptomatic treatment only and have not been demonstrated to alter the course of epilepsy (Devinsky et al., 2018 & Porter et al., 2012).

The choice of drug should be based on seizure type, epilepsy syndrome, clinical context, treating doctor preferences and patient wishes. First-line therapies are typically pharmacological agents, ASMs, that need to be carefully selected to ensure maximal efficacy for the subtype of epilepsy while considering the side effects profile of the agent (Goldenberg et al., 2010).

When post-stroke epilepsy is diagnosed, antiseizure treatment is recommended (Holtkamp et al., 2017). The choice of antiseizure medication should be based on the individual patient's profile. However, there is no evidence supporting the use of antiseizure medications as a primary prevention measure (Zelano et al., 2020).

Neural mechanisms responsible for epileptic seizures are relevant for ASM selection. In the healthy brain, there's a finely tuned balance between excitatory and inhibitory neurotransmission. Glutamate, the primary excitatory neurotransmitter, and gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter, are critical for maintaining this balance. When this balance is disrupted, it can lead to a state of neuronal hyperexcitability. If glutamatergic transmission becomes too potent or GABAergic transmission is diminished, neurons can become overly active, leading to seizure activity. This imbalance is thought to be a key factor in many forms of epilepsy (Avoli et al., 2002). However, many types of epilepsy are associated with genetic mutations that alter the function of ion channels, dysfunction in ion channels contributes to the generation and propagation of seizures (Steinlein et al., 1995). Also, neural network dysfunction is crucial importance, abnormal synchronization of large populations of neurons is a characteristic feature of epileptic seizures (Engel et al., 2009).

The lowest effective dose should be utilized during initial treatment of new-onset epilepsy, which permits an increase in dose later (if indicated) while reducing the risk of adverse events for the patient (Abou-Khalil et al., 2019). Factors associated with

the selection of a suitable ASM are diverse and include factors related to the individual patient, disease, and drug itself, as noted in Table 1. It is an important point to note that many ASMs are continued for at least two years, and often for life, and therefore a balance of risk and benefits needs to be considered not only for the short-term but also with respect to long-term treatment goals and outcomes, as well as risks (Scheffer et al., 2016).

Table 1. Factors considered in the selection of an antiseizure medication.

Category	Key factors and considerations
Individualfactors	Age
	Sex
	Ethnicity
	Genetics
	Lifestyle
	Socioeconomic factors (e.g., cost of drug)
Diseasefactors	Epilepsy characteristics (seizure type or syndrome)
	Etiology
	Comorbidities
	Familyhistory
	Pastmedicalhistory
Drugfactors	Concurrent medications (drug-drug interactions)
	Adversedrugreactions

The use of ASMs is intended to manage seizure activity, rather than modifying the underlying disease process itself. This has led to preferring the term 'antiseizure'

medications for epilepsy treatment. As the underlying disease process is not targeted by these drugs, their selection and suitability for specific classifications of epilepsy is largely reflected in cumulative trial data and a trial-and-error approach from clinical observations over time. However, as our understanding of epilepsy and associated therapies has developed, there are increasingly useful guidelines for selecting specific agents depending on the type of epilepsy and the characteristics of the patient and drug.

The success of phenytoin's discovery initiated a systematic search for compounds with antiseizure properties. This led to the development and marketing of more than ten novel antiseizure medications (ASMs), collectively known as the "first generation" ASMs. These drugs were primarily derived by modifying the barbiturate structure and included mephobarbital, primidone, trimethadione (oxazolidinediones), and ethosuximide (succinimides).

The "second generation" ASMs, introduced between 1960 and 1975, differed chemically from the first generation and included drugs like carbamazepine, valproate, and benzodiazepines. These second-generation drugs were noted for their improved tolerability compared to cyclic ureide-based structures, such as barbiturates, hydantoins, and succinimides.

This progression in ASM development, as depicted in Figure 3, highlighted the evolution from modifying existing structures to creating chemically distinct and better-tolerated medications (Löscher et al., 2017).

The third generation of antiseizure medications (ASMs) began in the 1980s with a shift towards "rational" drug development. Drugs like progabide and vigabatrin were designed with a specific focus on selectively targeting a mechanism known as GABAergic inhibition, which was believed to be crucial in the generation of seizures.

This shift in ASM development strategies aimed to improve the precision and effectiveness of treatments by directly addressing the underlying mechanisms of seizures. (Löscher et al., 1994).

Since the 1980s, several new antiseizure drugs (ASMs) have been introduced, offering various advantages over older medications. These advantages include improved pharmacokinetics, reduced drug-drug interactions, enhanced tolerability, and potentially fewer long-term adverse effects and lower teratogenicity. However, it's essential to note that the long-term effects and safety of these new drugs are still under investigation.

Despite these advancements, it's worth mentioning that the introduction of new ASMs has not significantly increased the percentage of patients achieving seizure freedom. The management of epilepsy remains a complex challenge, and achieving complete seizure control remains a goal yet to be fully realized(Devinsky et al., 2018, Chen et al., 2018, Perucca et al., 2020 &Löscher et al., 2011).

The development of third-generation antiseizure medications (ASMs) was greatly influenced by the Anticonvulsant Screening Program, now known as the Epilepsy Therapy Screening Program (ETSP). This program was established in 1975 by J. Kiffin Penry at the National Institutes of Neurological Disorders and Stroke, which is part of the National Institutes of Health. ETSP played a crucial role in screening and testing thousands of compounds, contributing significantly to the development of newer ASMs. It has been instrumental in advancing the field of epilepsy treatment by identifying and supporting promising drug candidates. (Porter RJ, et al., 2017).

Throughout its history, the Epilepsy Therapy Screening Program (ETSP) has conducted extensive testing on over 32,000 compounds, sourced from more than 600 pharmaceutical companies and various organizations. ETSP's contributions to the development of antiseizure medications (ASMs) have been substantial. Notable drugs that have benefited from ETSP's involvement include felbamate, topiramate, lacosamide, retigabine, and cannabidiol.

In addition to these major contributions, ETSP has also played a contributory role in the development of other ASMs, such as vigabatrin, lamotrigine, oxcarbazepine, and gabapentin. This program's comprehensive screening efforts have significantly advanced the field of epilepsy treatment by identifying and supporting the development of effective and innovative medications (Porter et al., 2017, Kehne et al., 2017 & Wilcox et al.,2020).

Cenobamate, a recent addition to the third generation of antiseizure medications (ASMs), received approval in 2019 for treating patients with focal-onset seizures. In randomized controlled trials, cenobamate demonstrated impressive results, with a significant proportion of subjects achieving seizure freedom. Specifically, during a 12-week maintenance period, the highest dose of cenobamate (400 mg/day) led to 20 out of 111 subjects (approximately 18%) becoming seizure-free. These findings

strongly suggest that cenobamate may outperform existing ASM options, offering new hope for individuals with focal-onset seizures. (French et al., 2020)

The positive results observed in the short-term randomized controlled trials for cenobamate have been confirmed and sustained in long-term open-label extension studies. This suggests that the promising seizure-free rates seen during the initial trials are maintained over an extended period. These findings provide additional evidence of cenobamate's effectiveness as an antiseizure medication and its potential as a valuable treatment option for individuals with focal-onset seizures. ((Klein et al., 2020).

Despite the positive results observed in both short-term and long-term studies, it is essential to emphasize that further safety studies and real-world clinical experiences are required to comprehensively assess the clinical value and safety profile of cenobamate.

While the initial findings are encouraging, ongoing research and monitoring will provide a more complete understanding of cenobamate's role in the treatment of epilepsy, ensuring that its benefits outweigh any potential risks.There is no difference between the first- and second-generation agents in terms of efficacy in managing epilepsy, providing treatment selectin is appropriate, although the second- (or third) generation agents are associated with more favorable side effect profiles and adverse event rates, often making them more attractive therapeutic options in contemporary practice (Mula et al., 2016). (Fig. 3),

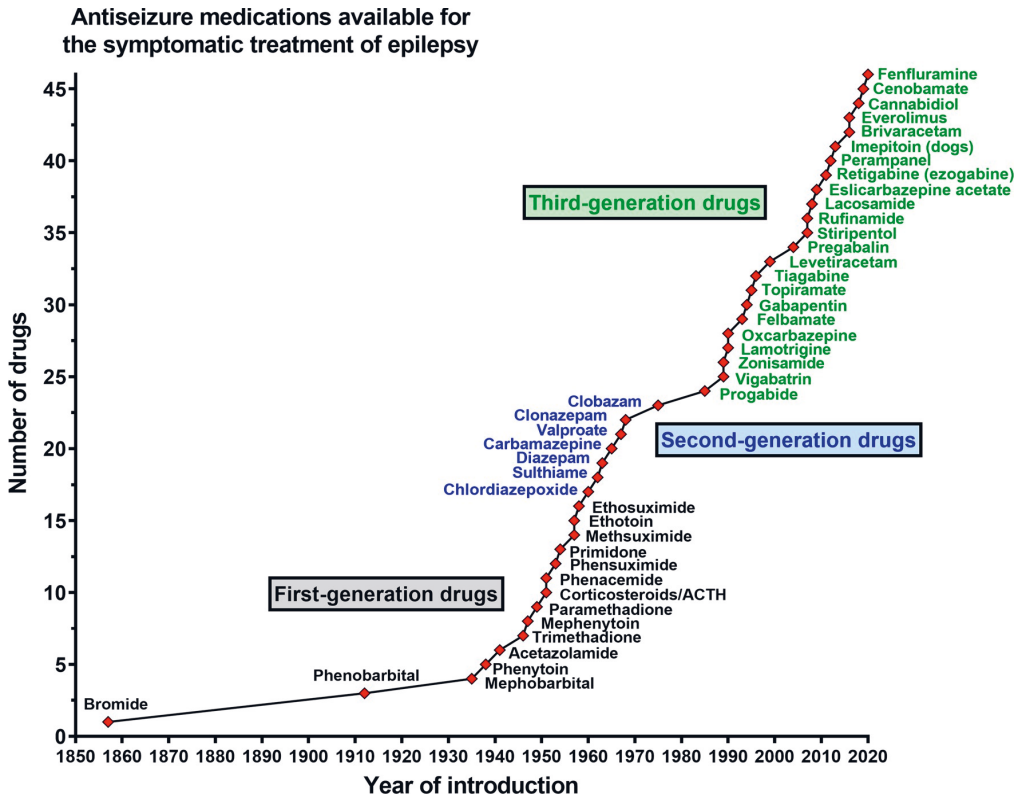


Figure.3 Introduction of antiseizure drugs (ASMs) to the market from 1853 to 2020. Licensing varied from country to country. Figureshows the year of first licensing or first mention of clinical use in Europe, the USA, or Japan. We have not included all derivatives of listed ASMs nor ASMs used solely for the treatment of status epilep- ticus. The first generation of ASMs, entering the market from 1857to1958,includedpotassiumbromide,phenobarbital,andavariety of drugs mainly derived by modification of the barbiturate structure, including phenytoin, primidone, trimethadione, and ethosuximide. Thesecond-generationASMs,includingcarbamazepine,valproate valproate,

and benzodiazepines, which were introduced between 1960 and1975, differed chemically from the barbiturates. The era of the third- generation ASMs started in the 1980s with "rational" (target-based) developmentssuchasprogabide,vigabatrin,andtiagabine,i.e.,drugs designed to selectively target a mechanism thought to be critical for the occurrence of epileptic seizures. Note that some drugs have been removed from the market. Modified from Löscher and Schmidt. For further details, see Löscher et al.2013. *ACTH* adrenocorticotropic hormone

The Standard versus New Antiepileptic Drugs (SANAD) study provided a comparison of numerous ASMs for the treatment of epilepsy for adults and children and noted how specific agents may be preferred for focal, generalized, or unclassified types of epilepsy (Marson et al., 2007). This study noted that, for focal epilepsies, CBZ, lamotrigine (LTG), and OXC were superior to GBP and topiramate (TPM), while LTG was associated with comparable efficacy and fewer side effects than CBZ in this context (Bonnett et al., 2012; Jacoby et al., 2015). Similar analyses (Bodalia et al., 2013) have tended to suggest that efficacy may be comparable between first- and second-generation agents when managing focal epilepsies, while safety and tolerability are often superior with second-generation agents, supporting the development of guidelines and treatment recommendations (Kanner et al., 2018; Perucca et al., 2018).

Additional outcomes from the SANAD study included an analysis of ASMs used for generalized and unclassified epilepsies (Bonnett et al., 2012). VPA was found to be superior to LTG and topiramate in this context, although VPA is not suitable in women of childbearing age (risk of teratogenesis), and side effects may also be limiting depending on individual patient characteristics and risk factors (Bodalia et al., 2013). It should be noted that the SANAD study focused on management of epilepsy in children and adults and, therefore, the likelihood of genetic epilepsies being included in the study is high (due to the frequency of genetic epilepsies in children) and may limit generalizability of the findings to etiologies linked to adult-onset epilepsy (Perucca et al., 2018). A summary of the ASMs typically used in practice and their efficacy in certain types of epilepsies is presented in Table 2.

Table 2. Efficacy of currently used antiepileptic drugs for specific types of epilepsy. Adapted from Perucca et al., 2018: 228).

Antiseizuremedication		Efficacyspectrum	Notes
Firstgeneration	Valproicacid	Allseizuretypes	Can induce tonic seizures when switching between drugs
	Benzodiazepines	Allseizuretypes	Can induce tonic seizures
	Carbamazepine	Focal and generalised tonic-clonic seizures	Can aggravate or precipitate absence seizures and myoclonic seizures
	Phenytoin	Focal and generalised tonic-clonic seizures	Can aggravate or precipitate absence seizures and myoclonic seizures
Second generation	Lamotrigine	Mostseizuretypes	Can aggravate or precipitate myoclonic seizures
	Levetiracetam	Mostseizuretypes	Efficacy limited against tonic and atonic seizures
	Oxcarbazepine	Focal and generalised tonic-clonic seizures	Can aggravate or precipitate absence seizures and myoclonic seizures
	Gabapentin	Focalseizures	Can aggravate or precipitate myoclonic seizures
Third-generation	Perampanel	Focal and generalised tonic-clonic seizures	-

ASM therapy, fundamental for the majority of epilepsy patients, centers around four primary objectives: to suppress seizures or significantly reduce their occurrence, to sidestep the long-term treatment's negative side effects, to support patients in upholding or reclaiming their customary psychosocial and professional pursuits, and to assist them in leading a standard lifestyle. (Bazil CW, at el., 2005). Initiating ASM therapy ought to be grounded in a thorough assessment of the potential for further seizures, the implications of persistent seizures on the patient, and the beneficial and adverse effects of the pharmacological agent chosen. (Ellenberg JH, at el., 1986).

Seizure activity should be closely monitored, and titration of the drug dose increased if seizure activity persists until a maximum tolerated dose is achieved or seizure freedom is achieved (Englot, 2018). When seizures are not controlled with first-line therapy, careful consideration should be given to factors such as the validity of the diagnosis and the degree of medication adherence exhibited by the patient before initiating a new treatment option (Perucca et al., 2018). It is estimated that 50% of patients should achieve seizure freedom based on low or moderate doses of the first-line ASM, although at least one-third of patients do not respond to this first-line agent even when dose escalation occurs (Kwok et al., 2017). In the event of treatment failure, a second-line ASM should be considered in monotherapy for that patient, based on the same criteria (i.e., patient factors, disease factors, and drug factors) as for the first-line therapeutic decision-making. Where the second agent fails to establish seizure control at appropriate or maximally tolerated doses, the patient can be considered to have DRE, which provides a management challenge, as considered below. Some ASMs like levetiracetam, brivaracetam, oxcarbazepine, eslicarbazepine, lacosamide, zonisamide, phenytoin, phenobarbital, and carbamazepine have straightforward titration or no titration, making them easier for patients to use and adhere to. In contrast, other medications like lamotrigine, topiramate, perampanel, or cenobamate may require more complicated and slower initiation to mitigate potential side effects.

2.6.1 Mechanisms of action ASMs.

In recent years, there have been significant breakthroughs in our comprehension of the mechanisms through which ASMs mitigate seizures. Current ASMs, as shown in Figure 4 and detailed in Table 3, exhibit a range of molecular mechanisms. These ASMs can be grouped into two categories: those that selectively target a single molecular pathway (e.g., certain sodium channel modulators) and those that have a broader spectrum of action, affecting multiple targets (e.g., valproate, topiramate, felbamate, and cenobamate). Typically, ASMs with multiple molecular targets also have a wider range of clinical applications (see Table 3).

The actions of most ASMs on molecular targets can be broadly categorized into four mains (Sills GJ, et al., 2020 &Rogawski MA, et al., 2016). Modulation of voltage-gated ion channels, which includes sodium, calcium, and potassium channels. 2. Enhancement of GABA-mediated inhibition by affecting various aspects of the GABAergic system, such as GABAA receptors, the GABA transporter (GAT)-1, GABA transaminase, or the GABA synthesizing enzyme glutamate decarboxylase.

3. Inhibition of synaptic excitation mediated by ionotropic glutamate receptors, including N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) receptors. 4. Direct modulation of synaptic release by targeting components of the release machinery, such as SV2A and the α2δ subunit of voltage-gated calcium channels (as outlined in Table 4).

These diverse interactions with various targets ultimately lead to changes in the inherent excitability of neurons or the modulation of fast inhibitory or excitatory neurotransmission. ASMs achieve a reduction in the likelihood of seizures by altering the bursting characteristics of neurons (lowering their ability to generate high-frequency action potentials), decreasing synchronization among specific groups of neurons, and inhibiting the propagation of abnormal firing to nearby and distant regions of the brain (Rogawski et al., 2016). Inhibition of carbonic anhydrases plays a role in the mechanism of action of certain ASMs, including acetazolamide, topiramate, and zonisamide (as shown in Table 3). This inhibition affects the $HCO3^{-}/CO2$ buffering system, resulting in systemic acidosis, including in the brain. The decrease in brain pH helps to dampen neuronal excitability, contributing to the antiseizure effects of these medications (Rogawski et al., 2016). Carbonic anhydrase inhibitors' protective effect in generalized seizures is linked to the heightened pH sensitivity of hyperpolarization-activated and cyclic nucleotide-gated (HCN) channels in thalamocortical neurons. Dysregulation of HCN channels has been strongly implicated in various epilepsy models and human epilepsy, including temporal lobe epilepsy (TLE). Apart from carbonic anhydrase inhibitors, other ASMs like lamotrigine and gabapentin have been reported to influence the hyperpolarization activated (Ih) current conducted by HCN channels (Brennan et al., 2016).

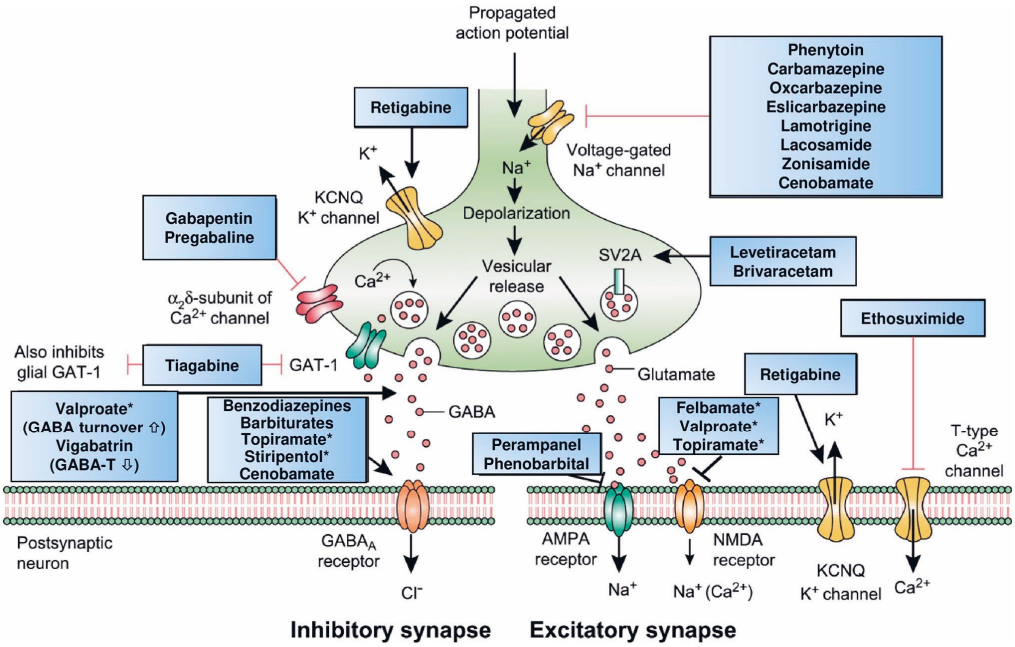


Figure.4 Mechanism of action of clinically approved antiseizure medi- cations (ASMs) [Schidlitzki A et al., 2020). Updated and modified from Löscher and Schmidt and Löscher et al. 2012. Asterisks indicate that these compounds act by multiple mechanisms (not all mechanisms shown here).SomeASMs,e.g.,fenfluramine,arenotshownhere,buttheir mechanism(s) of action are described in Table 2. *AMPA* α-amino-3- hydroxy-5-methyl-4-isoxazolepropionic acid, *GABA* γ-aminobutyric acid, *GABA-T* GABA aminotransferase, *GAT-1* GABA transporter 1, *KCNQ*Kv7potassiumchannelfamily,*NMDA*N-methyl-D-aspartate, *SV2A* synaptic vesicle protein 2A.

Table3. Spectrum of antiseizure effects of approved antiseizure medications in preclinical seizure models and patients with epilepsy

Drug	Efficacy in preclinical rodent models					Clinical efficacy					
	Primary generalized tonic-clonic seizures (MES Test)	Focal seizures (6-Hz test; 32 or 44 mA)	Focal seizures (kindling)	Absence seizures rat strains) (GAERS or WAG/R	Focal-onset ij seizures	Primary generalized seizures			Lennox–Gastaut syndrome	Infantile spasms (West syndroe)	Dravet syndrome
						Tonic-clonic	Absence	Myoclonic			
Acetazolamidea	+	?	?+	?	?+	?+	?+	?+	?	?	?
Brivaracetam	+	+	+	+	+	?+	?+	?+	?	?	?
Cannabidiol	+	+	?+	?	+	?	?	?	+	?	+
Carbamazepine	+	?+	+	0	+	+	0	0	0	0	0
Cenobamate	+	+	+	+	+	?	?	?	?	?	?
Clobazam	+	+	+	?	+	+	?	+	+	?+	+
Clonazepama	+	+	+	+	+	+	?	+	?+	?+	?+
Eslicarbazepine acetate	+	+	+	?	+	?	?	?	?	?	?
Ethosuximide	0	0	0	+	0	0	+	0	0	0	?+
Felbamate	+	+	+	?	+	+	?+	?	+	+	?
Fenfluramine	?+	?+	0	?	?	?	?	?	?	?	+
Gabapentin	+	+	+	0	+	?+	0	0	?	?	0
Lacosamide	+	+	+	?	+	+	?	?	?	?	?
Lamotrigine	+	0	+	+	+	+	+	+	+	?+	0

Levetiracetam	0	+	+	+	+	+	?+	+	?+	?	+
Oxcarbazepine	+	?	+	0	+	+	0	0	0	0	0
Perampanel	+	+	+	0	+	+	?+	?+	?+	?	?+
Phenobarbital	+	+	+	+	+	+	+	0	?	?	?+
Phenytoin	+	? +	+	0	+	+	0	0	0	0	0
Pregabalin	+	+	+	0	+	?	?	?	?	?	0
Primidone	+	?	0	0	+	+	0	?	?	?	?
Retigabine (ezogabine)b	+	+	+	0	+	?	?	?	?	?	?
Rufinamide	+	+	0	?	+	+	?+	?+	+	?	0
Stiripentol	+	?	?	?	+	+	?+	+	?+	?+	+
Sulthiamec	+	?	?	?+	?	?	?	?	?	?+	?
Tiagabine	0	+	+	0	+	?	0	?	?	?+	0
Topiramate	+	0	+	+	+	+	?	+	+	?	+
Valproate	+	+	+	+	+	+	+	+	+	+	+
Vigabatrin	0	?	+	0	+	?+	0	0	?	+	0
Zonisamide	+	+	+	?	+	?+	?+	?+	?+	?+	+

Data sourced from various publications, (Shorvon et al., 2020) (Löscher et al., 2016)(Guignet et al., 2020)(Stephen et al., 2009)(Welzel et al., 2021)(Wirrel et al., 2019) and a PubMed search of recent literature

GAERS genetic absence epilepsy rat from Strasbourg, *Hz* Herz, *MES* maximal electroshock seizures, *WAG/Rij*Wistar Albino Glaxo from Rijswijk, + indicates efficacy, 0 indicates inefficacy or worsening of seizures,?+ indicates inconsistent or preliminary findings, ? indicates insufficient data

ALoss of efficacy (tolerance) during chronic administration

B Withdrawn in 2017

CUsed in Europe in self-limited childhood (rolandic) epilepsy with centrotemporal spikes

Table 4. Molecular targets of clinically used antiseizure medications. Mechanistic classes of antiseizure medications. Anti seizure medications that belong to this mechanistic class.

Modulatorsofvoltage-gatedsodiumchannels	
Increaseoffastinactivation(transientsodiumcurrent;I_{NaT})	Phenytoin,fosphenytoin[a],carbamazepine,oxcarbazepine[b],eslicarbazepineacetate[c],lamotrigine;possiblytopiramate,zonisamide,rufina- mide, brivaracetam
Increaseofslow inactivation	Lacosamide
Block of persistent sodium currents (I_{NaP})	Cenobamate,lacosamide,carbamazepine,oxcarbazepine,eslicarbazepine, lamotrigine, phenytoin, topiramate, valproate, gabapentin, cannabidiol
Blockersofvoltage-gatedcalciumchannels(T-type)	
High-voltageactivated	Phenobarbital,phenytoin, levetiracetam
Low-voltage activated T-type (Ca_v3)	Ethosuximide ($Ca_v3.2>Ca_v3.1$),methsuximide,eslicarbazepine ($Ca_v3.2$); possibly valproate
Activatorsofvoltage-gatedpotassiumchannels(K_v7)	Retigabine(ezogabine)
ModulatorsofGABA-mediatedinhibition	
Allosteric modulators of $GABA_A$ receptors	Phenobarbital,primidone,stiripentol,benzodiazepines,(includingclonazepam, clobazam, diazepam, lorazepam, and midazolam), topira- mate, felbamate, retigabine (ezogabine), cenobamate
InhibitorsofGAT1GABAtransporter	Tiagabine
InhibitorsofGABAtransaminase	Vigabatrin

Activatorsofglutamicaciddecarboxylase	Possiblyvalproate,gabapentin,pregabalin
Inhibitorsofionotropicglutamatereceptors	
AntagonistsofNMDAreceptors	Felbamate,topiramate,possibly valproate
AntagonistsofAMPAreceptors	Perampanel,phenobarbital, levetiracetam
Modulatorsofthepresynapticreleasemachinery	
SV2A	Levetiracetam,brivaracetam
α2δsubunitofcalciumchannels	Gabapentin, pregabalin
Inhibitorsofcarbonicanhydrase	Acetazolamide,sulthiame,topiramate,zonisamide;possibly lacosamide
Serotonin-releasingagents	Fenfluramine
Disease-specificmodulators	
InhibitorsofmTORC1signaling[d]	Everolimus
Lysosomalenzymereplacement[e]	Cerliponasealfa(recombinanttripeptidylpeptidase1)
Mixed/unknown	Valproate,felbamate,topiramate,zonisamide,rufinamide,adrenocorticotrophin, cannabidiol, cenobamate, potassium bromide

AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *GABA* γ-aminobutyric acid, *GAT* GABA transporter, *mTORC1* mechanistic tar- get of rapamycin complex 1, *NMDA* N-methyl-D-aspartate, *SV2A* synaptic vesicle protein 2A

[a]Fosphenytoinisaprodrugforphenytoin

[b]Oxcarbazepineserveslargelyasaprodrugforlicarbazepine,mainlyS-licarbazepine (eslicarbazepine)

[c]Eslicarbazepineacetateis aprodrugfor S-licarbazepine(eslicarbazepine)

[d]Inpatientswith epilepsydue totuberous sclerosiscomplex

[e]Inpatients with epilepsydue to neuronal ceroid lipofuscinosis type 2

It's important to note that the mechanisms of action of ASMs, as outlined in Table 4 and Figure 4, primarily focus on their primary modes of action when known. Many of the drugs currently used to treat epilepsy may also have additional, less well-characterized pharmacological effects that become evident at therapeutic concentrations and could contribute to the drug's overall clinical effectiveness (Sills et al., 2020).

Furthermore, in recent years, novel epilepsy therapies have emerged that operate through disease-specific mechanisms. For instance, everolimus inhibits mTOR signaling in tuberous sclerosis complex (TSC), and cerliponase alfa is used for lysosomal enzyme replacement in neuronal ceroid lipofuscinosis type 2 (Sills et al., 2020). These treatments represent examples of "precision medicine," a relatively new field focused on disease-specific therapies that have the potential to revolutionize the treatment of genetic epilepsies (Sisodiyaet al., 2021).

There is growing optimism that we are on the brink of a new era in which specific treatments can be tailored for genetically defined epilepsies using targeted approaches like disease-mechanism-targeted small molecules, antisense, gene therapy utilizing viral vectors, and other biological methods (Sills et al., 2020). Such innovative therapies hold the potential to provide a cure for certain epilepsies (Carvill et al., 2020)

Additionally, it's worth noting that many scientists are actively working on developing novel antiepileptogenic therapies aimed at preventing epilepsy in individuals at risk following head injuries (Löscheret al., 2020). Antiepileptogenic and disease-modifying therapies are subjects of intense research in childhood epilepsies as well (Jozwiak et al., 2020). However, it's important to acknowledge that the involvement of the pharmaceutical industry in the development of these types of therapies for individuals at risk is currently limited.

2.7 Drug-resistant epilepsy and treatment options

Drug-resistant epilepsy is defined by the ILAE as the failure of two well-tolerated and appropriately chosen ASM schedules (either as single medications or in combination) to achieve sustained seizure freedom. (Kwan et al., 2010). It is estimated that only 15% of patients who fail two drug trials according to this definition achieved seizure-free status following the use of an additional ASM (Marson et al., 2007). It’s essential to rule out pseudo-resistance factors before labeling a patient as drug resistant. These factors include misdiagnosis of non-

epileptic conditions, improper antiseizure medication choice or dosage, and issues with patient adherence to treatment (Kwan et al., 2011).

The importance of DRE is that this patient group typically experiences excess disability, morbidity, and mortality compared to other patients with epilepsy, reflecting the persistence of seizures and long-term effects on wellbeing (Kwan et al., 2011). There are multiple factors linked to remission and terminal drug-resistant epilepsy, including the type of epilepsy (either idiopathic or symptomatic), EEG outcomes, frequency of seizures, and previous treatment. Notably, within the symptomatic epilepsy category, those with an encephalitis or meningitis origin tend to have a poorer prognosis compared to patients with different etiologies (Yang et al., 2021).

The biological basis of DRE is complex and not fully understood, but is likely to be multifactorial, involving various changes in neuronal circuitry, neurotransmitter receptors, ion channelopathies, reactive autoimmunity, and drug penetration to the seizure focus. Some of these changes may be a consequence of seizures. (Kwan and Brodie, 2000, Kwan et al., 2011).

The main hypotheses of the mechanisms leading to refractory epilepsy are summarized below, starting from the most-cited theories. None of the theories can explain the mechanisms of pharmacoresistance alone. (Kwan et al., 2011, Tang et al., 2017).It has been proposed that when the first ASM fails due to lack of efficacy, add-on therapy should be initiated immediately because it is more effective than its application after the second ASM failure, possibly due to the concept of seizures begetting seizures, i.e., secondary epileptogenesis (Kwan & Brodie et al.,2000)

Options to manage these patients are therefore typically linked to non-pharmacological treatments, including surgery and neuromodulation therapies, which may play a role in modifying disease course and outcomes (Kwan et al., 2011; Perucca et al., 2018).

It is estimated that approximately one-fifth of patients with epilepsy are eligible for surgical treatment on a global level (Vaughan et al., 2018). Surgical intervention is aimed at resecting or disrupting connections within epileptic tissue in the brain and may be considered one of the most effective treatment options in selected patients with DRE (Sheng et al., 2018). Eligibility for surgery requires a complex investigation to structural features of brain tissue, metabolic characteristics of tissue, and functional neuroimaging to determine the epileptogenic zone, as well as consideration of individualized patient risk based on post-operative morbidity and functional capacity (Nair et al., 2016).

While surgical intervention may be advised in patients who have failed appropriate drug trials of ASMs, there are concerns that delays in surgical intervention are often considerable, suggesting that surgical options are not considered in accordance with guidelines (Nair et al., 2016). However, although some authors support the use of surgical interventions after one or two failed drug trials, eligibility requirements for surgery, patient preferences, and the potential for morbidity following surgery may warrant the use of alternative treatments, including further attempts at pharmacological management (Sheng et al., 2018).

Challenges have been noted in predicting seizure freedom potential due to surgical intervention, where even comprehensive assessment and risk factor tools fail to predict outcomes with accuracy, supporting the need for careful consideration of treatment options in this patient group (Gracia et al., 2019; Witt et al., 2019). Indeed, as newer ASMs are developed and approved for use in practice, the criteria determining the use of surgical intervention should be revised accordingly (Perucca et al., 2018).

Alternative therapies may also be considered in additional to surgery in patients with DRE, although the evidence base supporting the use of such therapies is prone to some variability (Perucca et al., 2018). Neuromodulation therapies, such as vagus nerve stimulation, transcutaneous stimulation of the trigeminal nerve, and deep brain stimulation, have been associated with some clinical success but rarely lead to complete resolution of seizure activity (Nair et al., 2016). Refractory epilepsy poses a significant burden on the quality of life for its sufferers (Taylor et al. 2011). While resective epilepsy surgery is a potentially curative treatment (Wiebe et al. 2001, Téllez-Zenteno, Dwivedi et al. 2017), not all patients are eligible. For those who are not, deep brain stimulation (DBS) of the anterior nucleus of thalamus (ANT) offers a promising alternative.

In vagus nerve stimulation (VNS), electrical stimulation of the 10th cranial nerve is thought to exert antiepileptic effects by potentially modulating the thalamus within the limbic system via the nucleus tractus solitarius. However, the precise mechanism of this action remains a subject of ongoing research and is not yet fully understood (Rutecki et al., 1990). VNS has been reported to reduce focal seizure frequency by 30–50% in at least half of treated patients (Ryvlin et al. 2014, Cukiert et al., 2015). Responsive focal cortical neurostimulation (RNS) has shown promise in treating refractory focal onset seizures, but it is currently only available in the United States (Heck et al. 2014).

Dietary modification, including adoption of a ketogenic diet, may have a role in some patients, but, again, there is little consistent evidence supporting the potential

for seizure-free outcomes across patients with epilepsy (D'Andrea et al., 2019). Considering the limitations of these strategies in current practice, an increasing focus is placed on targeted therapies and pharmacogenomic or tailored approaches to intervention, based on an improved appreciation of etiological factors underlying epilepsy (Franco & Perucca et al., 2015).

The use of precision medicine in this manner remains an attractive therapeutic possibility, and further evaluation of drug therapies in concert with an appreciation of molecular mechanisms or epilepsy should be considered (Balestrini &Sisodiya, et al., 2018). Combined drug therapies and rational approaches to ASM use may present opportunities to overcome many limitations linked to drug-resistant epilepsy therapy, as considered below.

2.8 Rational combination therapy and polytherapy

It has often been considered that monotherapy is the optimal strategy for drug treatment of epilepsy in order to minimize the risk of drug-drug interactions and adverse events linked to drugs that often have a risk of serious side effects (Verrotti et al., 2020). However, it is increasingly recognized that rational approaches to combining therapies may be a reasonable treatment strategy based on patient prognostic profiling and may even be indicated prior to introducing a second-line agent for some patients (Abou-Khalil et al., 2017). Indeed, combining therapies has the potential to target multiple or complementary pathways relating to neurotransmitter signaling and seizure activity, enhancing efficacy and potentially facilitating dose reduction of individual agents (Park et al., 2019). However, selection of therapies when used in combination are typically based on the need to reduce drug-drug interactions and ensure treatment safety, given the current limitations relating to knowledge of molecular pathways and synergy in drug targeting approaches (Verrotti et al., 2020).

Combinations of ASMs have been successfully used in clinical trials, and there is some evidence supporting the synergistic effects of drugs in combination and a high level of tolerability in specific patients or patient groups (Abou-Khalil et l., 2017). The synergistic effects of combined therapy with LTG and VPA has been demonstrated in the literature (Gavzan et al., 2015), although there is little evidence for consistent synergistic effects with other drug combinations outside of unique syndromes (Abou-Khalil et al., 2017; Perucca et al., 2018).

It has been observed in *in vitro* investigation of drug combinations that the use of LTG and VPA provides a unique approach to targeted multiple pathways that are linked to seizure activity (epileptiform discharges), while VPA and phenytoin

combinations may also have a pronounced effect on such activity (Taing et al., 2017). However, clinical evidence is needed to support synergistic effects and to justify the use of these combinations in patients. Combining therapies rationally requires an appreciation of the side effects of the individual agents and careful dose monitoring to ensure that interactions are minimized, and patient safety achieved (Perucca et al., 2018). Local and national guidelines should be followed in such instances, while further evidence is needed to support evidence-based practice in this field of complex management and long-term care (Perucca et al., 2018).

Polytherapy is typically only used when at least two or three drug trials (monotherapy) have failed or where dual therapy has been used and the addition of alternative agents is considered (Verrotti et al., 2020). The decision to combine three or more drugs should be carefully weighed against the use of alternative therapies and the potential benefits of exploring alternative agents and regimens. The likelihood of drug-drug interactions and poor tolerability in polytherapy is high, and there is little evidence supporting the use of polytherapy based on clinical trial data. However, for a subset of patients unresponsive to monotherapy or dual therapy and ineligible for surgical interventions, there may be little alternative to achieve seizure freedom in the long term (Verrotti et al., 2020). It remains important to ensure that key treatment outcomes are achieved, and that dose control is optimised to ensure a favourable risk-benefit profile to patients, even with polytherapy, as discussed in the following section.

3 TREATMENT OUTCOMES AND MEASUREMENTS

The outcomes of pharmacological therapy are generally based on the potential for seizure-freedom, taking into account the retention rates of drugs when used according to the defined daily dose (DDD) assigned by the WHO (2019). Seizure-freedom is defined according to a lack of seizure activity for at least one year without any change in drug dosage at last follow-up (Brodie et al., 2013). It has been noted that this definition is commonly employed in clinical trials, although variability in follow-up and in methods to determine seizure activity presents some issues in interpreting data for different drugs and when applying the data to long-term seizure freedom contexts (Halford and Edwards, 2020).

Furthermore, there is often discrepancy between DDD and prescribed daily dose (PDD) among patients with epilepsy (Kim et al., 2021). This discrepancy relates to the application of DDD to patients taking combined ASMs (the original intention of DDDs was to define safe doses for combined therapy), in addition to dose alterations to promote tolerability or to tailor therapy to patient characteristics (Horvath et al., 2017). It has been noted that PDDs at approximately 75% of recommended DDDs is common for both monotherapy and dual therapy with ASMs and is associated with seizure freedom without any compromised efficacy (Horvath et al., 2017).

This is an important finding, as this level of dosing below the DDD is only efficacious in newer ASMs, while older agents (e.g., CBZ and VPA) were often prescribed at higher doses, which was required to achieve seizure freedom (Kim et al., 2021). Therefore, the DDD should be carefully considered as a criterion for achieving seizure freedom, as newer agents may achieve seizure freedom at lower doses, potentially reducing adverse events and risks, suggesting a favourable risk-benefit profile compared to older agents (Perucca et al., 2018). Careful quantification of DDD is therefore needed for both monotherapy and combined therapy with ASMs, and evaluation of the PDD/DDD is needed for newer agents to predict the potential for seizure freedom.

Retention rates of ASMs are often reported in the published literature but may be difficult to apply to the clinical setting due to inconsistencies in measuring retention rates and challenges in comparing trial data (Toledo et al., 2018). However, an analysis of ASM retention rates in clinical trials suggests that, over 52 weeks, the retention rate is typically 63–70% (Toledo et al., 2018). This figure is generally reflected across trials, and long-term data suggest that retention rates continue to fall

over time, averaging between 44.2 and 74.1% over two years of follow-up (Chung et al., 2007).

The primary reasons for poor retention rates for specific agents included poor efficacy and sedating side effects, while other side effects and reactions or adverse events were also key causes of low retention rates over a period of months to years (Chung et al., 2007). Due to heterogeneity in the method used to calculate retention rates, there is little evidence to suggest that one agent is superior to another consistently across patient groups (Toledo et al., 2017; Toledo et al., 2018). Therefore, both clinical criteria and patient preferences may determine retention rates of ASMs in practice (Perucca et al., 2018).

The optimal design of trials to consider retention rates of ASMs should include measures of efficacy and tolerability, as well as patient preferences, adherence, and discontinuation rates (Van der Meer et al., 2019). These trials are challenging to conduct over a long-term period, and, therefore, there remains uncertainty over the optimal assessment of ASM retention to inform the potential for long-term benefits and retention (Perucca et al., 2018).

A recent evaluation that considered the role of competing risks/events (e.g., death) in modifying retention rates noted that epilepsy survival rates after 2- and 5-years may be significant factors influencing estimations of retention rates of ASMs (Van der Meer et al., 2019). Other studies have also suggested that estimation of retention rates by two years of follow-up appears to be sufficient to predict long-term retention, based on the occurrence of side effects or poor tolerability by this point and sustained efficacy, leading to a flattening of the retention rate curve over time (Liguori et al., 2018).

However, questions remain regarding the degree to which ASM use is retained consistently across patient groups and in subtypes of epilepsy. Therefore, optimization of drug choice and use, including strategies to minimize poor tolerability and enhance efficacy, need to be considered in the effective long-term management of epilepsy (Van der Meer et al., 2019).

4 PURPOSE OF THE STUDY

This dissertation presents the design and results of a study intended to provide a basis for optimizing the management of patients with epilepsy through the use of ASMs, which may have an impact on patient wellbeing and long-term health outcomes. As noted in the review of the literature, there remain significant gaps in the evidence base regarding the use of ASMs, including new agents, on clinical outcomes in patients with epilepsy, as well as long-term retention rates of ASMs in patient populations. The aim of this study was to determine the optimal ASM approach to minimizing adverse events and maximizing the efficacy of ASM therapy, taking into account patient characteristics and drug characteristics over the long term. To achievethisaim, thefollowingobjectiveswereassessed:

- To investigate the interaction among the efficacy, tolerability, and overall effectiveness of the first antiseizure medication in patients 16 years or older with newly diagnosed epilepsy.

- To study evaluated the seizure freedom rates of substitution or add-on and subsequent ASM therapies using different proposed definitions of DRE or ASM trials in patients with a failed first ASM. We also identified prognostic factors for 1-year seizure freedom.

- To evaluate the effect of distinct clinical features on required ASM doses to achieve seizure freedom with newly diagnosed epilepsy.

- To investigate the ASM doses required to achieve seizure-freedom and their correlation with the WHO DDDs in newly diagnosed epilepsy.

5 SUBJECTS AND METHODS

5.1 Definitions

Key definitions are provided here to ensure consistency in the terminology applied to the research process and analysis of data, as well as facilitating validity in the research process with regards to the defined outcomes. The definition of epilepsy includes two main criteria: at least two unprovoked or reflex seizures occurring more than 24 hours apart, or one unprovoked seizure and a probability of further seizures equivalent to at least 60% (general recurrence risk) after two unprovoked seizures occurring over the next ten years. The seizures should be attributable to an underlying etiological mechanism consistent with epilepsy or status epilepticus and not associated with other causes (Fisher et al., 2014). However, patients with epilepsy of a known or unknown etiology were considered in this evaluation, consistent with the classification employed by Scheffer (Scheffer et al., 2016).

All patients included in the study were adults eligible for treatment at the epilepsy clinic, which, according to local guidelines, led to the definition of adults as individuals 16 years or older (at the time of the study initiation). All patients were diagnosed with some form of epilepsy, either focal epilepsy or generalized epilepsy, according to standardized procedures and local guidelines to ensure consistency in the definition of this patient group. In contrast, refractory epilepsy was defined according to persistent seizures after trials of at least two ASMs with maximally tolerated doses, either sequentially or as part of combination therapy (Kwan et al., 2011). The definition of seizure-free status in the present study was dependent on a lack of any seizure activity (recorded or self-reported) over the past 12 months (Falco-Walter et al., 2018).

With regards to the use of ASMs and outcomes associated with pharmacological therapy, adverse events (AEs) were classified according to standard criteria, with intensity defined as mild, moderate, or severe. Mild AEs were defined as those that did not interfere with daily activities; moderate AEs interfered with, but did not prevent, daily activities; and severe AEs were defined as incapacitating or severely restricting daily activities (Goldfarb et al., 2012).

5.2 Study patients

The patients were previously untreated patients who were referred to Tampere University Hospital for the diagnosis and treatment of epilepsy. No criteria were used to limit or exclude participation among different sociodemographic groups or according to other patient characteristics that may inadvertently introduce discriminatory practice or bias in the final data set (Piantadosi et al., 2017). The ethical recruitment and treatment of patients for the study are both considered at the end of this chapter, despite the lack of active patient participation and reliance on retrospective evaluation of clinic notes.

Sampling was conducted in a purposive manner to ensure that all participants met the inclusion criteria of the study, with analysis of patient charts and review notes used to identify those eligible for inclusion. Patients aged 16 years or older referred to the Tampere University Hospital between January 1, 1995, and December 31, 2006, who were diagnosed with epilepsy were identified. Data was collected until December 31, 2007, or until reaching at least one year of seizure freedom, or until their deaths if before this cut-off date. Medical records of the patients, including clinic visits, demographic, and clinical information from the patients, were examined retrospectively. Additional studies carried out were registered.

All the epilepsy diagnoses were re-evaluated by a neurologist Hersi Hire (HH) applying the new criteria for the definition of epilepsy. Any ambiguities were resolved by discussions with three neurologists (HH, JS, JP) until consensus was reached. Patients with alcohol and recreational drug abuse were excluded.

5.3 Methods

This study was a retrospective chart review, a method selected to allow for data collection from a large number ofparticipants meeting key criteria defined above. The retrospective chart review included data based on demographic and baseline clinical characteristics of the included patients, along with drug dosing and details, seizure freedom rates, and drug retention rates according to a multitude of therapeutic regimens.

Although all patients included in the study were diagnosed with epilepsy, the chart data were evaluated to confirm this diagnosis and to relate the epilepsy classification to possible etiology, based on available clinical and neuroimaging data. Nearly all

patients underwent at least once a surface EEG performed by neurophysiologists, either using a standard approach or testing the patients after sleep deprivation, to look for interictal changes that might aid in the diagnosis, help to identify the seizure focus, and facilitate the classification of epilepsy type. Clinical practice at the time of the patient treatment showed a preference for avoiding a diagnosis of unknown epilepsy type; all patients with no evidence of generalized epilepsy were diagnosed as focal epilepsy patients.

Neuroimaging, particularly computed tomography, or magnetic resonance imaging was performed and evaluated by neuroradiologists to screen for underlying structural abnormalities that might have caused epilepsy. Information obtained from the history, physical examination, and other studies were used to classify the patient's epilepsy etiology, since it has implications for prognosis and the approach to treatment.

For all patients who were given a diagnosis of epilepsy, ASM therapy was initiated according to standard clinical practice at that period. Subsequently, patients were followed at the epilepsy clinic according to routine clinical practice, at least until one year of seizure freedom was achieved with the first ASM regimen in the present study. At the follow-up visit, clinical information, and the response to ASM therapy were recorded. ASM doses were adjusted as clinical circumstances dictated, with particular attention paid to efficacy and tolerability.

5.4 Data analysis and statistical methods used at first publication.

This retrospective study included 584 previously untreated patients aged 16 years or older who were referred to Tampere University Hospital for the diagnosis and treatment of epilepsy. After thorough validation of epilepsy diagnosis, 459 patients were finally included in the study. The patients were followed until they reached at least one year of seizure freedom or until their deaths. The medical records of the patients were examined, and the epilepsy diagnoses were re-evaluated using new criteria. The study analyzed the impact of the first ASM regimen on clinical outcomes, the effects of age, sex, and patient characteristics on long-term retention rates of ASMs, and the effectiveness of second- and third-line ASM therapy.

The data were analyzed using statistical tests such as the Mann-Whitney U-test, Pearson's chi-squared test, Fisher's exact test, and binary logistic regression also with Stata version 15.1 (College Station, TX: StataCorp LLC). The study was approved by the Head of Tampere University Science Centre, and there was no contact with patients as the information was collected from the patient register.

5.5 Data analysis and statistical methods used at second, third and fourth publications.

A total of 459 patients were finally included in these studies. ASM therapy was initiated according to standard clinical practice, and patients were followed up until at least 1 year of seizure freedom was achieved or until death.

Baseline characteristics were described using medians or frequencies. Group comparisons were made using Pearson's chi-square test, Mann-Whitney U test, or Fisher's exact test, and binary logistic regression was used to examine the association between seizure freedom and various factors.

Depending on the variable group, comparisons were performed by using the Mann–Whitney U-test, the Kruskal–Wallis test, the Pearson's chi-squared test, or the Fisher's exact test. Binary logistic regression was used to examine the association between seizure freedom by 1st ASM and sex. Age at date of diagnosis (continuous), seizure type (with focal to bilateral tonic-clonic seizures as a reference group), epilepsy type (focal as a reference group), and ASM (OXC as a reference group) were examined as potential confounding factors. An odds ratio (OR) with a 95% confidence interval (CI) was calculated for each covariate; statistical significance was set at the level of alpha < 0.05. The data were analyzed with Stata version 16.1 (College Station, TX: StataCorp LLC).

5.6 Ethical aspects

In this retrospective study, there was no contact on patients and the information was collected from patient register of Tampere University hospital. The study was approved by the head of the Tampere University Science Center This study does not require ethics committee approval according to Finnish Law on Research.

No patient identifiable information was used in the process of data analysis and in the presentation of the findings, and any such data were stored on encrypted hard drives and managed according to local data management procedures to ensure confidentiality and privacy of participants (Breault et al., 2013). Only the lead researcher always had access to such information; if additional researchers were needed, then access was granted only if appropriate to do so for completion of the study. No information was shared outside of the research group to ensure that confidentiality was maintained and that the risk of inappropriate use of private patient data was minimal. The minimum data needed to complete the study was used to ensure that patient privacy was maintained (Vassar & Matthew et al., 2013).

6 RESULTS

6.1 Study I. Response to first antiseizure medication in patients diagnosed with epilepsy.

After thorough validation of the epilepsy diagnosis, 101 patients were excluded because of uncertainty of epilepsy diagnosis or because epilepsy was not newly diagnosed. Additionally, 24 patients (5.0%) died within the first year after ASM therapy was initiated and were excluded for not being able to reach the end point of the one-year follow- up for the study. A total of 67.1% patients (308 of 459) became seizure-free following administration of the first ASM.

At time of diagnosis, 56.6% (n=260) of patients were aged 25 to 60 years. Age at diagnosis of epilepsy was 16–25 years in 20.3% (n=93) and above the age 60 years in 23.1% (n=106). The seizure freedom rate, defined as at least one whole year without seizures after initiation of the first ASM therapy, was 67.1% (n=308). Structural etiology for epilepsy was seen in 52.5% (n=241) of patients, with EEG reports available for 89.1% (n=409).

Focal epilepsy had a median age of diagnosis of 48 years. The seizure freedom rate was 66.8% (n=290), with significant differences according to sex (60.1% for females vs. 72.2% for males; P=0.008), etiology (69.4%, 66.7% and 46.2% for presenting seizure types FBTCS, FAS and FIAS, respectively) and epileptiform EEG (34.6% with a normal EEG). Patients with focal epilepsy were most often prescribed OXC (64.5%), CBZ (17.7%), VPA (10.8%), PHT (3.2%), and LTG (2.3%) as the first ASM. Seizure freedom rates for OXC, CBZ and VPA were 65.7%, 70.1% and 74.5%, respectively.

Patients with generalized epilepsy were younger than patients with focal epilepsy, with a median age of 18 years at diagnosis. The seizure freedom rate was 72.0% overall (90.0% in males vs 60.0% in females). VPA (68.0%) and LTG (20.0%) were the most prescribed ASMs.

Patients with epilepsy due to an unknown etiology had a higher rate of seizure freedom than patients with a structural etiology (OR 2.22; p = 0.003). In contrast, epileptiform activity in EEG decreased the odds of seizure freedom (OR 0.55; p=0.036). FIAS as a presenting seizure was linked to a lower rate of seizure freedom than patients with FBTCS (OR 0.52; p = 0.091).

OXC was discontinued due to side effects in 12.5% of patients. Discontinuation rates due to side effects were not significantly different for other first-line ASMs, such CBZ, LTG and VPA, with rates of 14.3%, 20.0% and 12.8%, respectively.

6.2 Study II: Response to subsequent antiseizure medications after first antiseizure medication failure in newly diagnosed epilepsy.

The responses to the first and subsequent ASM schedules of the 459 patients (see study I) are presented in Table 5. 151 patients who continued to have seizures constituted the present study group (Figure 5). The clinical characteristics of all 151 (32.9%) patients who did not become seizure-free either after the second ASM or after fulfilling the criteria for DRE (3rd or subsequent ASM regimens) are summarized in Table 6.

Patients who became seizure-free with the 2nd ASM regimen were older (mean age 51 years), more likely to have FBTCS or FAS as the presenting seizure type and had EEG without epileptiform activity. Patients with persistent seizures were significantly more likely to have epileptiform activity on EEG than those responding to the second ASM regimen. Patients aged 60 years or over were more likely to become seizure-free than those aged 25–60 years (75.6% vs 50.6%; OR = 2.75, p = 0.014).

Prognostic factors (sex, age at diagnosis, type of first seizure, etiology, and EEG) are shown statistically significant association with the chances of seizure freedom. Patients with epilepsy due to an unknown reason had a trend for higher odds (OR = 2.05, p = 0.114, 95% CI: 0.84–5.01) of seizure freedom than patients with structural etiology.

The seizure freedom rate with a second or subsequent ASM in focal epilepsy was 61.8%. The efficacy of individual ASMs when used in monotherapy and polytherapy was combined for the treatment of focal epilepsy, was not significantly different except for tiagabine, ORs for seizure freedom 0.08 (0.007-0.98). CBZ had the highest seizure freedom rate (64.4%), followed by OXC, PHT, and VPA (55.8%, 55.2%, and 54.7%, respectively). There was no significant difference in achieving seizure freedom in any of the monotherapy regimens, whereas combinations of regimens had lower odds of seizure freedom: OXC/VPA (14.3%), OXC/GBP (23.1%), and OXC/LTG (30.8%). The highest rates of seizure freedoms were seen with LTG/LEV (57.1%), OXC/LEV (50.0%) and VPA/LTG (44.4%). The efficacy of different ASM groups based on the ASM (MOA) in focal epilepsy are presented. ASMs with enhanced GABA-mediated inhibitory neurotransmission were less effective than ASMs that modulated voltage-gated sodium channels (14.3% vs. 64.5%, OR = 0.08, p = 0.037).

Table 5. Antiseizure medication schedules

			Seizure freedom			
	# ASM Regimen	Total patients using these ASMs (*n*)	Total (*n*)	% of patients achieving seizure freedom with ASM	% of the total achieving seizure freedom (*n* = 406)	% of the total study cohort (*n* = 459)
All patients regardless of the reasons for the initiation of subsequent antiseizure medication	1	459	308	67.1	75.9	67.1
	2	151	59	39.1	14.5	12.9
	3	66	22	33.3	5.4	4.8
	4	30	9	30.0	2.2	2.0
	5	10	4	40.0	1.0	0.87
	6	6	2	33.3	0.5	0.44
	Total	459	406*	na	99.5	88.0
Patients who used subsequent antiseizure medication only due to lack of efficacy	1	459	346	75.4	85.2	75.4
	2	102	38	37.3	9.4	8.3
	3	40	11	27.5	2.7	2.4
	4	18	6	33.3	1.5	1.3
	5	5	3	60.0	0.7	0.65
	6	2	0	-	-	-
	Total	459	406*	na	99.5	88.0

ASM = antiseizure medication; na = not applicable; *n* = number; * = including two patients who became seizure free with epilepsy surgery

Table 6. Background characteristics (median and interquartile range or frequency and percentage) at the last clinic visit for all patients with epilepsy who did not become seizure free following administration of the first antiseizure medication.

	All patients	Seizure freedom		Persistent seizures	p^1	p^2
		After 2nd ASM	After 3rd or later ASM			
	151	59	39	53		
Sex, *n* (%)					0.178[3]	0.992[3]
Female	83 (55.0)	30 (50.8)	26 (66.7)	27 (50.9)		
Male	68 (45.0)	29 (49.2)	13 (33.3)	26 (49.1)		
Duration of follow-up, med (IQR)	4.2 (2.5–6.9)	2.6 (1.4–4.6)	4.7 (2.9–7.0)	6.0 (4.2–9.0)	0.001[4*]	<0.001[4*]
Age at diagnosis, med (IQR)	44 (27–59)	51 (35–70)	28 (21–53)	42 (31–53)	0.007[4*]	0.088[4]
Epilepsy type, *n* (%)					0.063[3]	0.497[5]
Focal	144 (95.4)	57 (96.6)	34 (87.2)	53 (100)		
Generalised	7 (4.6)	2 (3.4)	5 (12.8)	0		
Etiology, *n* (%)					0.161[3]	0.224[5]
Structural	94 (62.3)	35 (59.3)	22 (56.4)	37 (69.8)		
Genetic	7 (4.6)	2 (3.4)	5 (12.8)	0		
Infectious	6 (4.0)	1 (1.7)	2 (5.1)	3 (5.7)		
Unknown	44 (29.1)	21 (35.6)	10 (25.6)	13 (24.5)		
Type of 1st seizure, *n* (%)					0.021[3*]	0.095[5]
FBTCS	98 (64.9)	42 (71.2)	22 (56.4)	34 (64.2)		
FAS	25 (16.6)	12 (20.3)	4 (10.2)	9 (17.0)		

FIAS	21 (13.9)	3 (5.1)	8 (20.5)	10 (18.9)		
GTCS	3 (2.0)	1 (1.7)	2 (5.1)	0		
Myoclonic	4 (2.6)	1 (1.7)	3 (7.7)	0		
EEG, *n* (%)					0.004[3*]	0.011[3*]
Normal	51 (33.8)	28 (47.5)	9 (23.1)	14 (26.4)		
Epileptiform activity	42 (27.8)	9 (15.3)	17 (43.6)	16 (30.2)		
Focal slowing	20 (13.2)	7 (11.9)	5 (12.8)	8 (15.1)		
Unspecific	18 (11.9)	3 (5.1)	5 (12.8)	10 (18.9)		
No EEG	20 (13.2)	12 (20.3)	3 (7.7)	5 (9.4)		

[1] = p-value for comparison between seizure freedom after the 3rd or later ASM (two patients who became seizure-free after epilepsy surgery are not included) and seizure freedom after the 2nd ASM

[2] = p-value for comparison between persistent seizures and seizure freedom after the 2nd ASM

[3] = Chi-squared test

[4] = Mann-Whitney U test

[5] = Fisher's exact test

* Denotes statistically significant association using the Holm-Bonferroni correction (thresholds for the lower and higher p-value are 0.025 and 0.05)

ASM = antiseizure medication; FBTCS = focal to bilateral tonic-clonic seizures; FAS = focal aware seizures; FIAS = focal impaired awareness seizures; GTCS = generalised tonic-clonic seizures, IQR = interquartile range, med = median

Table 7. Odds ratios and 95% confidence intervals and p values from the logistic regression models for seizure freedom after second or subsequent antiseizure medications in patients with focal epilepsy

	Model 1		Model 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Sex (ref. = female)	0.95 (0.47–1.94)	0.898	0.81 (0.38–1.73)	0.594
Age at date of diagnosis	1.02 (1.00–1.04)	0.123	1.02 (0.99–1.04)	0.229
Type of 1st seizure (ref. = FBTCS)				
FAS	0.96 (0.38–2.44)	0.934	0.76 (0.28–2.01)	0.575
FIAS	0.63 (0.24–1.67)	0.352	0.64 (0.23–1.74)	0.382
Etiology (ref. = structural)				
Infectious	0.88 (0.16–4.90)	0.882	0.83 (0.14–4.79)	0.835
Unknown	2.05 (0.84–5.01)	0.114	1.72 (0.66–4.43)	0.264
EEG (ref. = normal)				
Epileptiform activity			0.60 (0.23–1.53)	0.283
Focal slowing			0.57 (0.17–1.91)	0.359
Unspecific activity			0.34 (0.10–1.14)	0.080
No EEG			1.05 (0.28–3.86)	0.944

CI = confidence interval; FAS = focal aware seizures; FBTCS = focal to bilateral tonic-clonic seizures; FIAS = focal impaired awareness seizures; OR = odds ratio; ref = reference group

In two logistic regression models, which were used to study seizure freedom after the administration of a second or subsequent antiseizure medication in patients diagnosed with focal epilepsy, none of the factors examined (sex, age, type of first seizure, etiology and EEG) showed a statistically significant association with the chances of seizure freedom.

Patients who had either an additional ASM added (add-on group, n=52) or their initial ASM substituted (substitution group, n=50) due to lack of efficacy, had nearly equal distribution of males and females in both groups with no significant difference (p=0.6981). Median follow-up duration was similar between groups (4.6 years for add-on, 4.5 years for substitution, p=0.3572), and median age at diagnosis was

slightly higher in the substitution (32.5 vs. 49.0) group but not significantly (p=0.0742).

Most patients had focal type epilepsy (over 94%) in both groups. Structural etiology was most common in both groups, followed by unknown etiology. No significant differences were noted in epilepsy type, etiology, or type of first seizure (p values: 0.9611, 0.5401, 0.5191, respectively). FBTCS was the most common type of first seizure in both groups.

Regarding EEG results, a normal EEG was most common, followed by epileptiform activity and unspecific activity, but differences were not statistically significant (p=0.7341).

Table 8. Different substitutions or add-on combinations of antiseizure medications were used at least five patients. Odds ratios (ORs) and 95% confidence intervals (CIs) and p values for seizure freedom from the multilevel logistic regression model adjusted for the order of medications.

	Seizure freedom				
	No, n (%)	Yes, n (%)	Total	OR (95% CI)	*p*
OXC	107 (35.8)	192 (64.2)	299	0.59 (0.33–1.06)	0.079
VPA	24 (29.6)	57 (70.4)	81	1.00 (reference group)	
CBZ	24 (30.8)	54 (69.2)	78	0.71 (0.34–1.48)	0.365
LTG	14 (48.3)	15 (51.7)	29	0.52 (0.21–1.29)	0.158
PHT	9 (37.5)	15 (62.5)	24	0.72 (0.27–1.91)	0.512
LTG+OXC	10 (71.4)	4 (28.6)	14	0.26 (0.07–0.96)	0.044
GBP+OXC	10 (76.9)	3 (23.1)	13	0.18 (0.04–0.77)	0.020
LEV+OXC	6 (50.0)	6 (50.0)	12	0.43 (0.11–1.67)	0.223
OXC+TPM	7 (63.6)	4 (36.4)	11	0.32 (0.08–1.30)	0.113
LTG+VPA	5 (55.6)	4 (44.4)	9	0.57 (0.13–2.59)	0.471
LEV	5 (55.6)	4 (44.4)	9	0.42 (0.09–1.90)	0.259
TPM	5 (62.5)	3 (37.5)	8	0.32 (0.07–1.51)	0.150
LEV+LTG	3 (42.9)	4 (57.1)	7	0.66 (0.11–3.88)	0.644
OXC+VPA	6 (85.7)	1 (14.3)	7	0.09 (0.01–0.86)	0.036
GBP	2 (40.0)	3 (60.0)	5	0.88 (0.13–5.77)	0.891

CBZ = carbamazepine; GBP = gabapentin; OXC = oxcarbazepine; LEV = levetiracetam; LTG = lamotrigine; PHT = phenytoin; TPM = topiramate; VPA = valproicacid

There was no significant difference in efficacies of different ASM groups based on the ASM mode of action in focal epilepsy, expectASMs with enhanced GABA-mediated inhibitory neurotransmission were less effective compared with ASMs that

modulated voltage-gated sodium channels (14.3% vs. 64.5%) but the finding was not significant when controlling the ASM regimen or combination number (OR = 0.04, p = 0.098).

OXC was the most discontinued medication with 73 total cases, primarily due to side effects (38 cases) and lack of efficacy (32 cases). CBZ and VPA were next, with total discontinuations of 20 and 19 cases respectively. Side effects were a leading reason for CBZ discontinuation, while lack of efficacy and side effects were nearly equal for VPA. LTG and PHT each had 11 total discontinuations, while TPM, Tiagabine, and Clobazam each had 7. The least discontinued drugs were Gabapentin and Levetiracetam, both due to lack of efficacy and side effects.

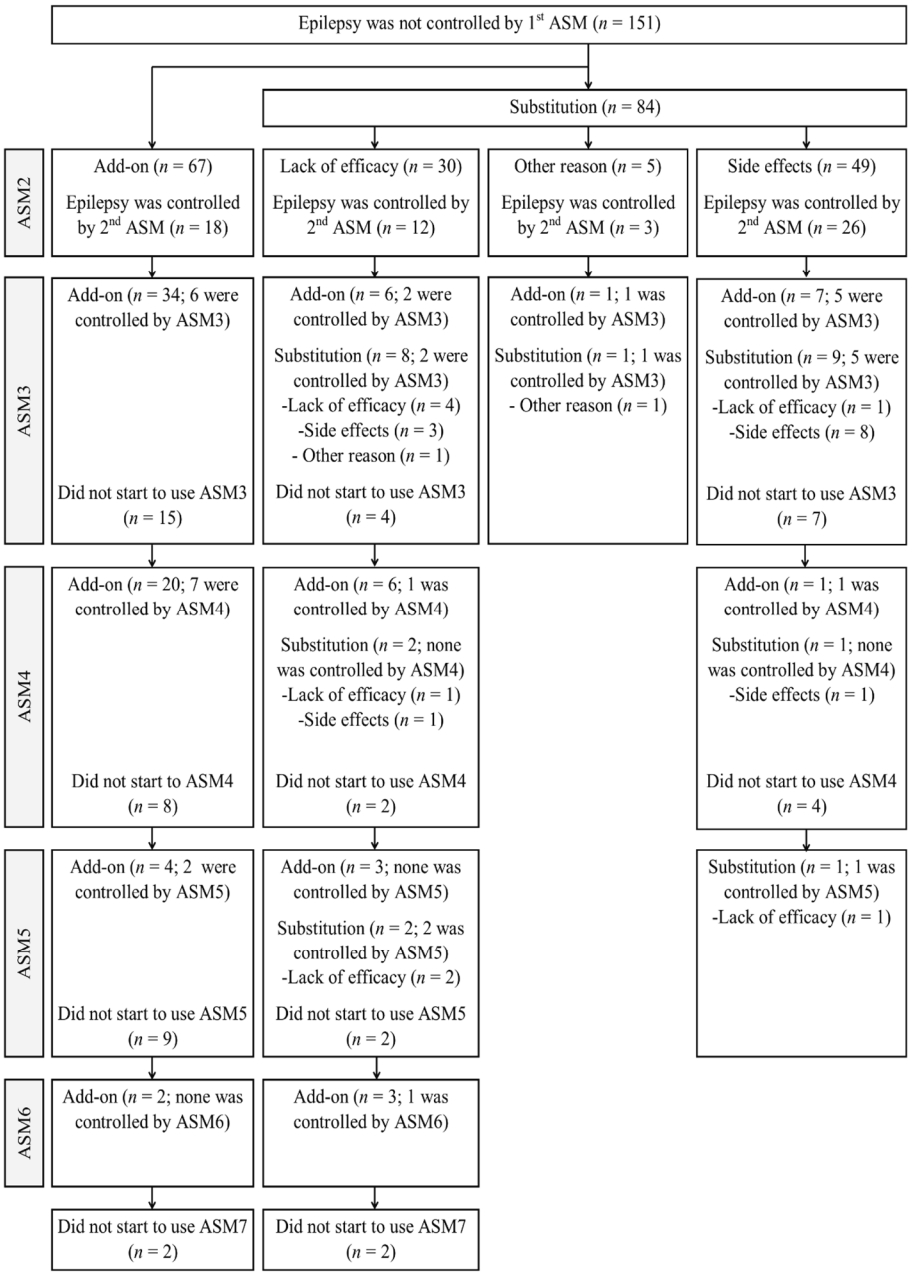


Figure 5. Patient responses to different combinations of the add-on and substitution ASM after seizure freedom.

6.3 Study III. The Effect of Clinical Features on Antiseizure Medication Doses in Patients with Newly Diagnosed Epilepsy

The study cohort comprised 251 (54.7%) male patients and 208 (45.3%) female patients. The median age at diagnosis was 45 years; 76.9% (353/459) of patients were aged ≤60, whereas 23.1% (106/459) were aged >60 years. The seizure freedom rate with the first or subsequent ASM was 88.0% (404/459). A total of 308 patients (75.9% of all patients achieving seizure freedom) became seizure-free following the administration of the first ASM regimen, 59 of 151 patients (14.5% of all patients achieving seizure freedom) became seizure-free following the administration of the second ASM regimen, and 37 patients became seizure-free after the third to fifth ASM regimens when all ASM trials were counted. The most prescribed ASMs were OXC (307, 66.9%) followed by VPA (115 25.1%), CBZ (81, 17.6%), and LTG (67, 14.5%). Among the patients who achieved one-year seizure freedom in the entire cohort, 10.1% (41/404) were on combination therapy.

Based on the unadjusted median regression model, difference in median doses of OXC between the seizure-free (median dose 900 mg) and not seizure-free (median dose 900 mg) patients with focal epilepsy was not found (Table 9, Model 1). However, after controlling age, the median dose of OXC was significantly lower (300 mg, $p=0.018$) for the seizure-free patients compared to not seizure-free patients (Table 7, Model 2. Moreover, there is also a significant relationship between age and dose of OXC in a way that the median dose of OXC was 300 mg lower among older patients than among their younger counterparts ($p<0.001$).

In seizure-free patients with focal epilepsy receiving mono- or polytherapy, no difference was found in median doses of OXC between males and females or between seizure-free and not seizure-free patients (both differences were 0 mg, Model 1 in Table 10). However, when adding age as an adjustment, a significant relationship between OXC dose and seizure-free and not seizure-free patients was found (difference in medians was 300 mg; $p=0.032$). Conversely for VPA using the same model there was a significant relationship in a way that the median dose of VPA was 400 mg higher in males than in females ($p<0.001$) and, also, 400 mg higher in not seizure free patients compared to seizure free patients ($p<0.001$). The latter finding remained when adding age as an adjustment (Model 2 in Table 9). There were no significant differences in medians between sexes in other ASMs (Table 10).

When combining age and sex categories to four different combinations (men ≤60 years, men >60 years, females ≤60 years, females >60 years), the median OXC doses for males aged ≤60 years was 300 mg higher than for females >60 years (900mg vs. 600mg, $p=0.021$). When applying same analysis for VPA, significant findings

emerged with women in both age groups with 400 mg lower median doses compared with men ≤60 years (600mg vs. 1000mg).

There were no significant differences in the doses of OXC according to seizure type (Table 11). In Model 2, where outcome was defined as ASM dose and exposure variables were seizure-freedom and 1st seizure type, significantly higher median doses for CBZ were registered with FAS compared with FBTCS (difference in medians 200 mg; p=0.017).

CBZ median dose was 200mg higher among patients with unspecific activity in EEG compared to patients with normal EEG (p=0.031). In contrast, median VPA dose was 400mg lower in patients with unspecific activity in EEG compared to patients with normal EEG (p=0.006).

Table 9. Antiseizure medication doses (median and interquartile range) in either mono- or polytherapy in categories of age in patients with focal epilepsy with seizure-freedom. Other antiseizure medications were used in less than 5 patients.

		Age ≤60 years		Age >60 years		Model1	Mode2	
	szf	*n*	median (IQR)	*n*	median (IQR)	Est. (p)[1]	Est. (p)[2]	Est. (p)[3]
Oxcarbazepine	Yes	178	900(600)	34	600(300)	0 (1.000)	-300 (0.018)	-300 (<0.001)
	No	71	1200(900)	22	600(300)			
Carbamazepine	Yes	43	400 (200)	15	400(200)	-200 (0.058)	-200 (0.070)	0 (1.000)
	No	17	750 (400)	5	400(200)			
Valproic acid	Yes	34	1000(400)	30	900(400)	0 (1.000)	-100 (0.616)	-100 (0.483)
	No	20	1100(950)	10	1000(800)			
Lamotrigine	Yes	27	200 (300)	2	138 (125)	-100 (0.075)	-100 (0.161)	0 (1.000)
	No	29	300 (200)	3	300 (400)			
Phenytoin	Yes	3	200 (300)	13	250 (100)	-50 (0.382)	-50 (0.555)	0 (1.000)
	No	5	300 (100)	6	250 (200)			
Levetiracetam	Yes	14	1000(1000)	3	1000 (0)	-500 (0.278)	-500 (0.299)	0 (1.000)
	No	19	1500(1500)	3	1000(700)			
Topiramate	Yes	8	300 (225)	2	175 (150)	0 (1.000)	50 (0.635)	-50 (0.631)
	No	18	275 (200)	1	200			
Gabapentin	Yes	4	2600 (800)	3	900 (400)	200(0.770)	400 (0.397)	-1200 (0.026)
	No	10	1900 (800)	2	1500(600)			

szf, seizure-freedom; IQR, interquartile range; n, number; Coef., estimate from the median regression model; p, significance; na, convergence not achieved.

Model 1: outcome = antiseizure medication dose, exposure variable = seizure-freedom

Model 2: outcome = antiseizure medication dose, exposure variables = seizure-freedom and age

[1] = estimate and significance of the seizure-freedom (ref. = no) from model 1

[2] = estimate and significance of the seizure-freedom (ref. = no) from model 2

[3] = estimate and significance of the age (ref. = ≤60) from model 2

Table 10. Antiseizure medication doses (median and interquartile range) in either mono- or polytherapy according to sex in seizure-free patients with focal epilepsy. Other antiseizure medications were used in less than 5 patients.

		Women		Men		Model 1		Model 2
	szf	*n*	median (IQR)	*n*	median (IQR)	Est. (p)[1]	Est. (p)[2]	Est. (p)[3]
Oxcarbazepine	Yes	90	900(600)	122	900(300)	0(1.000)	0 (1.000)	-300 (0.032)
	No	51	900(750)	42	1425(900)			
Carbamazepine	Yes	25	400(200)	33	400 (200)	-200 (0.065)	0 (1.000)	-200 (0.057)
	No	12	600(400)	10	650 (400)			
Valproic acid	Yes	22	750(400)	42	1000(400)	-400 (<0.001)	400(<0.001)	-400 (0.002)
	No	18	950(400)	12	1800(500)			
Lamotrigine	Yes	17	200(200)	12	150 (200)	-100 (0.188)	0 (1.000)	-100 (0.174)
	No	19	200(350)	13	350 (100)			
Phenytoin	Yes	10	225(100)	6	250 (100)	-100 (0.111)	-50 (0.420)	-50 (0.528)
	No	6	350(150)	5	300 (100)			
Levetiracetam	Yes	8	1000(1500)	9	1000 (0)	-500 (0.201)	0 (1.000)	-500 (0.253)
	No	11	2000(1500)	11	1000(1500)			
Topiramate	Yes	2	250 (300)	8	225 (225)	50 (0.583)	-100(0.229)	100(0.294)
	No	9	300 (200)	10	200 (250)			
Gabapentin	Yes	4	1450(1750)	3	2400(1600)	400(0.520)	800(0.071)	400(0.349)
	No	5	1200 (4009	7	2000 (600)			

szf, seizure-freedom; IQR, interquartile range; n, number; Est., estimate from the median regression model; p, significance.

Model 1: outcome = antiseizure medication dose, exposure variables = seizure-freedom and sex

Model 2: Additionally adjusted for age

[1] = estimate and significance of the seizure-freedom (ref. = no) from model 1

[2] = estimate and significance of the sex (ref. = female) from model 1

[3] = estimate and significance of the seizure-freedom (ref. = no) from model 2

Table 11. Antiseizure medication doses (median and interquartile range) in either mono- or polytherapy according to seizure type in patients with focal epilepsy with seizure freedom. Other antiseizure medications were used in fewer than 5 patients.

		Seizure-free		Not seizure-free		Model		
	sz type	*n*	median (IQR)	*n*	median (IQR)	Est. (p)[1]	Est. (p)[2]	Est. (p)[3]
Oxcarbazepine	FBTCS	157	900(600)	63	900 (900)	0(1.000)	0(1.000)	300 (0.115)
	FAS	40	900(600)	18	900 (600)			
	FIAS	15	1200(600)	12	1275 (900)			
Carbamazepine	FBTCS	47	400 (200)	13	600 (400)	-200 (0.082)	200 (0.017)	0 (1.000)
	FAS	9	600 (100)	5	600 (400)			
	FIAS	2	400 (0)	4	725 (125)			
Valproic acid	FBTCS	48	900 (400)	20	1000 (550)	-100 (0.576)	100 (0.656)	100 (0.718)
	FAS	10	1000(600)	4	1200(1450)			
	FIAS	6	800 (400)	6	1500 (600)			
Lamotrigine	FBTCS	21	200 (200)	21	300 (300)	-100 (0.074)	200 (0.248)	0 (1.00)
	FAS	4	500 (200)	4	200 (150)			
	FIAS	4	175 (175)	7	400 (300)			
Phenytoin	FBTCS	14	200 (100)	7	250 (200)	-50 (0.385)	100 (0.103)	100 (0.116)
	FAS	1	300	2	350 (100)			
	FIAS	1	300	2	350 (100)			
Levetiracetam	FBTCS	11	1000(1000)	16	1000 (750)	0 (1.000)	2000 (0.090)	1000 (0.138)
	FAS	1	3000	1	1000			
	FIAS	5	1000 (0)	5	3000 (500)			
Topiramate	FBTCS	7	250 (250)	10	250 (250)	-50 (0.583)	-50 (0.572)	0 (1.000)
	FAS	1	200	3	250 (100)			
	FIAS	2	250 (300)	6	250 (200)			
Gabapentin	FBTCS	4	2400(1550)	7	1800 (800)	0 (1.000)	-800 (0.063)	400 (0.342)
	FAS	2	1000 (400)	2	1000 (400)			
	FIAS	1	2400	3	2400(1000)			

szf, seizure-freedom; SD, standard deviation; IQR, interquartile range; n, number; Est., estimate from the median regression model; p, significance.

Model: outcome = antiseizure medication dose, exposure variables = seizure-freedom and 1st seizure type

[1] = estimate and significance of the seizure-freedom (ref. = no)

[2] = estimate and significance of the 1st seizure type (FAS vs. FBTCS)

[3] = estimate and significance of the 1st seizure type (FIAS vs. FBTCS)

Among the 193 seizure-free patients with focal epilepsy using OXC in monotherapy on either the first ASM regimen or first substitution, in an estimate comparing OXC doses between seizure-free and not seizure-free patients applying five models separately adjusted for sex, age, seizure type, EEG, and etiology, no significant findings emerged (Table 12).

In the 17 patients with generalized epilepsy achieving seizure freedom, the median dose of VPA was 900 mg in monotherapy or polytherapy. The doses of VPA were not significantly different between females and males (950 vs. 900 mg).

Table 12. Antiseizure medication doses (mean and standard deviation, median and interquartile range) in either mono- or polytherapy according to etiology in patients with focal epilepsy with seizure freedom. Other antiseizure medications are used in less than 5 patients.

		Structural / Infectious		Unknown			Model	
	szf	*n*	median (IQR)	*n*	mean (SD)	median (IQR)	Est. (p)[1]	Est. (p)[2]
Oxcarbazepine	Yes	116	900(600)	96	958(355)	900(600)	0 (1.000)	0 (1.000)
	No	66	900(1200)	27	1111(449)	900(900)		
Carbamazepine	Yes	36	400 (200)	22	532 (189)	400(200)	-200 (0.068)	0 (1.000)
	No	14	650 (400)	8	631 (237)	600(400)		
Valproic acid	Yes	35	1000 (600)	29	938 (327)	900(400)	-100 (0.542)	100 (0.383)
	No	22	1300 (900)	8	1100(670)	1000(250)		
Lamotrigine	Yes	14	200 (300)	15	247 (147)	200 (300)	-100 (0.094)	0 (1.000)
	No	19	200 (200)	13	316 (188)	300 (300)		
Phenytoin	Yes	13	200 (100)	3	250 (50)	250 (100)	-100 (0.064)	-100 (0.055)
	No	9	300 (100)	2	400 (0)	400 (0)		
Levetiracetam	Yes	12	1000(1000)	5	1300(975)	1000 (0)	-500 (0.290)	0 (1.000)
	No	14	1250(1500)	8	1625(791)	1250 (1250)		
Topiramate	Yes	8	300 (275)	2	225 (35)	225 (50)	0 (1.000)	50 (0.605)
	No	12	325 (225)	7	229 (76)	200 (100)		
Gabapentin	Yes	6	1800(1900)	1	2000	2000	600(0.458)	400(0.609)
	No	12	1800(1000)	0				

szf, seizure-freedom; SD, standard deviation; IQR, interquartile range; n, number; Est., estimate from the median regression model; p, significance.

Model: outcome = antiseizure medication dose, exposure variables = seizure-freedom and etiology

[1] = estimate and significance of the seizure-freedom (ref. = no)

[2] = estimate and significance of the etiology (ref. = unknown)

Table 13. Oxcarbazepine doses according to clinical features (mean and standard deviation; and median and interquartile range) in monotherapy as either first antiseizure medication or first substitution in seizure-free patients with focal epilepsy

	Seizure-free		Not seizure-free		
	n	median (IQR)	*n*	median (IQR)	Est. (p)[1]
Sex					0 (1.000)
Male	114	900 (300)	22	900 (600)	
Female	79	900 (300)	37	750 (300)	
Age of diagnosis					0 (1.000)
≤60 years	161	900 (600)	40	900 (600)	
>60 years	32	600 (300)	19	600 (300)	
Seizure type					0 (1.000)
FBTCS	142	900 (450)	42	600 (300)	
FAS	39	900 (600)	13	900 (0)	
FIAS	12	900 (450)	4	750 (300)	
EEG					0 (1.000)
Normal	88	900 (450)	21	900 (300)	
Epileptiform activity	35	900 (600)	14	675 (300)	
Unspecific activity	21	900 (450)	8	750 (600)	
Focal slowing	32	900 (600)	9	900 (300)	
Etiology					0 (1.000)
Structural	98	900 (600)	39	900 (300)	
Infectious	5	1500 (750)	2	900 (600)	
Unknown	90	900 (600)	18	900 (300)	

IQR, interquartile range; FBTCS, focal to bilateral tonic-clonic seizures; FAS, focal aware seizures; FIAS, focal impaired awareness seizures; and EEG, electroencephalography

[1] = estimate and significance of the seizure-freedom (ref. = no), five models separately adjusted for sex, age, seizure type, EEG, and etiology

6.4 Study IV. Prescribed Antiseizure Medication Doses and Their Relation to Defined Daily Doses for Achieving Seizure Freedom in Newly Diagnosed Patients with Epilepsy.

The combined seizure-freedom rate with 1st and subsequent ASMs was 88.0% (404 of 459), and all patients with generalized epilepsy became seizure-free following the administration of a second or subsequent ASM. Among patients who achieved 1-year seizure-freedom in the entire cohort, 10.1% (41 of 404) were on combination therapy. In total, 70 different ASM monotherapies or polytherapies (ASM combinations) were used (Publication 2). In Table 14, the clinical characteristics of patients who became seizure-free with the 1st or subsequent monotherapy or combination therapy are compared with those of patients who did not achieve seizure-freedom.

To ensure statistical robustness, ASMs with a sample size of less than 40 patients were excluded from the current and subsequent analyses. Specifically, the following ASMs were excluded along with their corresponding sample sizes: topiramate (N=31), phenytoin (N=27), gabapentin (N=19), tiagabine (N=14), clobazam (N=11), clonazepam (N=8), diazepam (N=2), pregabalin (N=2), and phenobarbital (N=1). By excluding these ASMs with smaller sample sizes, we aimed to ensure the reliability and statistical power of the analysis.

The results were analyzed focal epilepsy because the limited number of patients with generalized epilepsy. OXC, CBZ, and VPA demonstrated statistically significant differences in terms of mean prescribed doses and PDD/DDD ratio between patients with 1-year seizure-free and non-seizure-free status (992 mg and 0.99 vs 1132 mg and 1.13; 547 mg and 0.55 vs 659 mg and 0.66; and 953 mg and 0.64 vs 1260 mg and 0.84, respectively. Remarkably, the PDD/DDD ratio for seizure-free patients was 0.99 OXC whereas the ratio was 0.55 for CBZ and 0.64 for VPA. There was no difference in VPA dosing between seizure-free patients with focal or generalized epilepsy (the mean dose of VPA for seizure free patients with generalized epilepsy was 924 mg and those not achieving seizure freedom 1200mg).

The only third generation ASM widely used in patients with focal epilepsy was LTG. More than 40 patients used LTG, with an absolute mean dose of 248 mg for seizure-free patients and a PDD/DDD ratio of 0.83.

No statistically significant differences in doses were observed, regardless of whether the drugs were used as 1st-line epilepsy treatment or as a 1st or subsequent substitution. The doses and PDD/DDD ratios for the most used ASMs (OXC,

CBZ, and VPA) were comparable to the doses in Table 2. Only LTG, which was initiated seldom as the 1st monotherapy, had a lower mean dose and PDD/DDD ratio (189 mg and 0.63, respectively) than in all patients with LTG (including also polytherapy usage).

The mean OXC doses and PDD/DDD ratio were somewhat, but not significantly, higher for non-seizure-free patients (1588 mg, 1.50, respectively). The number of patients taking CBZ or VPA in polytherapy was too low to draw any conclusions. Among the third generation ASMs, a sufficient number of polytherapy patients using LEV were available for meaningful analysis. The comparison between patients with and without seizure-freedom showed no significant difference in the PDD/DDD ratio. Specifically, the PDD/DDD ratio for patients with seizure-freedom was 1615 mg and 1.08, while for patients without seizure-freedom, it was 1800 mg and 1.20. These findings suggest that the use of LEV in polytherapy did not demonstrate a significant impact on achieving seizure-freedom based on the PDD/DDD ratio.

Overall, 13 patients received LTG in combination with VPA. Of those, 4 became seizure-free with a low dose of LTG (dose and PDD/DDD ratio: 94 mg and 0.31, respectively). Nine patients did not achieve seizure-freedom with a mean LTG dose of 303 mg (PDD/DDD ratio: 1.01).

Finally, we analyzed the value of the OXC dose as the 1st failed monotherapy for predicting the likelihood of achieving seizure-freedom with subsequent ASM regimens during the follow-up period. There were 281 patients who used OXC as the 1st ASM, including 97 who did not achieve seizure-freedom with OXC. During the follow-up, 59 of these 97 patients (60,8%) became seizure-free with any subsequent ASM regimen. When addressing the dose of OXC as a failed 1st ASM categorized into 3 different levels (300–600 mg, 900 mg, or 1050–2400 mg with the PDD/DDD ratios up to 0.60 or 0.90 and more than 0.90, the effect of the dose of OXC as the 1st failed ASM on the possibility of achieving seizure-freedom was significant (Fisher's exact test, $p = 0.002$). Thirty-four of 43 patients (79%) in whom 1st-line OXC failed to achieve seizure-freedom at a dose of 900 mg or lower subsequently became seizure-free, as compared with 24 of 54 patients (44%) in whom 1st-line OXC at a dose of more than 900 mg was unsuccessful. (Figure 6).

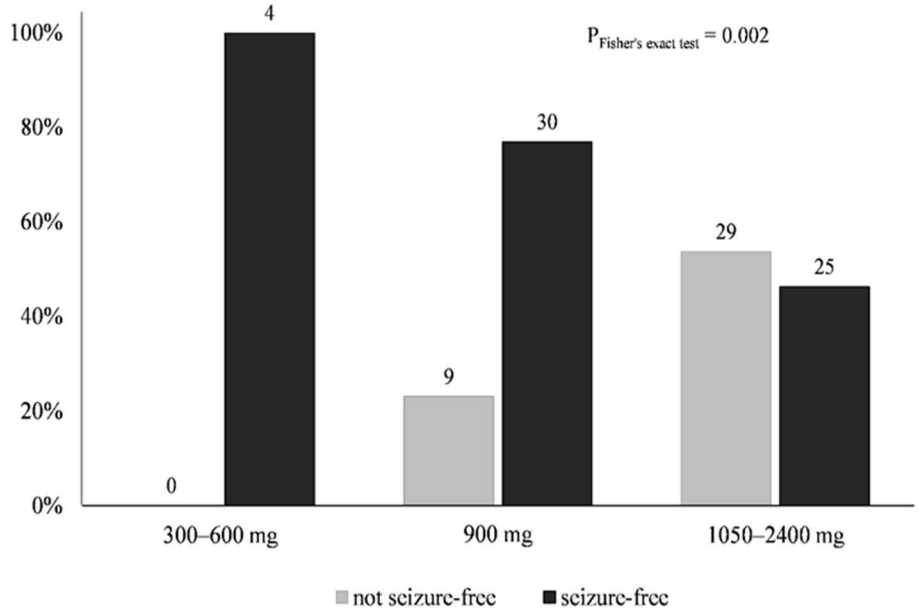


Figure 6. The predictive value of OXC dose as the 1st failed monotherapy for possibility of seizure freedom with subsequent ASM regimens.

Table 14. The clinical characteristics of patients who became seizure-free with the 1st or subsequent monotherapy or combination therapy are compared with those of patients who did not achieve seizure-freedom.

	1. All seizure-free patients	1A. Seizure-free after 1st ASM	1B. Seizure-free after 2nd or later monotherapy	1C. Seizure-free with polytherapy	**2. Persistent seizures**
N	404	308	55	41	55
Sex, n (%)					
Female	179 (44.3)	125 (40.6)	33 (60.0)	21 (51.2)	29 (52.7)
Male	225 (55.7)	183 (59.4)	22 (40.0)	20 (48.8)	26 (47.3)
Age at date of diagnosis, med (IQR)	46.0 (31.5)	45.5 (31.0)	52.0 (36.0)	36.0 (31.0)	42.0 (24.0)
Etiology, n (%)					
Structural	203 (50.2)	147 (47.5)	31 (56.4)	25 (61.0)	38 (69.1)
Genetic	25 (6.2)	18 (5.8)	1 (1.8)	6 (14.6)	0
Infectious	12 (3.0)	9 (2.9)	2 (3.6)	1 (2.4)	3 (5.5)
Unknown	164 (40.6)	134 (43.5)	21 (38.2)	9 (22.0)	14 (25.5)
Epilepsy type, n (%)					
Focal	379 (93.8)	290 (94.2)	54 (98.2)	35 (85.4)	55 (100)
Generalized	25 (6.2)	18 (5.8)	1 (1.8)	6 (14.6)	0
ASM					
Carbamazepine, n (%)	72 (17.8)	54 (17.5)	10 (18.2)	8 (19.5)	9 (16.4)
Lamotrigine, n (%)	47 (11.6)	12 (3.9)	15 (27.3)	20 (48.8)	20 (36.4)
Levetiracetam, n (%)	26 (6.4)	4 (1.3)	4 (7.3)	18 (43.9)	17 (30.9)
Oxcarbazepine, n (%)	258 (63.9)	184 (59.7)	44 (80.0)	30 (73.2)	49 (89.1)
Valproic acid, n (%)	98 (24.3)	51 (16.6)	34 (61.8)	13 (31.7)	17 (30.9)

ASM = antiseizure medications; IQR = interquartile range; med = median.

The table 14 patients achieving seizure freedom during follow-up were further subdivided to those becoming seizure free after first ASM regimen (1A), second or later monotherapy regimen (1B) and with any polytherapy (1C).

By other logistic regression models of PDD of ASMs and the ratio of PDD to DDD in patients with focal epilepsy. The data is divided based on seizure outcome status (seizure-free vs. not seizure-free). For OXC, patients who were not seizure-free had a higher mean dose and PDD/DDD ratio compared to those who were seizure-free. Similar trends were observed for CBZ and VPA, where the mean doses and PDD/DDD ratios were higher in the not seizure-free group. For LTG and LEV, although the mean doses and PDD/DDD ratios were higher in the not seizure-free group, the differences were not statistically significant. It's worth noting that all p-values for OXC, CBZ, and VPA are less than 0.05, indicating that the differences observed are statistically significant.

This information suggests that a higher dose and PDD/DDD ratio might be associated with patients not achieving seizure freedom, though individual ASM responses may vary.

Also, other logistic regression models of PDD and the ratio of PDD to DDD of the first or subsequent ASM used in monotherapy, depending on whether patients achieved seizure freedom (SF) or not (NSF). ForOXCin both first ASM and subsequent monotherapies, the mean and median absolute doses and PDD/DDD ratios were similar between seizure-free and not seizure-free patients. For CBZ similarly to OXC, no significant difference in doses and ratios between seizure-free and not seizure-free groups were presented. For VPA the mean, median, and PDD/DDD ratios for first ASM and subsequent monotherapies were comparable in both groups. For LTG there was a slight increase in dose and PDD/DDD ratio in subsequent monotherapy for patients not seizure-free. For LEV the only available data shows a slightly lower dose and ratio for seizure-free patients using subsequent monotherapies.

Overall, the differences in doses and ratios across groups were not statistically significant for any of the ASMs, indicating comparable dosage patterns between seizure-free and not seizure-free patients.

7 DISCUSSION

7.1 General Discussion

In our study, we examined a cohort of newly diagnosed epilepsy patients with both generalized and focal seizures who were referred to Tampere University Hospital's neurology clinic. These patients were treated with first-, second-, and third generation antiseizure medications (ASMs). Notably, a higher proportion of our patients tried subsequent ASMs compared to previous reports (Chen et al 2018). We found that 10.1% of the patients who achieved one-year seizure freedom were taking polytherapy, indicating the use of multiple medications for seizure control.

Firstly, the data were collected from a specific geographical region and had a retrospective nature, which may impact the generalizability and reliability of the findings. The analysis of ASM doses in patients with generalized epilepsy was limited due to a small sample size and limited statistical power, which could affect the robustness of the study outcomes. Additionally, our analysis of patients who achieved seizure freedom on ASM therapy was constrained by a lack of available information on drug-drug interactions, comorbidities, and other factors that may have influenced dose decisions.

Moreover, our cohort consisted of patients treated prior to the widespread use or availability of newer ASMs. However, it is noteworthy that CBZ, OXC, and VPA are still commonly chosen as first-line ASMs for focal epilepsy in Finland due to reimbursement policies. It is worth considering that newer ASMs, such ascenobamate, may exhibit greater efficacy compared to previous generations of ASMs (Lattanzi, et al 2022). The retrospective trail, with + reference

To enhance the clinical relevance of our findings, it is crucial to evaluate long-term seizure freedom rates in future studies. This would provide a more comprehensive understanding of the outcomes and efficacy of different ASM therapies over extended periods.

7.2 Discussion of the response to first antiseizure medication in patients diagnosed with epilepsy.

The present study, which applied the recent ILAE guidelines for the diagnosis (Fisher et al., 2014) and classification of epilepsy (Scheffer et al., 2017). Epileptic

seizures (Fisher et al., 2017). And definitions of an adequate ASM trial (Kwan et al., 2010), provides new insights into the prognosis of newly diagnosed epilepsy. In our study, the seizure freedom rate for at least one year with the first ASM was 67% for all patients, which is higher than the 50% seizure freedom rate observed in previous studies (Kwan et al., 2001, Chen et al., 2018)

Our study provides new evidence suggesting that the prognosis of new- onset epilepsy is more granular depending on the age of the patient, etiology and presenting seizure type, as well as the sex of the patient. Patients with focal epilepsy with unknown etiology, normal EEG or FBTCS as the presenting seizure type have a better chance of obtaining seizure freedom than patients with structural or infectious etiology, epileptiform activity on EEG or FIAS as the presenting seizure type.

The age distribution of patients in each cohort does indeed have a significant effect on the total seizure freedom outcomes because refractory epilepsy is most commonly associated with an earlier onset of epilepsy. In the landmark study by Kwan and Brodie (Kwan & Brodie et al., 2001) addressing the response the first ASM therapy as a further sub-analysis of main publication (Kwan et al., 2000). The mean age at onset of epilepsy in the whole study group was 32.8 years compared to 44.5 years at the time of diagnosis in our study. Moreover, the proportion of the patients with an age of diagnosis less than 25 years but 16 years or more was 20.3% (93 of 459) in our study, whereas 9.8% were between 9 and 15 years in Kwan and Brodies study (Kwan and Brodie et al., 2001)

In randomized controlled trials for the first ASM monotherapy, the patients were typically adults with a mean age of approximately 40 years at the time of diagnosis (Kim et al., 2017). In a trial in which eslicarbazepine acetate (ESL) was compared to CBZ, 71.1% of ESL-treated patients and 75.6% of CBZ- treated patients were seizure-free for ≥6 months (Villanueva et al., 2018).Even though the initial 6- month response to ASMs is a valuable predictor of long- term response, the seizure freedom rate, in general, is lower when the follow-up time is longer. In a recent study, the initial 6- month seizure freedom rate was 64%, but the 3-year seizure freedom rate declined to 46% (Xia et al., 2017).

Similarly, with lacosamide (LCM) monotherapy, the 6- month seizure freedom rate was 66% and declined to 60% at one year (Villanueva et al., 2018). According to a recent meta-analysis, there were no statistical differences in the seizure freedom rates in newly diagnosed focal epilepsy between LEV, ZNS, LCM, ESL and CBZ (Lattanzi et al., 2019). In another study, OXC was compared to CBZ in 235 patients aged 15– 65 years with similar one-year seizure freedom rates for both ASMs (52% with OXC and 60% with CBZ) (Dam et al., 1989).With OXC, 59% of patients with focal or generalized onset seizures have been reported to be seizure- free after one year (Bill et al., 1997).

In elderly patients with newly diagnosed epilepsy, 59% became seizure- free with the first ASM. Moreover, Mohanraj and Brodie (Mohanraj and Brodie, 2006) reported a high responder rate for elderly patients older than 64 years, with

85% achieving at least one- year remission, although the response to the first ASM regimen for this age group was not reported separately. In a recent systematic review and meta- analysis, there were no significant differences in the seizure freedom rates in newly diagnosed elderly patients between CBZ, GBP, LCM, LTG, LEV, PHT and VPA (Lattanzi et al., 2019).

In our study, the responses in the 25–60 and more than 60 years age groups were similar in focal epilepsy. These demographic characteristics may have influenced the increased percentage of patients achieving seizure freedom in our study. Therefore, the age distribution of epilepsy patients' needs to be taken into consideration when assessing the probability of seizure freedom with the first ASM.

According to our study, men with focal epilepsy were more likely to achieve seizure freedom with their first ASM than were females, but we could not identify any particular reason, including etiology, for this unexpected finding. Underreporting is one potential explanation because a significant proportion of patients with epilepsy underreport their seizures. Forty per cent of patients who anonymously reported a seizure in the past year held a driving licence, but only a quarter of these admitted to not being seizure- free (Dalrymple et al., 2000).Neurology's role is not only to treat epilepsy but also to regulate the rights of epileptic patients to hold a driving licence or access certain occupations. This could cause males to underreport their seizures compared to females.

In this study, we applied the new 2017 ILAE classifications of seizure and epilepsy type (Fisher et al., 2017, Scheffer et al., 2017). However, none of the patients were categorized as having combined generalized and focal epilepsy, which is a new epilepsy type compared with the previous classification system, most likely due to the age distribution of our study group. In the seminal study by Kwan et al. 2001, epilepsies were classified into i) idiopathic, ii) cryptogenic and iii) remote symptomatic, making the comparison with the new 2017 ILAE classification ambiguous. The number of patients with generalized epilepsy was much lower in our study (5%) than in the idiopathic group (25%) in a previous study (Kwan et al., 2001).

An overview of the doses of OXC given to patients with focal epilepsy who have achieved seizure freedom, were broken down by several factors. For both seizure-free and non-seizure-free groups, the average dosage is quite close, though slightly higher in the non-seizure-free group. Men seem to receive a higher average dose than women in both seizure-free and non-seizure-free categories. Patients diagnosed at or below 60 years of age appear to receive a higher mean dose than those diagnosed over 60 in both categories.

Among different seizure types, focal aware seizures (FAS) seem to receive the highest average dose in both categories, followed by focal impaired awareness seizures (FIAS) and focal to bilateral tonic-clonic seizures (FBTCS). Based on EEG, patients with normal readings and epileptiform activity get higher doses

compared to other categories. However, in the seizure-free group, patients with epileptiform activity have the highest average dose.

Regarding etiology, patients with unknown causes receive a slightly higher average dosage than those with structural or infectious causes in the non-seizure-free group. In the seizure-free group, the doses are quite similar across different etiologies.

7.3 Discussion of the response to subsequent antiseizure medications after first antiseizure medication failure in newly diagnosed epilepsy

The initial 1-year seizure freedom rate for all ASM regimens was 88.0%, higher than the rate observed in previous studies (Kwan, 2000A; Bonnett et al., 2014). Using the ILAE-defined ASM trial, the seizure freedom rate for the first ASM increased from 67.1% to 75.4% in the total study cohort and from 75.9% to 85.2% in patients who achieved seizure freedom with subsequent ASMs. However, defining an adequate ASM trial decreased the proportion of patients achieving seizure freedom with the second ASM to 8.3% of the total cohort and 9.4% of patients who achieved seizure freedom with ASMs. Overall, 16.6% of the study population met the ILAE criteria for drug-resistant epilepsy (DRE), while in 20.0% of the patients, two ASMs failed to control the seizures.

The proportion of patients achieving seizure freedom decreased with each subsequent ASM regimen, from 2.7% to 0.74%, highlighting the significance of the ILAE definition of drug-resistant epilepsy (DRE) (Kwan et al., 2010).

Increasing the number of ASM regimen trials increased the likelihood of seizure freedom, but not all patients in whom two ASM regimens failed to stop seizures initiated further ASM regimens. Therefore, uncontrolled epilepsy is not equivalent to DRE. The most common reason for this is the inadequate use of prescribed ASM(s) (Hao X, at al 2013). A Scottish study reported that 74.2% (742/1,000) of patients who did not achieve seizure freedom with the first ASM tried a second one (Brodie MJ, at al 2011).

In our study, all patients received a second ASM, and 71.7% (66/92) of patients tried additional ASMs. Surprisingly, a significant number of patients (40.2%, 37/92) achieved seizure freedom even after failing two to five previous ASMs. This finding demonstrates a notably higher seizure freedom rate compared to previous reports (Schiller et al., 2008). It is important to note that patients with a history of recreational drug use had a 64% reduced chance of achieving terminal seizure freedom (Hao et al., 2013). To maintain consistency, our study excluded patients with alcohol and recreational drug use, as their seizures were considered provoked. This exclusion may partially explain the elevated rates of seizure freedom observed in our study.

Age distribution significantly influenced seizure-free outcomes in our study, but our patient population did not include individuals with epilepsy onset in infancy and childhood (<16 years), who may respond differently to ASMs. Previous studies have shown no difference in terminal remission rates between adults and children, with the lowest remission probability observed in patients with epilepsy onset in their 20s (Bell et al., 2016; Park et al., 2020). A Scottish longitudinal cohort study reported a median age of referral at 33 years, compared to 45 years at diagnosis in our study (Publication 1; Chen et al., 2018). In a previous study, multivariable analysis of patients aged >70 years revealed an odds ratio of 2.25 for achieving 12-months remission after the first treatment failure (Bonnett et al., 2014). Elderly patients with focal epilepsy in our study were also more likely to be seizure-free. Furthermore, patients achieving seizure freedom with the second ASM regimen were significantly older (mean age 51 years) compared to those achieving freedom with the third or subsequent regimens (mean age 32 years). Even in drug-resistant poststroke epilepsy, a recent study found that patients tended to be younger, with a mean age of 52 years (Lattanzi, 2022).

All patients with generalized epilepsy in our study became seizure-free, consistent with our previous study (Publication 1). Additionally, patients who became seizure-free with the second ASM regimen were more likely to have FBTCS or FAS as the presenting seizure type and to have EEG without epileptiform activity compared with those who became seizure-free with the third or subsequent regimens. In addition, patients with persistent seizures were significantly more likely to have epileptiform activity on EEG than those responding to the second ASM regimen. Both features were also significant for the possibility of seizure freedom with the first ASM (Publication 1).

The follow-up time for patients with either persistent seizures or becoming seizure-free after the third or later ASMs was significantly longer compared with those responding to the second ASM (6.0 years, 4.7 years, and 2.6 years, respectively), which is explained by the treatment guidelines in Finland where patients are followed up in a specialist center until 1-year seizure freedom is reached.

We did not detect significant differences in seizure freedom related to sex or etiology, which may be due to the limited number of patients in our cohort. It has been proposed that when the first ASM fails due to lack of efficacy, add-on therapy should be initiated immediately because it is more effective than its application after the second ASM failure, possibly due to the concept of seizures begetting seizures, that is, secondary epileptogenesis (Kwan P, at al 2000A).

However, our study found no differences in efficacy when add-on therapy was used after the first ASM failed. This finding may be explained by a bias from the treating physician, who may have chosen substitution for patients who were estimated to have a better prognosis, and add-on therapy was offered to patients who were thought to have a worse prognosis in achieving seizure freedom. This

bias may explain why patients in the add-on strategy tended to be younger than those in the substitution strategy.

When analyzing the efficacy of different ASMs, the highest seizure freedom rate was achieved with CBZ (65.9%) either either in monotherapy or polytherapy in focal epilepsy without significant difference compared with other ASMs, where seizure freedom rates ranged from 11.8% (clobazam) to 55.8% (OXC); only tiagabine had a significantly lower seizure freedom rate (6.7%). The low proportion of FIAS in our cohort may also be due to the lack of recognition of these seizures (Beghi E. at al 2020). This result may also explain why VPA had favorable efficacy in our study because it had good efficacy in FBTCS but was suboptimal in FAS and FIAS compared with CBZ (Tomson et al 2015). The favorable efficacy of VPA likely reflects physicians' preference to initiate VPA in older patients who generally have better responses to ASM.

In monotherapy, ASMs with multiple MOA or with modulation of voltage gated sodium channels had the highest seizure freedom rates (67.4 and 64.5%, respectively) compared with ASMs modulating neurotransmitter release via a presynaptic action (53.9%) without a significant difference. Conversely, ASMs that enhanced GABA-mediated inhibitory neurotransmission had the lowest seizure freedom rate (14.3%; p =0.098). This is in line with an earlier study reporting that none of the patients who received a combination of a sodium channel blocker and GABAergic agent became seizure-free (Beghi et al., 2003). Overall, the ASM mechanism of action doesn't significantly impact seizure freedom likelihood, but individual responses vary.

This may suggest that the mechanism of action of the ASM does not significantly impact the likelihood of achieving seizure freedom. However, individual patient response can vary greatly, and the optimal ASM selection often depends on individual patient characteristics and the specific type of epilepsy.

Lack of efficacy (45%) and side effects (47%) were the most common reasons for discontinuation of the initial and subsequent ASMs. CBZ had the highest rate of discontinuation owing to side effects when used in monotherapy and polytherapy. Treatment with CBZ is associated with a higher risk of discontinuation than treatment with LTG, LEV, or VPA in elderly individuals (Lattanzi S at al 2019).

Owing to the retrospective study design, selection bias is a potential limitation of the present study. A modest sample size reduced the power required to determine the effect of combined ASMs. We were unable to document the possible underreporting of seizures. Our cohort also consisted of patients from an era when newer ASMs were nonexistent or not widely used. However, CBZ, OXC, and VPA are currently chosen as first-line ASMs for focal epilepsy in Finland owing to the reimbursement policy, and many newer ASMs are reimbursed only when used as an add-on therapy but not as a substitution. However, new ASMs have not improved the probability of seizure freedom (Chen Z, at al 2018). On the other hand, there is a paucity of studies that have

been performed recently analyzing in more detail the efficacy of subsequent ASM regimens including more newer generation ASMs. Therefore, a new study with a similar approach to our study but from a more recent period would be much warranted.

A major contribution to timely referral for epilepsy surgery was based on the official ILAE definition of DRE as a failure of two appropriate drug trials introduced in early 2010 (Kwan P, at al 2010). Because of our study design, an initial seizure freedom rate of at least 1 year (time to first remission) was used; however, long-term seizure freedom rates were not available. The proportion of relapsing-remitting courses of epilepsy was estimated as 16–52% depending on the patient population (Brodie et al., 2012). Owing to the reasonably long follow-up time, some patients may have become seizure-free due to the natural disease course, regardless of medication. Finally, we did not have information available about psychiatric comorbidities or the number of pre-treatment seizures limiting the analysis of all possible relevant factors.

One of the key issues about the present study is how well the results from our single center can be generalized to other regions and patient populations? First, we have only included patients from adult neurology department (i.e., patients aged 16 years or more); which also explains why there are so few patients with generalized epilepsy because in the majority of those patients the onset of epilepsy is <16 years. On the other hand, our center covers a well-defined geographical area and is practically population-based. Moreover, our patient population does not represent a typical DRE population, because in order to be included in the original study population the patients needed to be newly diagnosed and the development of DRE was one of the outcomes of the study.

Our study provides new data for the prediction of seizure freedom in the adult population, providing a more positive outlook than previous studies. The results of our study support the feasibility and applicability of the ILAE concept of an adequate ASM trial, with further emphasis on the prognostic significance of the first adequate ASM trial and the failure of two ASMs as a definition of DRE.

7.4 Discussion of the effect of clinical features on ASM doses in patients with newly diagnosed epilepsy.

The present study provides new insights into the median ASM doses based on clinical features and patient characteristics. Due to the distribution of ASM in our study, we were able to provide meaningful analysis results mainly for OXC, VPA and CBZ. Significant OXC dose differences were detected between age

groups, whereas VPA dosing was different in men and women. Moreover, CBZ doses were dependent on some seizure types and EEG findings.

Age was the main factor influencing ASM doses in this study. Patients aged ≤60 years needed higher doses of OXC to achieve seizure freedom compared with older patients, whereas the doses of other ASMs showed no statistically significant differences. However, in our study the median dose of VPA for patients achieving seizure freedom was 1000 mg for those younger than 60 years and for those over 60 years 900mg.

This finding is in line with a previously study showing that 83.3% of older patients became seizure-free with a mean VPA monotherapy dose of 626mg (Craig et al., 1994). In contrast, in a cohort of younger (mean age of 33 years) focal epilepsy patients, with a seizure freedom rate of 62%, an average dose of 1066mg of VPA was required (Richens et al., 1994).

In our previous studies examining the percentage of seizure-free patients, age did not have an effect on patients achieving seizure freedom on their first ASM regimen (Publication 1), whereas in patients with failed achievement of seizure freedom on their first ASM regimen, an age >60 years was a favorable prognostic factor for seizure freedom with subsequent ASM regimens (Publication 2). However, it is unclear if decisions to modify doses were based only on the achievement of seizure freedom or caution over age-related exposure and adverse events with ASMs in this study. The median dose of OXC (600 mg) was slightly lower in patients >60 years with focal epilepsy than in a previously published the older cohort (874 mg) (Dogan et al., 2008). In another study, seizure freedom was achieved with a lower mean daily dose of OXC in older individuals (900 mg/day) compared to mean doses of 1200 mg/day in the whole cohort (Kutluay et al., 2003). Similarly, in our study, the median difference in OXC dose was 300 mg between older females and younger males.

Age-related differences can partly be explained by drug disposition and elimination. A comparative pharmacokinetic study of OXC in older (age, 60–82 years) versus young (age, 18–32 years) healthy volunteers showed that the mean concentrations of the OXC metabolite (monohydroxy derivative) were higher in the former population than in the latter population (Heiningen et al., 1991). OXC has been shown to have a good safety profile among older patients, which is consistent with the safety outcomes and adverse event rates noted in the general population. However, the concomitant use of drugs in this age group (polypharmacy) and pre-existing chronic conditions and comorbidities may influence drug safety and adverse event rates (Beydoun et al., 2000). The rate of hyponatremia linked to OXC therapy is higher in older patients, which may be an important consideration for dose adjustment and therapeutic monitoring (Berghuis et al., 2017).

Epilepsy management in older patients should consider a range of factors linked to the efficacy and safety outcomes of ASMs in this context (Brodie et al., 2005), including diagnosed epileptic syndrome, patient sex, comorbidities,

concomitant medications, tolerability, and safety of ASM, while ensuring compatibility with local guidelines. Similarly, the decision to increase or decrease the doses of ASM should be guided by these factors to reflect an individualized assessment process (Cerdá et al., 2020, Kwan et al., 2004), which also denotes that patient age also plays a significant role in influencing health outcomes during the ASM treatment process (Acharya et al., 2017, Pisani et al., 2017).

In our previous publication addressing the effect of sex on seizure outcomes in the same patient population, men with focal epilepsy were more likely to achieve seizure freedom than their female counterparts on their first ASM (Publication 1) but not with subsequent ASM regimens (Publication 2). In a recent Taiwanese study not taking into consideration seizure outcomes, the mean doses of OXC in monotherapy were 641 and 614 mg for males and females, respectively ($p=0.024$). The authors speculated that this could be attributable to the fact that males typically weigh more than females (Liang et al., 2022). There is no clear evidence that sex differences influence the efficacy of OXC therapy among patients with focal epilepsy (Perucca et al., 2014). Therefore, the reasons underlying this observation are unclear, potentially reflecting the differences in patient risk profiles or other factors that were not investigated in this study.

While the adjustment of OXC dose may be based on weight in children (Sallas et al., 2003), there is no evidence that weight needs to be considered in adults, excluding the possibility of anthropometric differences between male and female patients accounting for variations in OXC dosing (Andreasen et al., 2007). OXC is known to be a weak inducer of CYP3A4, which plays a role in estrogen metabolism and may reduce the efficacy of oral contraceptive pills if used at high doses (Andreasen et al., 2007). However, it is unlikely that prescribers avoided higher doses of OXC to avoid drug-drug interactions in women taking oral contraceptive pills since the mean dose of OXC was higher among women who did not become seizure-free than among those who did. It is possible that seizure freedom is achieved with a lower dose of OXC in women with focal epilepsy.

In our study female patients with focal epilepsy required lower doses of VPA to achieve seizure freedom. This is in line with a previous finding that the mean doses of VPA in monotherapy were 1139mg and 969mg for males and females, respectively ($p<0.001$) (Liang et al., 2022). Further studies to explore the influence of sex on ASM prescription in this population are warranted.

It was also noted that CBZ median dose was significantly higher with FAS compared with FBTCS, which is consistent with our previous finding that patients with FBTCS as the presenting seizure type are more likely to achieve seizure freedom (Publication 1). There is no evidence in the literature to suggest the variable efficacy of ASM for achieving seizure freedom in different seizure types in patients with focal epilepsy (Glauser et al 2013). However, further research to confirm the potential for variation, as noted in this study, and explore the implications of drug dose optimizations is warranted.

In the present study, some significant differences in median doses between patients with normal and unspesific EEG findings were detected; however, there were no statistically significant differences in seizure freedom rate and these findings are difficult to interpret in a clinical context. There were no differences in ASM dosing regarding etiology.

This study demonstrated that the doses of ASMs associated with seizure freedom in patients with epilepsy were influenced by age for OXC and by sex for VPA. The largest dose differences were observed between males aged ≤60 years and females aged >60 years. Significant dose differences were inconsistent across different ASMs, and further research is needed to clarify the effects of age and sex on ASM efficacy and prescription practices due to limitations inherent to the retrospective design of our study.

7.5 Discussion of the prescribed ASM doses and their relation to DDD for Achieving Seizure Freedom in Newly Diagnosed Patients with Epilepsy.

We identified marked variation in the ratio of the PDD to DDD, which renders a general PDD/DDD comparison highly problematic, particularly for OXC. Finally, we demonstrated that failure of OXC, the most-prescribed ASM, as the 1st-line monotherapy at a dose of ≤ 900 mg was predictive of achieving seizure-freedom with subsequent ASMs.

We were able to offer a highly representative analysis for OXC given its use as the most-commonly selected 1st-line ASM for focal epilepsy (305 patients in our study). The significant findings included the observation that, in focal epilepsy, a median dose of 900 mg of OXC as monotherapy was registered for seizure-freedom, whereas in the polytherapy context, the median dose for seizure-freedom was 1500 mg. In previous studies, the OXC dose was variable. In a Chinese study of newly diagnosed focal epilepsy patients, 62 out of 102 patients treated with OXC as the 1st choice became seizure-free with either 600 or 900 mg of the drug, whereas only 10% of the patients with OXC were titrated to doses over 900 mg (Zou et al., 2015). In our previous study from Tampere, 80% of patients became seizure-free with OXC as the 1st-line ASM with doses ≤ 900 mg, whereas 20% of patients achieved seizure-freedom with doses of 1200 mg or 1500 mg (Rainesalo et al., 2005).

The 2nd and 3rd most-commonly used ASMs in our study were CBZ and VPA, respectively, accounting for 80 and 94 patients, respectively. In patients with focal epilepsy, the mean dose of the ASM for achieving seizure-freedom was 547 mg for CBZ and 953 mg for VPA, whereas in patients who did not achieve seizure-freedom, the doses were slightly but significantly higher (659 mg and

1260 mg, respectively). These doses were comparable to those previously published (Kwan et al 2001). The number of patients treated with CBZ or VPA as part of polytherapy was too small to draw conclusions. Furthermore, the mean dose of LTG for achieving seizure-freedom (248 mg) was comparable with previously reported data, with lower doses when used as 1st-line monotherapy (189 mg) or in combination therapy with VPA (97 mg) (Kwan, 2001). The number of patients using a third generation ASMs in our study was too small to allow firm conclusions, particularly regarding monotherapy. However, LEV was the second most-commonly used ASM in polytherapy (29 patients), with a mean daily dose of 1615 mg in patients who became seizure-free and 1800 mg in those who did not become seizure-free.

The PDD/DDD ratios of the most-commonly used ASMs in patients with focal epilepsy in our study varied significantly, with a mean seizure-freedom PDD/DDD ratio of 0.99 for OXC, 0.55 for CBZ, and 0.64 for VPA. For all ASMs, the PDD/DDD ratios were higher when seizure-freedom was not achieved. The high mean PDD/DDD ratio for OXC compared to those for CBZ and VPA signifies that the DDD-based comparison is not valid when OXC is part of the ASM equation. Brodie et al. previously speculated about the outlier status of OXC questioning the WHO defined DDD for CBZ and OXC, which were both assigned the same DDD (1,000 mg/day), since a dose ratio of 1:1.5 for CBZ vs OXC is often assumed in clinical practice and in research (Brodie et al., 2013).

Our study now provides data to support the aforementioned notion. Moreover, in a Hungarian cross-sectional study, the mean PDD/DDD ratio for OXC in seizure-free patients was only slightly lower than that noted in our patients (Horváth et al 2017). Additionally, the mean PDD/DDD ratios for achieving seizure-freedom with CBZ and VPA in our study were in line with those reported in previous studies (Brodie et al., 2013, Horváth et al, 2017). The outlier values for OXC also implies that the 75% DDD dose as a definition of an adequate ASM trial cannot be applied to OXC. Conversely, the significance of an OXC dose of ≤ 900 mg as the 1st failed monotherapy for predicting an increased possibility of seizure-freedom for subsequent ASMs was in line with reported outcomes for other ASMs, such as CBZ, VPA, and LTG (Brodie et al., 2013).

Pharmacokinetic interactions between ASMs complicate the assessment of dosing further in polytherapy settings in our study. CBZ is strong inducers of cytochrome P450 and glucuronizing enzymes whereas OXC has weaker inducing properties, and a lower propensity to cause interactions mediated by enzyme induction. Conversely, enzyme inhibitors such as VPA results in decreased metabolic clearance of the affected drug, such as LTG and CBZ (Zaccara et al., and Perucca et al., 2014). Furthermore, different combinations of ASMs may produce either increased (synergism) or decreased (antagonistic) efficacy or tolerability, (Verrotti Aet al., 2020)

In conclusion, the present study provided new insights into the doses of the commonly used ASM, OXC, that leads to seizure-freedom in patients with newly diagnosed epilepsy when used as 1st-line or subsequent monotherapy, as well as when used in combination therapy. We demonstrated marked variation in the ratio of PDDs to DDDs, rendering a generalized PDD/DDD comparison highly problematic, for OXC in particular, but also for LTG as 1st-line monotherapy or in combination therapy with or without VPA. Finally, for OXC, we demonstrated the value of a dose of ≤ 900 mg of OXC as 1st failed monotherapy for predicting achievement of seizure-freedom, suggesting a decision-point dose for an adequate trial of OXC for ILAE definition.

7.6 Study limitations

This research, conducted retrospectively between 1995 to 2006, provides valuable insights into epilepsy, based on a well-delineated patient cohort conforming to the ILAE epilepsy definitions, which led to a minimal percentage of unclassified epilepsies. The timeframe for the study was selected based on the availability of comprehensive data, aiming to evaluate medical practice trends and outcomes over a specified period. Nonetheless, several limitations were acknowledged, including its single-center nature, potential selection biases due to its retrospective design, and lack of control over various influencing factors like medication adherence, comorbidities, and lifestyle factors, although a large sample size might have lessened the effects of non-ASM dose factors on seizure freedom.

Key issues arose from its retrospective framework, such as reliance on past record accuracy, potential physician biases in drug choices, and the absence of systematic ASM titration data which might affect evaluations on drug tolerabilityArif et al., 2009. The analysis was further constrained due to the absence of data on concomitant medications, potential drug-drug interactions, and unavailability of long-term seizure freedom rates. The small sample size for some ASMs, the lack of serum level measurements, and an emphasis on older ASMs due to local reimbursement policies in Finland, while newer ASMs were not yet widely used, added to the study's limitations. Moreover, the study didn't delve into the reasons for discontinuation of a given ASM, whether due to lack of efficacy or tolerability issues, to keep the analysis concise and clear.

Although our cohort consisted of patients from an era prior to the extensive use of newer ASMs and before advancements in neuroimaging and neurophysiology, the study remains relevant as the first line ASMs used are still

prevalent in contemporary treatment in Finland and globally. The re-evaluation of all epilepsy diagnoses according to the new epilepsy definition criteria and the focus on an initial seizure freedom rate of at least one year are notable aspects of the study. Future research should aim to include long-term seizure freedom rates to improve the clinical relevance of these findings.

8 SUMMARY AND CONCLUSIONS

In our study, we observed a higher seizure freedom rate of 67% for all patients with the first antiseizure medication (ASM), which is higher than the 50% seizure freedom rate reported in previous studies (Kwan et al., 2001, Chen et al., 2018). This suggests a more positive prognosis for new-onset epilepsy, and our study provides new evidence indicating that the prognosis can vary depending on factors such as patient age, etiology, presenting seizure type and sex.

Specifically, we found that patients with focal epilepsy of unknown etiology, normal EEG, or FBTCS as the presenting seizure type had a better chance of achieving seizure freedom compared to patients with structural or infectious etiology, epileptiform activity in EEG, or FIAS as the presenting seizure type.

Regarding age, we observed similar responses in the 25-60 and over 60 years age groups for focal epilepsy. Additionally, the 6-month response to the first ASM was found to be a valuable predictor of long-term response.

Interestingly, our study also found that males with focal epilepsy were more likely to achieve seizure freedom with their first ASM compared to females, although the reasons for this finding remain unclear, including the influence of aetiology.

In terms of etiology, patients with unknown etiology had significantly higher seizure freedom rates (75%) compared to patients with structural etiology (61%). This finding contrasts with Kwan's study, 2000 which showed no difference in seizure freedom rates between patients with symptomatic and cryptogenic epilepsy. The new, more granular classification of etiologies allows for better comparisons between study populations, considering the heterogeneity in age and referral systems that can affect seizure freedom probabilities.

In our study, there were no significant differences in the number of ASM discontinuations, with OXC and CBZ being the most used ASMs.

Furthermore, our study revealed that the doses of ASMs in patients receiving OXC were influenced by various criteria, including age, sex, and seizure type. However, there is a need for clarification on the effects of age and sex on ASM efficacy and prescribing practices.

Another aspect of our research focused on dose variation for common ASMs in relation to seizure freedom rates in monotherapy and combination therapy. However, there were challenges in comparing prescribed daily doses (PDDs) and defined daily doses (DDDs), which should be further expanded and discussed.

It is important to note some limitations of our study, including sample size limitations for specific epilepsy types and the overall sample, potential

underreporting of seizures, and limitations in real-world data that may result in under diagnosis or misidentification of certain seizure types, such as FIAS.

In conclusion, our study sheds light on the prognosis and factors influencing seizure freedom in epilepsy, including age, etiology, seizure type, and sex. Further research and a more comprehensive understanding of these factors are needed to improve treatment strategies and outcomes for individuals with epilepsy.

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Response to first antiseizure medication in patients diagnosed with epilepsy

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Abstract

Objectives: To investigate the interaction among the efficacy, tolerability and overall effectiveness of the first antiseizure medication in patients 16 years or older with newly diagnosed epilepsy.

Materials and Methods: The study included 584 patients who were referred to the Tampere University Hospital between 1 January 1995 and 31 December 2005 and were diagnosed with epilepsy. All individuals were retrospectively followed up until 31 December 2006, until reaching at least one year of seizure freedom, or until death if before the cut-off date.

Results: Overall, after thorough validation of the epilepsy diagnosis 459 patients comprised the study cohort; among these patients, 73% of males and 60% of females became seizure-free for at least one year with the first antiseizure medication. The seizure freedom rate for focal epilepsy was 67%. There was no significant difference in focal epilepsy to achieve seizure freedom between oxcarbazepine, carbamazepine or valproic acid. The seizure freedom rate among patients above 60 years of age was 67%. For patients with structural and unknown aetiology, seizure freedom rates were 61.5% and 75.3%, respectively. Additionally, epileptiform activity on EEG in patients with focal epilepsy decreased odds of seizure freedom in adjusted logistic regression models (OR 0.55, p=0.036).

Conclusions: This study provides a more positive prediction of seizure freedom compared with previous studies with the onset of epilepsy at 16 years or older with an overall estimation that two-thirds of patients with new-onset epilepsy obtain seizure freedom with the first antiseizure medication.

KEYWORDS
antiepileptic drug, antiseizure medication, newly diagnosed epilepsy, seizure freedom, treatment outcomes

1 | INTRODUCTION

Epilepsy is one of the most common chronic brain disorders globally and affects people of all ages. It is estimated that approximately 0.6% of the population of Nordic countries has active epilepsy.[1] Epilepsy is still associated with stigma and psychological, social, cognitive, and economic repercussions.[2]

The response to the first antiseizure medication (ASM) is the strongest predictor of long-term seizure remission.[3] The effectiveness of the first ASM in newly diagnosed patients with epilepsy has been

previously studied in long-term outcome studies with seizure freedom rates below 50%, including children (older than 9 years), adolescents, adults and elderly patients with new-onset epilepsy, and these outcome measures have not improved during the past 20 years.[4,5] In randomized controlled ASM trials and in a recent network meta-analysis in adult populations, with focal epilepsy, the results are more variable, with one-year seizure-free rates ranging from 57 to 76%.[6-11]

Multiple factors affect the possibility of seizure freedom in patients with newly diagnosed epilepsy, and those factors are highly dependent on the patient population studied, ASM availability, definitions applied for the diagnostic criteria of epilepsy, seizure type and epilepsy type classifications. During recent years, new International League Against Epilepsy (ILAE) official guidelines have been published on the topics of the definition of epilepsy,[12] classification of seizures [13] and epilepsies,[14] as well as a definition of an adequate ASM trial in epilepsy in terms of dosage and ASM selection,[15] which could enhance the comparison between different studies on seizure-free rates in people with epilepsy. However, studies utilizing these new criteria are still infrequent.

According to the new 2014 ILAE criteria, epilepsy requires at least one unprovoked seizure. The term 'unprovoked' is, however, imprecise because we can never be sure that there was no provocative factor.[12] In the new ILAE classification of seizure types, a focal aware seizure (FAS) corresponds to the 1981 ILAE classification term 'simple partial seizure'. A focal impaired awareness seizure (FIAS) corresponds to the prior term 'complex partial seizure'. The seizure type 'focal to bilateral tonic–clonic' (FBTCS) is a special seizure type, corresponding to 'partial onset with secondary generalization'. FBTCS reflects a propagation pattern of a seizure rather than a unitary seizure type.[13] Of newly diagnosed focal epilepsy, 60% of patients have the FBTCS type.[16]

The use of valproic acid (VPA) and carbamazepine (CBZ) has been shown to be effective in treating patients with newly diagnosed epilepsy.[4] Phenytoin (PHT) and CBZ are similar in terms of effectiveness (retention) or efficacy (seizure recurrence and seizure remission) for individuals with focal onset or generalized onset seizures.[17] Since 1994, several newer ASMs, including lamotrigine (LTG) and oxcarbazepine (OXC), have been approved by the Food and Drug Administration or European Medicines Agency.[18] OXC is a second-generation ASM with proven efficacy as monotherapy and combination therapy in the treatment of focal seizures, and it is safe to use and well tolerated in elderly patients.[19]

The aim of this study was to evaluate the response to the first ASM therapy in terms of efficacy and tolerability by applying the recent ILAE criteria for i) the definition of epilepsy,[11] ii) the classification of seizures,[12] iii) the definition of epilepsy type and aetiology,[13] and iv) the definition of adequate ASM trial.[14] In addition, our study attempted to determine prognostic factors for seizure freedom in patients with newly diagnosed epilepsy.

2 | MATERIALS AND METHODS

Overall, 584 patients aged 16 years or older referred to the Tampere University Hospital between 1 January 1995 and 31 December 2005 were diagnosed with epilepsy. All individuals were retrospectively followed up until 31 December 2006, until reaching at least one year of seizure freedom, or until their deaths if before the cut-off date. According to the local practice guidelines, neurological patients who are at least 16 years old are treated in the adult neurology department. Medical records of the patients, including clinic visits and demographic and clinical information from the patients, were examined retrospectively. Additional studies carried out were registered. All epilepsy diagnoses were re-evaluated by a neurologist (HH) applying the new criteria for the definition of epilepsy.[11] Any ambiguities were resolved by discussions with three neurologists (HH, JS and JP) until consensus was reached.

Nearly all patients underwent at least one surface EEG performed by neurophysiologists, either using a standard approach or testing the patients after sleep deprivation. All the available original EEG reports were assessed and categorized to normal, epileptiform activity, focal slowing or unspecific by neurologist with special expertise in epilepsy (JP).

The clinical practice at that time favoured avoiding diagnosis of unknown epilepsy type, and all patients with no evidence of generalized epilepsy were usually diagnosed as focal epilepsy patients.[20] Neuroimaging, particularly computed tomography or magnetic resonance imaging, was performed and evaluated by neuroradiologists to screen for underlying structural abnormalities that might have caused epilepsy. Information obtained from the history, physical examination and other studies was used to classify the patient's epilepsy aetiology.

For all the patients who were given a diagnosis of epilepsy, ASM therapy was initiated according to standard clinical practice at that period. Subsequently, patients were followed at the epilepsy clinic according to routine clinical practice until at least one year of seizure freedom was achieved with the first ASM regimen in the present study. At the follow-up visit, clinical information and the response to ASM therapy were recorded. ASM doses were adjusted as clinical circumstances dictated, with particular attention given to efficacy and tolerability.

Depending on the variable group, comparisons were performed using the Mann-Whitney U test, Pearson's chi-squared test or Fisher's exact test. Binary logistic regression was used to examine the association between seizure freedom by first ASM and gender. Age at date of diagnosis (continuous), seizure type (FBTCS as a reference group), epilepsy type (focal as a reference group), ASM (OXC as a reference group) and EEG (normal as a reference) were examined as potential confounding factors. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each covariate. The Wilson score method without continuity correction was used to calculate two-sided CIs for the single proportion. The data were analysed with Stata version 15.1 (College Station, TX: StataCorp LLC).

In this retrospective study, there was no contact on patients and the information was collected from patient register of Tampere University hospital. This study was approved by the Head of Tampere University Science Centre.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

3 | RESULTS

After thorough validation of the epilepsy diagnosis, 101 patients were excluded because of uncertainty of epilepsy diagnosis or because epilepsy was not newly diagnosed. Additionally, 24 patients (5.0%) died within the first year after ASM therapy was initiated and were excluded for not being able to reach the end point of the one-year follow-up for the study.

Table 1 summarizes the clinical characteristics of all 459 patients with validated newly diagnosed epilepsy who remained in this study cohort. There were no significant changes in patient characteristics over the study period between therapy initiations during 1995–2000 and 2001–2005. At the time of diagnosis, the majority of the patients (260 of 459, 56.6%) were between 25 and 60 years of age. Only 20.3% (93 of 459) had their epilepsy diagnosed between 16–25 years of age and 23.1% (106 of 459) above age 60. The seizure freedom rate, defined as at least one whole year without seizures after initiation of the first ASM therapy in the whole study group, was 67.1% (308 of 459). The majority of the patients (241 of 459, 52.5%) had structural aetiology. EEG report was available of 409 (89.1%) patients.

Table 2 shows the baseline characteristics and seizure freedom outcomes by first ASM in patients with focal epilepsy. Focal epilepsy was more common among men (55.5%. The median age at diagnosis was 48, and 24.4% (106 of 434) were older than 60 years of age. In focal epilepsy, the seizure freedom rate was 66.8% (290 of 434, 95% CI 62.3% to 71.1%), with significant differences related to sex, aetiology and epileptiform activity on EEG. The seizure freedom rate was 60.1% (95% CI 53.1% to 66.8%) for females and 72.2% (95% CI 66.2% to 77.5%) for males (p = 0.008, chi-square test). With structural and unknown aetiology, seizure freedom rates were 61.5% (95% CI 55.2% to 67.4%) and 75.3% (95% CI 68.5% to 81.0%), respectively. Seizure freedom rates for FBTCS, FAS and FIAS as the presenting seizure type were 69.4% (95% CI 64.1% to 74.2%), 66.7% (95% CI 55.4% to 76.3%) and 46.2% (95% CI 31.6% to 61.4%), respectively. The seizure freedom rate among patients with normal EEG in focal epilepsy was 73.6% (134 of 182, 95% CI 66.8% to 79.5%) and with epileptiform activity on EEG 56.2% (50 of 89, 95% CI 45.8% to 66.0%). The seizure freedom rate among patients above 60 years of age was 67.0% (95% CI 57.6% to 75.2%).

Patients with focal epilepsy were most often prescribed OXC (280, 64.5%), followed by CBZ (77, 17.7%), VPA (47, 10.8%), PHT (14, 3.2%) and LTG (10, 2.3%) as the first ASM regimen. The seizure freedom rates for OXC, CBZ and VPA were 65.7% (95% CI 60.0% to 71.0%), 70.1% (95% CI 59.2% to 79.2%) and 74.5% (95% CI 60.5% to 84.7%), respectively.

Table 3 shows the baseline characteristics and seizure freedom outcomes with the first ASM in patients with generalized epilepsy.

TABLE 1 Background characteristics (median and interquartile range or frequency and percentage) at the last clinic visit for all patients divided by the year when first antiseizure medication treatment was initiated

	All patients	1995–2000	2001–2005
N	459	239	220
Sex, n (%)			
Female	208 (45.3)	109 (45.6)	99 (45.0)
Male	251 (54.7)	130 (54.4)	121 (55.0)
Duration of follow-up, years, med (IQR)	2.6 (4.0)	4.2 (5.7)	1.8 (2.3)
Age at date of diagnosis, med (IQR)	45.0 (31.0)	43.0 (29.0)	48.0 (34.5)
Aetiology, n (%)			
Structural			
Benign tumour	19 (4.1)	11 (4.6)	8 (3.6)
Hippocampal sclerosis	3 (0.7)	2 (0.8)	1 (0.5)
Malformation of cortical development	11 (2.4)	5 (2.1)	6 (2.7)
Malignant tumour	21 (4.6)	9 (3.8)	12 (5.5)
Other hippocampal pathology	12 (2.6)	5 (2.1)	7 (3.2)
Perinatal injury	5 (1.1)	5 (2.1)	0
Traumatic brain injury	27 (5.9)	15 (6.3)	12 (5.5)
Vascular lesion	113 (24.6)	61 (25.5)	52 (23.6)
Vascular malformation	30 (6.5)	9 (3.8)	21 (9.5)
Genetic	25 (5.4)	14 (5.9)	11 (5.0)
Infectious	15 (3.3)	9 (3.8)	6 (2.7)
Unknown	178 (38.8)	94 (39.3)	84 (38.2)
Epilepsy type, n (%)			
Focal	434 (94.6)	225 (94.1)	209 (95.0)
Generalized	25 (5.4)	14 (5.9)	11 (5.0)
Type of first seizure, n (%)			
FBTCS	320 (69.7)	172 (72.0)	148 (67.3)
FAS	75 (16.3)	37 (15.5)	38 (17.3)
FIAS	40 (8.7)	16 (6.7)	24 (10.9)
GTCS	15 (3.3)	10 (4.2)	5 (2.3)
Myoclonic	9 (2.0)	4 (1.7)	5 (2.3)
EEG			
Normal	188 (41.0)	94 (39.3)	94 (42.7)
Epileptiform activity	103 (22.4)	60 (25.1)	43 (19.5)
Focal slowing	66 (14.4)	38 (15.9)	28 (12.7)
Unspecific	52 (11.3)	25 (10.5)	27 (12.3)
No EEG	50 (10.9)	22 (9.2)	28 (12.7)

(Continues)

TABLE 1 (Continued)

	All patients	1995–2000	2001–2005
First antiseizure medication			
Carbamazepine	78 (17)	60 (25.1)	18 (8.2)
Clonazepam	2 (0.4)	1 (0.4)	1 (0.5)
Gabapentin	1 (0.2)	0 (0)	1 (0.5)
Lamotrigine	15 (3.3)	9 (3.8)	6 (2.7)
Levetiracetam	1 (0.2)	0 (0)	1 (0.5)
Oxcarbazepine	281 (61.2)	136 (56.9)	145 (65.9)
Phenobarbital	1 (0.2)	1 (0.4)	0 (0)
Phenytoin	14 (3.1)	10 (4.2)	4 (1.8)
Tiagabine	1 (0.2)	1 (0.4)	0 (0)
Topiramate	1 (0.2)	0 (0)	1 (0.5)
Valproic acid	64 (13.9)	21 (8.8)	43 (19.5)

Abbreviations: FAS, focal aware seizure; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizure; GTCS, generalized tonic-clonic seizures; IQR, interquartile range; med, median; n, number.

There were no significant differences with respect to clinical characteristics. Patients with generalized epilepsy were younger than patients with focal epilepsy, with a median age of 18 years at diagnosis. The seizure freedom rate was 72.0% (18 of 25, 95% CI 52.4% to 85.7%). The seizure freedom rate for females was 60.0% (95% CI 35.7% to 80.2%), and for males, it was 90.0% (95% CI 59.6% to 98.2%). Patients with generalized epilepsy were most often prescribed VPA (17 of 25, 68.0%), followed by LTG (5 of 25, 20.0%) as the first ASM regimen.

Among girls and women of childbearing age (ages 16–46 years), 12.6% (14 of 111) had VPA as the first ASM. Five had focal epilepsy, and nine had generalized epilepsy.

Table 4 provides detailed information about ORs for seizure freedom in patients with focal epilepsy with reference to sex, age at diagnosis, first ASM used, type of first seizure, aetiology and EEG. Patients with epilepsy due to an unknown aetiology had 2.2 times higher odds of seizure freedom than patients with a structural aetiology (OR 2.22, p = 0.003). In contrast, epileptiform activity on EEG decreased odds of seizure freedom (OR 0.55, p=0.036). Additionally, patients with FIAS as their presenting seizure showed tendency to less likely achieve seizure freedom than patients with FBTCS (OR 0.52, p = 0.091).

Table 5 summarizes the reasons for first ASM withdrawal in focal and generalized epilepsy and with ASM used. Only 12.4% (57 of 459, CI 95% CI 9.7% to 15.8%) of the patients discontinued their first ASM due to side effects. Furthermore, based on specific ASMs in focal epilepsy, OXC was discontinued due to side effects in 12.5% (35 of 280, 95% CI 9.1% to 16.9%) of patients. Discontinuation rates due to side effects were not significantly different for other first-line ASMs, such CBZ, LTG and VPA, with rates of 14.3% (11 of 77, 95% CI 8.2% to 23.8%), 20.0% (2 of 10, 95% CI 5.7% to 51.0%) and 12.8% (6 of 47, 95% CI 6.0% to 25.2%), respectively.

4 | DISCUSSION

The present study, which applied the recent ILAE guidelines for the diagnosis [12] and classification of epilepsy,[14] epileptic seizures [13] and definitions of an adequate ASM trial,[15] provides new insights into the prognosis of newly diagnosed epilepsy. In our study, the seizure freedom rate for at least one year with the first ASM was 67% for all patients, which is higher than the 50% seizure freedom rate observed in previous studies.[4,5] Our study provides new evidence suggesting that the prognosis of new-onset epilepsy is more granular depending on the age of the patient, aetiology and presenting seizure type, as well as the sex of the patient. Patients with focal epilepsy with unknown aetiology, normal EEG or FBTCS as the presenting seizure type have a better chance of obtaining seizure freedom than patients with structural or infectious aetiology, epileptiform activity on EEG or FIAS as the presenting seizure type.

The age distribution of patients in a given cohort does indeed have a significant effect on the total seizure freedom outcomes because refractory epilepsy is most commonly associated with an earlier onset of epilepsy. In the landmark study by Kwan and Brodie [4] addressing the response to the first ASM therapy as a further subanalysis of the main publication,[21] the mean age at onset of epilepsy in the whole study group was 32.8 years compared to 44.5 years at the time of diagnosis in our study. Moreover, the proportion of patients with an age of diagnosis less than 25 years but 16 years or more was 20.3% (93 of 459) in our study, whereas 9.8% were between 9 and 15 years in Kwan and Brodie's study.[4]

In randomized controlled trials for the first ASM monotherapy, the patients were typically adults with a mean age of approximately 40 years at the time of diagnosis.[22] In a trial in which eslicarbazepine acetate (ESL) was compared to CBZ, 71.1% of ESL-treated patients and 75.6% of CBZ-treated patients were seizure-free for ≥6 months.[6] Even though the initial 6-month response to ASMs is a valuable predictor of long-term response, the seizure freedom rate, in general, is lower when the follow-up time is longer. In a recent study, the initial 6-month seizure freedom rate was 64%, but the 3-year seizure freedom rate declined to 46%.[7] Similarly, with lacosamide (LCM) monotherapy, the 6-month seizure freedom rate was 66% and declined to 60% at one year.[8] According to a recent meta-analysis, there were no statistical differences in the seizure freedom rates in newly diagnosed focal epilepsy between levetiracetam (LEV), zonisamide (ZNS), LCM, ESL and CBZ.[11] In another study, OXC was compared to CBZ in 235 patients aged 15–65 years with similar one-year seizure freedom rates for both ASMs (52% with OXC and 60% with CBZ).[23] With OXC, 59% of patients with focal or generalized onset seizures have been reported to be seizure-free after one year.[9] In elderly patients with newly diagnosed epilepsy, 59% became seizure-free with the first ASM.[10] Moreover, Mohanraj and Brodie [24] reported a high responder rate for elderly patients older than 64 years, with 85% achieving at least one-year remission, although the response to the first ASM regimen for this age group was not reported separately. In a recent systematic review and meta-analysis, there were no significant differences in the seizure freedom rates in newly diagnosed

TABLE 2 Baseline characteristics (median and interquartile range or or proportion and 95% confidence interval) at the last clinic visit in categories of seizure freedom by first antiseizure medication for patients with focal epilepsy

	Seizure freedom by first ASM		
	Yes	No	*p*
N	290	144	
Sex, % (95% CI)			0.008[a]
Female	40.0 (34.5 to 45.7)	53.5 (45.3 to 61.4)	
Male	60.0 (54.3 to 65.5)	46.5 (38.6 to 54.7)	
Duration of follow-up, years, med (IQR)	1.9 (2.9)	4.2 (4.2)	<0.001[b]
Age at date of diagnosis, med (IQR)	47.5 (29.0)	48.0 (31.5)	0.90[b]
Aetiology, % (95% CI)			0.049[b]
Structural			
Benign tumour	3.4 (1.9 to 6.2)	6.3 (3.3 to 11.5)	
Hippocampal sclerosis	0.3 (0.1 to 1.9)	1.4 (0.4 to 4.9)	
Malformation of cortical development	1.7 (0.7 to 4.0)	4.2 (1.9 to 8.8)	
Malignant tumour	3.4 (1.9 to 6.2)	7.6 (4.3 to 13.2)	
Other hippocampal	2.8 (1.4 to 5.3)	2.8 (1.1 to 6.9)	
Perinatal	1.4 (0.5 to 3.5)	0.7 (0.1 to 3.8)	
Traumatic brain injury	6.6 (4.2 to 10.0)	5.6 (2.8 to 10.6)	
Vascular lesion	23.8 (19.3 to 29.0)	30.6 (23.6 to 38.5)	
Vascular malformation	7.2 (4.8 to 10.8)	6.3 (3.3 to 11.5)	
Infectious	3.1 (1.6 to 5.8)	4.2 (1.9 to 8.8)	
Unknown	46.2 (40.6 to 52.0)	30.6 (23.6 to 38.5)	
Type of first seizure, % (95% CI)			0.015[a]
FBTCS	76.6 (71.3 to 81.1)	68.0 (60.1 to 75.1)	
FAS	17.2 (13.3 to 22.0)	17.4 (12.0 to 24.4)	
FIAS	6.2 (4.0 to 9.6)	14.6 (9.7 to 21.3)	
EEG, % (95% CI)			0.0421
Normal	46.2 (40.6 to 52.0)	33.3 (26.2 to 41.4)	
Epileptiform activity	17.2 (13.3 to 22.0)	27.1 (20.5 to 34.9)	
Focal slowing	15.9 (12.1 to 20.5)	13.9 (9.2 to 20.5)	
Unspecific	11.0 (7.9 to 15.2)	12.5 (8.1 to 18.9)	
No EEG	9.7 (6.8 to 13.6)	13.2 (8.6 to 19.7)	

Abbreviations: ASM, antiseizure medication; CI, confidence interval; FBTCS, focal to bilateral tonic-clonic seizures; FAS, focal aware seizures; FIAS, focal impaired awareness seizures; IQR, interquartile range; med, median; n, number.

[a]Pearson's chi-squared test;; [b]Mann-Whitney U-test.

TABLE 3 Baseline characteristics (median and interquartile range or proportion and 95% confidence interval) at the last clinic visit in categories of seizure freedom by first antiseizure medication for patients with generalized epilepsy

	Seizure freedom by first ASM		
	Yes	No	*p*
n	18	7	
Sex, % (95% CI)			0.18[a]
Female	50.0 (29.0 to 71.0)	85.7 (48.7 to 97.4)	
Male	50.0 (29.0 to 71.0)	14.3 (2.6 to 51.3)	
Duration of follow-up in year, med (IQR)	2.8 (5.0)	4.3 (6.7)	0.15[b]
Age at date of diagnosis, med (IQR)	19.0 (7.0)	18.0 (3.9)	0.57[b]
Type of first seizure, % (95% CI)			0.21[a]
GTCS	72.2 (49.1 to 87.5)	42.9 (15.8 to 75.0)	
Myoclonic	27.8 (12.5 to 50.9)	57.1 (25.0 to 84.2)	
EEG, % (95% CI) *			0.33[a]
Normal	18.8 (6.6 to 43.0)	50.0 (18.8 to 81.2)	
Epileptiform activity	68.8 (44.4 to 85.8)	50.0 (18.8 to 81.2)	
Unspecific	12.5 (3.5 to 36.0)	0	

Abbreviations: ASM, antiseizure medication; CI, confidence interval; GTCS, generalized tonic-clonic seizures; IQR, interquartile range; med, median; n, number.

[a]Fisher's exact test;; [b]Mann-Whitney U-test.; *No EEG for three patients (yes 2, no 1).

TABLE 4 Odds ratios with their 95% confidence intervals and p-values from unadjusted and adjusted logistic regression models for seizure freedom in patients with focal epilepsy

	OR (95% CI)	*p*	OR (95% CI)	*p*
Gender (ref. = female)	1.70 (1.11 to 2.61)	0.016	1.78 (1.12 to 2.81)	0.014
Age at date of diagnosis			1.01 (0.99 to 1.02)	0.25
First ASM (ref. = Oxcarbazepine)				
Carbamazepine			1.20 (0.65 to 2.22)	0.56
Valproic acid			1.68 (0.71 to 3.98)	0.24
Lamotrigine			0.67 (0.17 to 2.56)	0.56
Phenytoin			0.80 (0.23 to 2.80)	0.73
Other ASM			0.39 (0.06 to 2.47)	0.32
Type of first seizure (ref. = FBTCS)				
FAS			1.08 (0.58 to 1.99)	0.81
FIAS			0.52 (0.25 to 1.11)	0.091
Aetiology (ref. = Structural)				
Infectious			0.86 (0.24 to 3.09)	0.82
Unknown			2.22 (1.32 to 3.72)	0.003
EEG (ref. = Normal)				
Epileptiform activity			0.55 (0.31 to 0.96)	0.036
Focal slowing			1.04 (0.54 to 2.01)	0.91
Unspecific			0.79 (0.39 to 1.59)	0.51

Abbreviations: ASM, antiseizure medication; CI, confidence interval; FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures; OR, odds ratio; ref, reference.

elderly patients between CBZ, gabapentin (GBP), LCM, LTG, LEV, PHT and VPA.[25] In our study, the responses in the 25–60 and more than 60 years age groups were similar in focal epilepsy. These demographic characteristics may have influenced the increased percentage of patients achieving seizure freedom in our study. Therefore, the age distribution of epilepsy patients needs to be taken into consideration when assessing the probability of seizure freedom with the first ASM.

According to our study, men with focal epilepsy were more likely to achieve seizure freedom with their first ASM than were females, but we could not identify any particular reason, including aetiology, for this unexpected finding. Underreporting is one potential explanation because a significant proportion of patients with epilepsy underreport their seizures. Forty per cent of patients who anonymously reported a seizure in the past year held a driving licence, but only a quarter of these admitted to not being seizure-free.[26] Neurology's role is not only to treat epilepsy but also to regulate the rights of epileptic patients to hold a driving licence or access certain occupations. This could cause males to underreport their seizures compared to females.

In this study, we applied the new 2017 ILAE classifications of seizure and epilepsy type.[13,14] However, none of the patients were categorized as having combined generalized and focal epilepsy, which is a new epilepsy type compared with the previous classification system, most likely due to the age distribution of our study group. In the seminal study by Kwan et al,[4] epilepsies were classified into i) idiopathic, ii) cryptogenic and iii) remote symptomatic, making the comparison with the new 2017 ILAE classification ambiguous. The number of patients with generalized epilepsy was much lower in our study (5%) than in the idiopathic group (25%) in a previous study.[4]

TABLE 5 Reasons for the withdrawal of the first antiseizure medication (proportion and 95% confidence interval).

	n	Reason for the withdrawal		Other reasons
		Lack of efficacy	Side effects	
Epilepsy type				
Focal	106	46.2 (37.0 to 55.7)	50.9 (41.6 to 60.3)	2.8 (1.0 to 8.0)
Generalized	5	40.0 (11.8 to 76.9)	60.0 (23.1 to 88.2)	0
Total	111	45.9 (37.0 to 55.2)	51.4 (42.2 to 60.4)	2.7 (0.9 to 7.6)
Antiseizure medication				
Carbamazepine	20	40.0 (21.9 to 61.3)	60.0 (38.7 to 78.1)	0
Clonazepam	1	1	0	0
Lamotrigine	4	25.0 (4.6 to 69.9)	75.0 (30.1 to 95.4)	0
Oxcarbazepine	69	44.9 (33.8 to 56.6)	53.6 (42.0 to 64.9)	1.4 (0.3 to 7.8)
Phenobarbital	1	1	0	0
Phenytoin	5	60.0 (23.1 to 88.2)	0	40.0 (11.8 to 76.9)
Tiagabine	1	0	1	0
Valproic acid	10	60.0 (31.3 to 83.2)	40.0 (16.8 to 68.7)	0

Abbreviation: n, number.

The seizure freedom rate for patients with idiopathic epilepsy was 58%,[4] compared with 72% in patients with generalized epilepsy in our study. The combined seizure freedom rate for symptomatic and cryptogenic epilepsy was 43.5% in the Kwan and Brodie study [4] compared to 67% with focal epilepsy in our study.

The new 2017 ILAE classification provides more categories based on the aetiology of epilepsy.[14] In our adult population, the vast majority fell into categories of either structural (53%) or unknown (39%) aetiology, whereas all patients with genetic aetiology (5%) were in the group of generalized epilepsy. Three per cent of our patient population had infectious aetiology. In addition, none of the patients had metabolic or immune aetiology for their epilepsy since metabolic epilepsies usually begin in childhood [27] and awareness of autoimmune epilepsy increased significantly in the 2010 s—over a decade after our patients were diagnosed with epilepsy.[28] Seizure freedom rates in patients with unknown aetiology were significantly higher (75%) than those in patients with structural aetiology (61%), whereas in Kwan's study, there was no difference between the patients with symptomatic (43%) and cryptogenic (44%) epilepsy. The new more granular classification of aetiologies makes the comparison between different study populations easier because the heterogeneity of different study populations with regard to age and referral system does have a substantial effect on the probabilities of achieving seizure freedom.

The major seizure types in the new 2017 ILAE classification are quite easily transferrable from the previous 1981 ILAE seizure classification.[14] In our study, FIAS as the first seizure type was associated with a trend to lower probability of seizure freedom than FBTCS and FAS. In our single-centre cohort, the proportion of patients with FIAS as their first seizure type was lower (9%) than that described in the classical incidence study from Rochester Minnesota (36%).[16] The low proportion of FIAS may also contribute to good seizure outcomes in our study. Epileptiform activity on EEG has been associated with an increased risk of seizure recurrence also in previous studies.[29]

Lack of efficacy (46%) and side effects (49%) was almost equally the most common reasons for the discontinuation of the first ASM. Lack of efficacy has been found to be the main reason for ASM discontinuation even with newer ASMs.[5] In our study, there were no significant differences between ASMs for the number of discontinuations, with OXC and CBZ as the most commonly used ASMs. In a previous study, OXC was compared to CBZ in 235 patients aged 15–65 years with newly diagnosed epilepsy, and the withdrawal rates due to significant adverse events were 14% with OXC and 26% with CBZ.[23] In a previous study from Finland, 3-year retention rates with OXC and CBZ were similar (72.7% and 79.6%, respectively).[30] In a recent network meta-analysis, discontinuation rates due to side effects for different ASMs were also between 11 and 19%.[11] Treatment with CBZ was associated with a higher risk of discontinuation than that with LTG, LEV or VPA in the elderly.[23]

Due to the retrospective study design, selection bias is a potential limitation of this study. In addition, our cohort consisted of patients from an era when newer ASMs were not yet widely used or existed. However, due to the reimbursement policy, CBZ, OXC

and VPA are currently chosen as first-line ASMs for focal epilepsy in Finland. Nevertheless, the new ASMs have not yet improved the probabilities of seizure freedom.[5,11,23] Due to our study design, an initial seizure freedom rate of at least one year was used, but long-term seizure freedom rates were not available. We were unable to document a possible underreporting of seizures. The low proportion of FIAS in our cohort may also be due to the lack of recognition of these seizures that has been previously described.[31]

5 | CONCLUSIONS

Our study provides new data for the prediction of seizure freedom in the adult population with the onset of epilepsy at 16 years or older, providing a more positive outlook compared with previous studies with an overall estimation that two-thirds of patients with new-onset epilepsy already obtain seizure freedom with the first ASM use. Additionally, favourable prognostic factors include male sex, unknown aetiology, no epileptiform activity on EEG or FBTCS or FAS as the presenting seizure type. Furthermore, only 12.4% of the patients discontinued their first ASM due to side effects.

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CONFLICT OF INTEREST

H.H, J.T.S and J.R report no conflicts of interest. J.P has participated in clinical trials for Eisai, UCB and Bial; received research grants from Eisai, Medtronic, UCB and Liva-Nova; received speaker honoraria from LivaNova, Eisai, Medtronic, Orion Pharma and UCB; received support for travel to congresses from LivaNova, Eisai, Medtronic and UCB; and participated in advisory boards for Arvelle, Novartis, LivaNova, Eisai, Medtronic, UCB and Pfizer.

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PUBLICATION II

Response to subsequent antiseizure medications after first antiseizure medication failure in newly diagnosed epilepsy.

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Response to subsequent antiseizure medications after first antiseizure medication failure in newly diagnosed epilepsy

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Objective: There is a lack of studies using the International League Against Epilepsy (ILAE) recommendation to define drug-resistant epilepsy (DRE). This study evaluated the seizure freedom rates of substitution or add-on and subsequent antiseizure medication (ASM) therapies using different proposed definitions of DRE or ASM trials in patients with a failed first ASM. We also identified prognostic factors for 1-year seizure freedom.

Methods: This study included 459 patients with epilepsy of whom 151 were not seizure-free after the first ASM. Multilevel mixed-effects logistic regression was used to examine the correlation between observations from the same patient.

Results: The overall seizure freedom rate with the first and subsequent ASMs was 88.0% (404/459). The rate of DRE when defined as the failure of two ASMs for any reason was 20.0%, and according to the ILAE definition of DRE, it was 16.3%. After failing the first ASM, 63.6% of patients (96/151) became seizure free with subsequent ASMs and tried an average of 1.9 ASMs (range 1–5). Of the patients who achieved 1-year seizure freedom, 10.1% (41/404) were taking polytherapy and there was no difference between substitution and add-on. All the patients with generalized epilepsy were seizure-free. A favorable prognostic factor was age >60 years and an EEG without epileptiform activity. The efficacies of the different ASMs were largely similar, but drugs that enhanced GABA-mediated inhibitory neurotransmission had the lowest seizure freedom rate.

Significance: In adults with newly-diagnosed epilepsy, 1-year seizure freedom was achieved for almost 90% of the patients. After failing the first ASM, two-thirds of the patients responded to subsequent ASM regimens. Our results support the feasibility and applicability of the ILAE concept of an adequate ASM trial and the failure of two ASMs as a definition of DRE.

KEYWORDS

seizure freedom after first antiseizure medication, drug-resistant epilepsy, ILAE classification, oxcarbazepine, valproic acid, carbamazepine

Key points

- The seizure freedom rate with the first and subsequent antiseizure medications was 88.0% (404/459). Therefore, 12.0% of the patients had absolute drug-resistant epilepsy.
- When the International League Against Epilepsy (ILAE) criteria for drug-resistant epilepsy–failure of two ASMs due to the lack of efficacy–was applied, 16.3% had drug-resistant epilepsy.
- Most patients (57.3%) who became seizure-free after failing their first antiseizure medication received monotherapy.
- Elderly patients (> 60 years old) were more likely to become seizure-free than patients aged 25–60 years (odds ratio = 2.75, $p = 0.014$).
- ASMs that enhanced GABA-mediated inhibitory neurotransmission had the lowest seizure freedom rate (14.3%).

Introduction

Multiple factors influence the probability of seizure freedom in patients with newly diagnosed epilepsy, including the patient population, antiseizure medication (ASM) availability, and classification applied for the diagnostic criteria of epilepsy, seizure type, and epilepsy type. A landmark study of previously untreated patients with epilepsy found that 47% and 14% became seizure-free during treatment with their first and second, or third ASM, respectively. Eventually, 63% achieved at least 1-year of seizure freedom (1). Most previous studies used the total number of failed ASMs as a marker of refractoriness; however, there is a clear difference in the probability of achieving seizure freedom, depending on the reason for the discontinuation of a given ASM. In a randomized controlled trial, 70% of patients achieved 12-months remission, with a first treatment failure in 65% and 80% due to inadequate seizure control and side effects, respectively (2).

The International League Against Epilepsy (ILAE) provided a standardized definition in 2010 to enhance uniformity across studies and defined drug-resistant epilepsy (DRE) as the failure of adequate trials of two tolerated, appropriately chosen, and used ASM schedules, as a monotherapy or in combination, to achieve sustained seizure freedom (3). However, epidemiological studies applying this official recommendation are lacking. Some studies suggested the concept of absolute DRE that requires the failure of six ASMs because a significant minority of patients were rendered seizure-free with the addition of newly administered ASMs after the failure of two to five past ASMs (4). A hypothesis for differentiation between DRE and uncontrolled epilepsy was proposed because some patients had inadequate use of ASMs (5).

Prognostic factors for seizure freedom in patients with epilepsy and first ASM have been extensively studied (6). We have recently reported in a group of patients with newly diagnosed epilepsy that those with focal epilepsy with unknown etiology, normal electroencephalogram (EEG), or focal to bilateral tonic-clonic seizures (FBTCS) as the presenting seizure type had a better chance of obtaining seizure freedom with the first ASM than patients with structural or infectious etiology, epileptiform activity on EEG, or focal impaired awareness seizures (FIAS) (7). However, prognostic factors for achieving remission with the second or subsequent ASM regimens have been less explored. According to a recent study, seizure freedom with the second ASM was more probable in men and patients >45 years, and patients with generalized TCS or FBTCS before initiation of the first ASM were more likely to respond to the second ASM (2).

Although the advantages of ASM monotherapy in the initial management of epilepsy are widely accepted, there is no global agreement on treatment strategies when seizures continue after the initial monotherapy. Two different strategies with similar outcomes according to some studies have been used, the substitution of the initially ineffective ASM with another ASM administered as monotherapy or the administration of a second ASM as an add-on polytherapy (8, 9). In contrast, a recent study of patients in whom the first monotherapy failed due to the lack of efficacy reported that 51.0% of patients following substitution and 38.1% of patients with add-on achieved seizure remission (10). The role of combination therapy as a treatment strategy for epilepsy is being re-evaluated. Based on the drugs' perceived primary mechanism of action (MOA), it has been suggested that more patients become seizure-free when the combination involves a sodium channel blocker and a drug with multiple MOA compared with other combinations (11).

This study evaluated seizure freedom rates after failing the first ASM using different proposed definitions of the DRE and ASM trials. We also determined prognostic factors for seizure freedom, including the effect of second substitution or add-on ASM therapy and subsequent ASM therapies with different MOA combinations in patients who did not become seizure-free with the first ASM.

Materials and methods

Originally, the study included 584 patients with epilepsy aged ≥16 years who were referred to the Tampere University Hospital (Pirkanmaa region, Finland) between January 1, 1995, and December 31, 2005. All individuals were retrospectively followed-up until at least 1-year of seizure freedom, December 31, 2006, or until death. Medical records were examined retrospectively, and after thorough validation of epilepsy diagnosis, 459 patients were finally included (7). Patients with alcohol and recreational drug abuse were excluded from our study because the seizures in these patients were considered provoked. According to the Finnish healthcare system, most newly diagnosed patients with epilepsy and practically all

patients who continue to have seizures after the first ASM failure are treated within a public specialist service system. When adult patients reach 1 year of seizure freedom, their care is usually transferred to the general practitioner level, and if these patients have seizure relapses, their care is transferred back to a specialist clinic. Patients who continue to experience seizures continue to receive care at the specialist level.

ASM therapy was initiated according to the standard clinical practice during that period. If seizure freedom was not achieved with the past ASM, substitution or add-on ASMs were initiated at the treating physician's discretion, which reflects decision-making in a real-world context. Adequate ASM trials were identified using the criteria provided by the ILAE definitions (3).

Baseline characteristics were described as medians with interquartile ranges (IQRs) or frequencies with percentages. Depending on the variable, group comparisons were performed using Pearson's Chi-square test, the Mann–Whitney U test, or Fisher's exact test. Binary logistic regression was used to examine the association between seizure freedom following a second or subsequent ASM and sex. The Holm–Bonferroni method was used for multiple tests. We selected covariates based on the findings from our first analysis (7). Age at diagnosis (continuous), etiology (structural as a reference group), and seizure type (FBTCS as a reference group) were examined as potential confounding factors. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each covariate. We also examined the association between seizure freedom and ASM or ASM combinations. The same patient may have received two or more ASMs or ASM combinations; therefore, we used a multilevel mixed-effects logistic regression adjusted for the ASM regimen number to consider the correlation between observations from the same patient. A group of sodium channel blockers was used as the reference group, and ORs with 95% CIs were reported for other ASMs or ASM combinations categorized by their putative primary MOA. The data were analyzed using the software Stata version 16.1 (College Station, TX, United States). There was no contact with patients, and information was collected from the patient register of the Tampere University Hospital. This study does not require ethics committee approval according to Finnish Law on Research. Following Finnish guidelines, this study was approved by the head of the Tampere University Science Center.

Results

Seizure freedom rates according to different definitions of DRE

The baseline characteristics of all 459 previously untreated patients with validated epilepsy diagnoses were presented in detail in our previous study (7). The responses to the first and subsequent ASM schedules in absolute numbers using the ILAE definition of an adequate ASM trial are presented in Table 1. A total of 308 patients (76.2% of all patients achieving seizure freedom with ASM) became seizure-free following the administration of the first ASM. Therefore, 151 patients who continued to have seizures constituted the present study group. When using the ILAE definition of an adequate ASM trial, 346 patients (85.2% of all patients achieving seizure freedom) became seizure-free after the first ASM regimen.

Fifty-nine of 151 patients (14.5% of all patients achieving seizure freedom) became seizure-free following the administration of the second overall ASM, and 38 of 102 patients became seizure-free with the second ASM regimen (9.4% of all patients achieving seizure freedom), according to the ILAE definition of an adequate trial (subsequent ASM was initiated only due to the lack of efficacy). Thirty-seven patients became seizure-free after the third to sixth ASM regimens when all ASM trials were included, compared with 20 patients who became seizure-free when the adequate ASM trial definition was used (5.4% third, 2.2% fourth, and 1.0% fifth ASM regimens vs. 2.7, 1.5, and 0.7% of all seizure-free patients, respectively). A minority of patients (28.3%, 26/92) did not start the third ASM due to shortness of follow-up or other reasons (Figure 1). Four patients had persistent seizures, even after six ASM trials. Two patients who had not become seizure-free with at least three ASMs underwent epilepsy surgery and subsequently became seizure-free.

The seizure freedom rate after the initiation of a second or subsequent ASM therapy in absolute numbers of patients in whom the first ASM treatment failed to control seizures was 63.6% (96/151) and 56.9% (58/102), according to the ILAE adequate trial definition. The seizure freedom rate with the first and subsequent ASMs was 88.0% (404/459). Therefore, 12.0% of the patients had an absolute DRE (six or more regimens were tried). The cumulative seizure freedom rate was 80.0% (367/459) after the second total ASM regimen and 83.7% (384/459) after two adequate trials, regardless of the reason for substitution or add-on. This indicates that 16.3% of the entire study population fulfilled the ILAE criteria for DRE. Conversely, in 20.0% of the patients, two ASMs failed to control seizures in absolute numbers.

Prognostic factors for achieving seizure freedom either after the second ASM or after fulfilling the criteria for DRE (third or subsequent ASM regimen)

The clinical characteristics of all 151 (32.9%) patients who did not become seizure-free following the first ASM with reference to achieving seizure freedom either after the

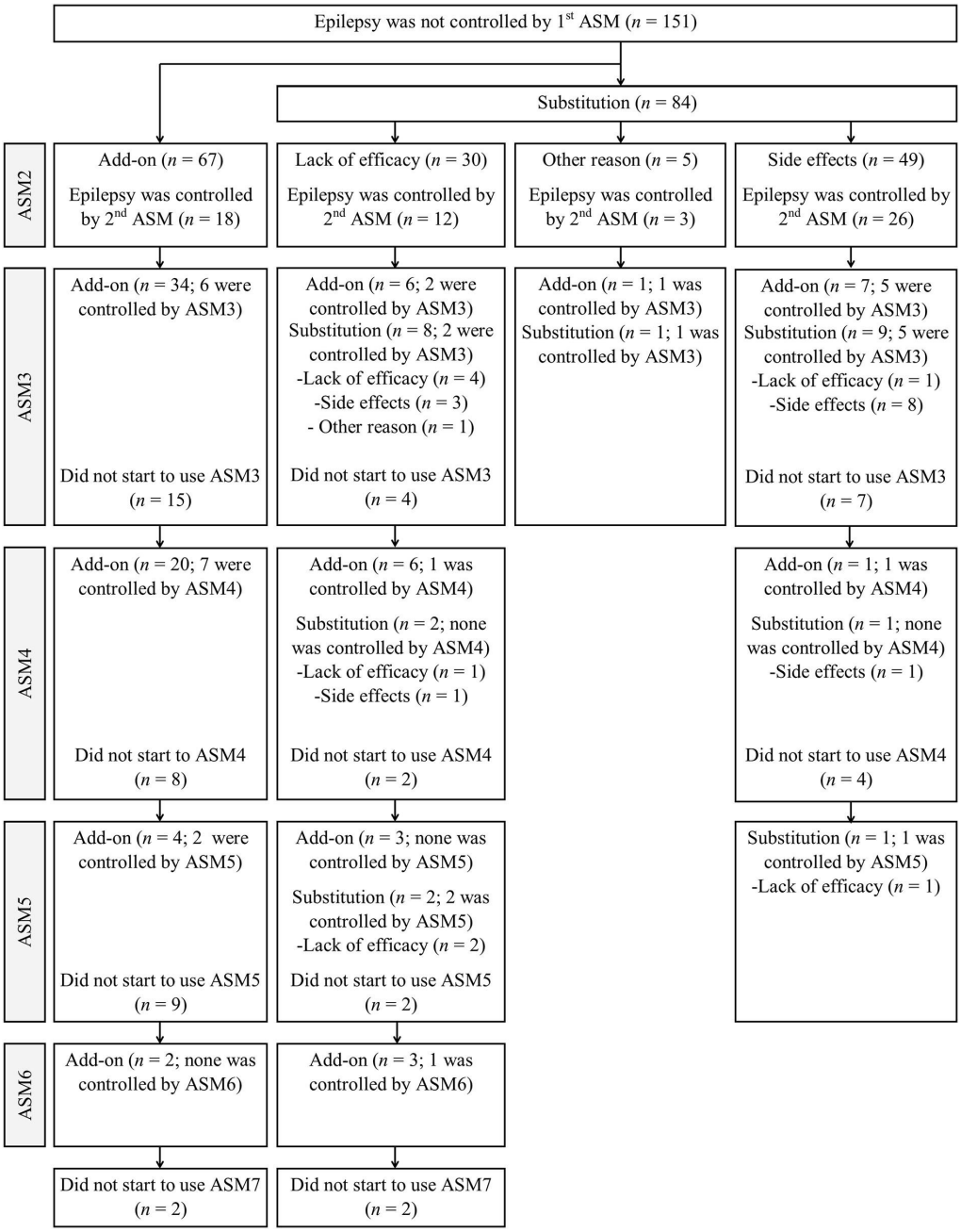

FIGURE 1
Patient responses to different combinations of the add-on and substitution ASMs after seizure freedom.

TABLE 1 Antiseizure medication schedules.

	# ASM Regimen	Total patients using these ASMs (*n*)	Seizure freedom			
			Total (*n*)	% of patients achieving seizure freedom with ASM	% of the total achieving seizure freedom (*n* = 406)	% of the total study cohort (*n* = 459)
All patients regardless of the reasons for the initiation of subsequent antiseizure medication	1	459	308	67.1	75.9	67.1
	2	151	59	39.1	14.5	12.9
	3	66	22	33.3	5.4	4.8
	4	30	9	30.0	2.2	2.0
	5	10	4	40.0	1.0	0.87
	6	6	2	33.3	0.5	0.44
	Total	459	406*	na	99.5	88.0
Patients who used subsequent antiseizure medication only due to lack of efficacy	1	459	346	75.4	85.2	75.4
	2	102	38	37.3	9.4	8.3
	3	40	11	27.5	2.7	2.4
	4	18	6	33.3	1.5	1.3
	5	5	3	60.0	0.7	0.65
	6	2	0	-	-	-
	Total	459	406*	na	99.5	88.0

ASM, antiseizure medication; na, not applicable; n, number; *, including two patients who became seizure free with epilepsy surgery.

second ASM or after fulfilling the criteria for DRE (third or subsequent ASM regimens) are presented in Table 2. All seven patients with generalized epilepsy failing the first ASM became seizure-free following the second or subsequent ASM. Patients who became seizure-free with the second or subsequent ASM regimens were found to be significantly associated with the presenting seizure type and EEG. The likelihood of having FBTCS or FAS as the presenting seizure type and EEG without epileptiform activity was higher in patients who became seizure-free with the second ASM regimen, and they were also significantly older than patients who became seizure-free with the third or subsequent ASM regimens. Patients with persistent seizures were more likely to have epileptiform activity on EEG than those responding to the second ASM regimen. The follow-up time for patients with either persistent seizures or who had become seizure-free after the third or later ASM was significantly longer compared with those responding to the second ASM (6.0 years, 4.7 years, and 2.6 years, respectively).

At the time of diagnosis, most patients (86/151, 57.0%) were 25–60 years of age, whereas 19.9% (30/151) had epilepsy diagnosed between 16–25 years, and 23.2% (35 of 151) were elderly (>60 years old). The cumulative seizure freedom rate for focal epilepsy was 85.7% (12/14) in patients aged 16–25 years, 50.6% (43/85) in patients aged 25–60 years, and 75.6% (34/45) in elderly patients, who were more likely to become seizure-free than those aged 25–60 years (OR = 2.75, $p = 0.014$). There was no difference in cumulative seizure freedom between young (18–25 years of age) and elderly patients (OR = 0.52, $p = 0.429$). Among women of childbearing age (ages 16–46 years), 25.0% (11/44) had valproic acid (VPA) as a second or subsequent ASM. Eight of these patients had focal epilepsy and three had generalized epilepsy. The seizure-freedom rate was 81.8% (9/11).

With regard to prognostic factors for seizure freedom in patients with focal epilepsy, detailed information about the association between sex, age at diagnosis, type of first seizure, etiology, and EEG is presented in Table 3. Patients with epilepsy due to an unknown reason had a trend for higher odds (OR = 2.05, 95% CI: 0.84–5.01) of seizure freedom than patients with structural etiology. Patients with FIAS as their presenting seizure were less likely to achieve seizure freedom than those with FBTCS but this trend was not significant. The seizure freedom rate with a second or subsequent ASM in focal epilepsy was 61.8% (89/144), with no significant differences related to sex, etiology, type of the first seizure, or EEG. The seizure freedom rate for focal epilepsy was 62.3% in females and 61.2% in males ($p = 0.888$). With structural and unknown etiologies, seizure freedom rates were 59.6 and 68.2%, respectively. The seizure freedom rates for the FBTCS, FAS, and FIAS as the presenting seizure types were 65.3, 64.0, and 52.4%, respectively.

TABLE 2 Background characteristics (median and interquartile range or frequency and percentage) at the last clinic visit for all patients with epilepsy who did not become seizure-free following administration of the first antiseizure medication.

	All patients	Seizure freedom		Persistent seizures	p^1	p^2
		After 2nd ASM	After 3rd or later ASM			
N	151	59	39	53		
Sex, *n* (%)					0.178[3]	0.992[3]
Female	83 (55.0)	30 (50.8)	26 (66.7)	27 (50.9)		
Male	68 (45.0)	29 (49.2)	13 (33.3)	26 (49.1)		
Duration of follow-up, med (IQR)	4.2 (2.5–6.9)	2.6 (1.4–4.6)	4.7 (2.9–7.0)	6.0 (4.2–9.0)	0.001[4*]	<0.001[4*]
Age at diagnosis, med (IQR)	44 (27–59)	51 (35–70)	28 (21–53)	42 (31–53)	0.007[4*]	0.088[4]
Epilepsy type, *n* (%)					0.063[3]	0.497[5]
Focal	144 (95.4)	57 (96.6)	34 (87.2)	53 (100)		
Generalized	7 (4.6)	2 (3.4)	5 (12.8)	0		
Etiology, *n* (%)					0.161[3]	0.224[5]
Structural	94 (62.3)	35 (59.3)	22 (56.4)	37 (69.8)		
Genetic	7 (4.6)	2 (3.4)	5 (12.8)	0		
Infectious	6 (4.0)	1 (1.7)	2 (5.1)	3 (5.7)		
Unknown	44 (29.1)	21 (35.6)	10 (25.6)	13 (24.5)		
Type of 1st seizure, *n* (%)					0.021[3*]	0.095[5]
FBTCS	98 (64.9)	42 (71.2)	22 (56.4)	34 (64.2)		
FAS	25 (16.6)	12 (20.3)	4 (10.2)	9 (17.0)		
FIAS	21 (13.9)	3 (5.1)	8 (20.5)	10 (18.9)		
GTCS	3 (2.0)	1 (1.7)	2 (5.1)	0		
Myoclonic	4 (2.6)	1 (1.7)	3 (7.7)	0		
EEG, *n* (%)					0.004[3*]	0.011[3*]
Normal	51 (33.8)	28 (47.5)	9 (23.1)	14 (26.4)		
Epileptiform activity	42 (27.8)	9 (15.3)	17 (43.6)	16 (30.2)		
Focal slowing	20 (13.2)	7 (11.9)	5 (12.8)	8 (15.1)		
Unspecific	18 (11.9)	3 (5.1)	5 (12.8)	10 (18.9)		
No EEG	20 (13.2)	12 (20.3)	3 (7.7)	5 (9.4)		

[1], p-value for comparison between seizure freedom after the 3rd or later ASM (two patients who became seizure-free after epilepsy surgery are not included) and seizure freedom after the 2nd ASM.
[2], p-value for comparison between persistent seizures and seizure freedom after the 2nd ASM.
[3], Chi-squared test.
[4], Mann-Whitney U test.
[5], Fisher's exact test.
[*]Denotes statistically significant association using the Holm-Bonferroni correction (thresholds for the lower and higher p-value are 0.025 and 0.05).
ASM, antiseizure medication; FBTCS, focal to bilateral tonic-clonic seizures; FAS, focal aware seizures; FIAS, focal impaired.
awareness seizures; GTCS, generalized tonic-clonic seizures, IQR, interquartile range, med, median.

Monotherapy vs. polytherapy after the first ASM failure

The differences in background characteristics between the add-on and substitution subgroups due to the lack of efficacy are shown in Table 4. Additionally, more details on patient responses to different combinations of the add-on and substitution ASMs after seizure freedom was not achieved with the administration of the first ASM are presented in Figure 1. Patients who became seizure-free after failing the first ASM had an average of 1.9 ASMs (standard deviation, 1.0; range: 1–5). Most patients (57.3%, 55/96) received monotherapy and two ASMs were used concurrently by 39.6% (38/96) of the patients. Only two patients (2.1%) used three ASMs simultaneously and one patient (1.0%) used four ASMs simultaneously. Among the patients who achieved 1-year seizure freedom in the entire cohort, 10.1% (41/404) were on combination therapy.

The seizure freedom rates were 53.0% (26/49) and 40.0% (12/30) in the subgroup of first substitutions when the substitution was due to side effects and lack of efficacy, respectively. When the patient was given the first add-on ASM after seizure freedom was not achieved, 26.9% (18/67) became

TABLE 3 Odds ratios and 95% confidence intervals and *p* values from the logistic regression models for seizure freedom after second or subsequent antiseizure medications in patients with focal epilepsy.

	Model 1		Model 2	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Sex (ref. = female)	0.95 (0.47–1.94)	0.898	0.81 (0.38–1.73)	0.594
Age at date of diagnosis	1.02 (1.00–1.04)	0.123	1.02 (0.99–1.04)	0.229
Type of 1st seizure (ref. = FBTCS)				
FAS	0.96 (0.38–2.44)	0.934	0.76 (0.28–2.01)	0.575
FIAS	0.63 (0.24–1.67)	0.352	0.64 (0.23–1.74)	0.382
Etiology (ref. = structural)				
Infectious	0.88 (0.16–4.90)	0.882	0.83 (0.14–4.79)	0.835
Unknown	2.05 (0.84–5.01)	0.114	1.72 (0.66–4.43)	0.264
EEG (ref. = normal)				
Epileptiform activity			0.60 (0.23–1.53)	0.283
Focal slowing			0.57 (0.17–1.91)	0.359
Unspecific activity			0.34 (0.10–1.14)	0.080
No EEG			1.05 (0.28–3.86)	0.944

CI, confidence interval; FAS, focal aware seizures; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures; OR, odds ratio; ref, reference group.

seizure-free. When the first ASM was substituted ($n = 30$) or another ASM was combined owing to the lack of efficacy after subsequent ASMs ($n = 67$), the final seizure freedom rate was 54.6% (53/97). When the first ASM was changed due to side effects or other reasons after subsequent ASMs, 79.6% (43/54) eventually became seizure-free.

The efficacy of individual ASMs when used in monotherapy and polytherapy was combined for the treatment of focal epilepsy was not significantly different compared with VPA when controlling the ASM regimen or combination number (Table 5). Carbamazepine (CBZ) had the highest seizure freedom rate (64.4%), followed by oxcarbazepine (OXC), phenytoin, and VPA (55.8, 55.2, and 54.7%, respectively).

The seizure freedom rates for the 15 most commonly used monotherapy or polytherapy ASM combinations (of the total 70 regimens) in focal epilepsy, using VPA monotherapy (70.4% seizure-free) as the reference group, are presented in Table 6. There was no significant difference in achieving seizure freedom in any of the monotherapy options compared with the reference group (VPA). The combinations consisting of OXC/VPA (14.3% seizure-free), OXC/gabapentin (23.1% seizure-free), and OXC/lamotrigine (LTG) (28.6%) had significantly lower odds for seizure freedom compared with VPA. The combination of VPA with LTG reached a seizure-free rate of 44.4%, which was the third highest among polytherapy combinations after LTG/LEV and OXC/LEV (57.1% and 50.0%, respectively).

The efficacies of different ASM groups based on the ASM MOA in focal epilepsy are presented in Table 7. Antiseizure medications (ASMs) with enhanced gamma-aminobutyric acid (GABA)-mediated inhibitory neurotransmission was less effective compared with ASMs that modulated voltage-gated sodium channels (14.3% vs. 64.5%) but the finding was not significant when controlling the ASM regimen or combination number (OR = 0.04, $p = 0.098$). The combination of two ASMs, compared with one ASM that modulated voltage-gated sodium channels alone, was not effective. The results were similar even when levetiracetam was separated into this group. Patients >60 years of age used VPA more frequently than patients aged 25–60 years (37.7% vs. 14.6%).

Table 8 summarizes the reasons for the first, second, and subsequent ASM withdrawal in patients with focal epilepsy. A total of 73 and 78 ASMs were discontinued owing to lack of efficacy and side effects, respectively. Oxcarbazepine (OXC), CBZ, LTG, and VPA were discontinued because of side effects in 12.1% (37/307), 42.3% (11/26), 13.5% (7/52), and 13.8% (8/58) of patients, respectively. These differences were statistically significant ($p = 0.004$).

Discussion

Our study provides new insights into the prognosis of newly diagnosed epilepsy and emphasizes the significance of different definitions of ASM trials and DRE. We provide evidence that the age of onset-related composition of the study group plays a major role in the probability of achieving seizure freedom. We also identified that factors other than age influenced seizure outcomes, including seizure type and EEG findings. Owing to the limitations in statistical power, many of these findings are trending. Our analyses of the selection of specific ASMs demonstrate the inherent difficulty in achieving significant

TABLE 4 Baseline characteristics of the patients when the first ASM was substituted or another ASM was combined (add-on) because of lack of efficacy.

	Add-on	Substitution	*p*
N	52	50	
Sex, *n* (%)			0.698[1]
Female	24 (46.2)	25 (50.0)	
Male	28 (52.8)	25 (50.0)	
Duration of follow-up, med (IQR)	4.6 (3.2–7.6)	4.5 (2.6–6.5)	0.357[2]
Age at diagnosis, med (IQR)	32.5 (21–52)	49.0 (28–55)	0.074[2]
Epilepsy type, *n* (%)			
Focal	49 (94.2)	47 (94.0)	0.961[1]
Generalized	3 (5.8)	3 (6.0)	
Etiology, *n* (%)			0.540[1]
Structural	39 (57.7)	35 (70.0)	
Genetic	3 (5.8)	3 (6.0)	
Infectious	2 (3.8)	2 (4.0)	
Unknown	17 (32.7)	10 (20.0)	
Type of 1st seizure, *n* (%)			0.519[1]
FBTCS	30 (57.7)	33 (66.0)	
FAS	7 (13.5)	9 (18.0)	
FIAS	12 (23.1)	5 (10.0)	
GTCS	1 (1.9)	1 (2.0)	
Myoclonic	2 (3.8)	2 (4.0)	
EEG			0.734[1]
Normal	18 (34.6)	16 (32.0)	
Epileptiform activity	16 (30.8)	14 (28.0)	
Focal slowing	5 (9.6)	8 (16.0)	
Unspecific activity	6 (11.5)	8 (16.0)	
No EEG	7 (13.5)	4 (8.0)	

[1]Chi-squared test; [2]Mann–Whitney U test.
FBTCS, focal to bilateral tonic-clonic seizures; FAS, focal aware seizures; FIAS, focal impaired awareness seizures; GTCS, generalized tonic-clonic seizures; IQR, interquartile range; med, median.

findings in a real-world setting owing to a large number of available ASM choices.

The overall initial 1-year seizure freedom rate for all ASM regimens was 88.0%, which was higher than the 63.7% seizure freedom rate observed in previous studies (1,2). When the ILAE-defined ASM trial was used, the seizure freedom rate for the first ASM increased from 67.1 to 75.4% in the total study cohort and from 75.9 to 85.2% in patients who achieved seizure freedom with the use of subsequent ASMs. The use of an adequate ASM trial definition decreased the proportion of patients who achieved seizure freedom with the second ASM from 12.9 to 8.3% of the total study cohort and from 14.6 to 9.4% of patients who achieved seizure freedom with the use of ASMs. Taken together, 16.6% of the entire study population fulfilled the ILAE criteria for DRE, but in 20.0% of the patients, two ASMs failed to control the seizures in absolute numbers. The proportion of patients achieving seizure freedom following the administration of the third to fifth ASM regimens decreased from 2.7 to 0.74% with each subsequent ASM regimen, further validating the relevance of the ILAE definition of DRE (3).

Increasing the number of ASM regimen trials increased the likelihood of seizure freedom, but not all patients in whom two ASM regimens failed to stop seizures initiated further ASM regimens. Therefore, uncontrolled epilepsy is not equivalent to DRE. The most common reason for this is the inadequate use of prescribed ASM(s) (5). A Scottish study reported that 74.2% (742/1,000) of patients who did not achieve seizure freedom with the first ASM tried a second one (12). In our study, all patients tried the second ASM, and 71.7% (66/92) of the patients tried a subsequent ASM. A significant number of patients (40.2%) (37/92) were also rendered seizure-free with the addition of ASMs, even after the failure of two to five previous ASMs. This finding indicates a substantially higher seizure freedom rate than previously reported (4). Patients with a history of recreational drug use have a 64% reduced chance of achieving terminal seizure freedom (5). Patients with alcohol and recreational drug use were excluded from our study because the seizures in these patients were considered provoked. This exclusion may at least partly explain the high seizure-free rates in our study.

The age distribution of patients did have a significant effect on the total seizure-free outcomes in our study, which did not include a large patient population with the onset of epilepsy in infancy and childhood (<16 years of age) who might respond differently to ASMs. Previous studies reported that there was no difference in the rate of terminal remission between adults and children, but patients with epilepsy with the onset in their 20s had the lowest remission probability (13, 14). In a 30-year Scottish longitudinal cohort study, the median age at referral was 33 years compared with 45 years at the time of diagnosis in our study (7, 12). Multivariable analysis of patients aged >70 years in a previous study revealed an OR of 2.25 for 12-months remission after the first treatment failure (2). Elderly patients with focal epilepsy were also more likely to be seizure-free in our study. Moreover, in our study, the patients who became seizure-free with the second ASM regimen were significantly older (mean age 51 years) than those who were free with the third or subsequent regimens (mean age 32 years). Even patients with drug resistant poststroke epilepsy tended to be younger with a mean age of 52 years according to a recent study (15).

All patients with generalized epilepsy in our study became seizure-free, consistent with our previous study (7). Additionally, patients who became seizure-free with the second ASM regimen were more likely to have FBTCS or FAS as the presenting seizure type and to have EEG without epileptiform activity compared with those who became seizure-free with the third or subsequent regimens. In addition, patients with persistent seizures were significantly more likely to have epileptiform activity on EEG than those responding to the second ASM regimen. Both features were also significant for the

TABLE 5 Efficacy of antiseizure medications used in mono- or polytherapy.

	Seizure freedom				
	No, *n* (%)	**Yes, *n* (%)**	**Total**	**OR (95% CI)**	***p***
Oxcarbazepine	168 (44.2)	212 (55.8)	380	0.83 (0.19–3.64)	0.809
Valproic acid	53 (45.3)	64 (54.7)	117	1.00 (reference group)	
Carbamazepine	32 (35.6)	58 (64.4)	90	0.83 (0.11–6.25)	0.853
Lamotrigine	52 (63.4)	30 (36.6)	82	1.19 (0.18–7.65)	0.856
Levetiracetam	23 (57.5)	17 (42.5)	40	1.17 (0.12–11.2)	0.889
Topiramate	26 (72.2)	10 (27.8)	36	0.57 (0.50–6.57)	0.656
Phenytoin	13 (44.8)	16 (55.2)	29	2.21 (0.13–38.1)	0.585
Gabapentin	16 (69.6)	7 (30.4)	23	0.58 (0.04–9.18)	0.700
Clobazam	15 (88.2)	2 (11.8)	17	0.14 (0.003–7.46)	0.330
Tiagabine	15 (93.8)	1 (6.2)	16	0.12 (0.004–33.6)	0.464
Clonazepam	9 (75.0)	3 (25.0)	12	0.30 (0.002–41.6)	0.635
Phenobarbital	3 (100)	0	3		
Benzodiazepine	1 (100)	0	1		
Pregabalin	1 (100)	0	1		

Odds ratios (ORs) and 95% confidence intervals (CIs) and *p* value for seizure freedom from multilevel mixed-effects logistic regression model adjusted for the regimen number.

TABLE 6 Different substitutions or add-on combinations of antiseizure medications were used at least five patients.

	Seizure freedom				
	No, *n* (%)	Yes, *n* (%)	Total	OR (95% CI)	*p*
OXC	107 (35.8)	192 (64.2)	299	0.59 (0.33–1.06)	0.079
VPA	24 (29.6)	57 (70.4)	81	1.00 (reference group)	
CBZ	24 (30.8)	54 (69.2)	78	0.71 (0.34–1.48)	0.365
LTG	14 (48.3)	15 (51.7)	29	0.52 (0.21–1.29)	0.158
PHT	9 (37.5)	15 (62.5)	24	0.72 (0.27–1.91)	0.512
LTG + OXC	10 (71.4)	4 (28.6)	14	0.26 (0.07–0.96)	0.044
GBP + OXC	10 (76.9)	3 (23.1)	13	0.18 (0.04–0.77)	0.020
LEV + OXC	6 (50.0)	6 (50.0)	12	0.43 (0.11–1.67)	0.223
OXC + TPM	7 (63.6)	4 (36.4)	11	0.32 (0.08–1.30)	0.113
LTG + VPA	5 (55.6)	4 (44.4)	9	0.57 (0.13–2.59)	0.471
LEV	5 (55.6)	4 (44.4)	9	0.42 (0.09–1.90)	0.259
TPM	5 (62.5)	3 (37.5)	8	0.32 (0.07–1.51)	0.150
LEV + LTG	3 (42.9)	4 (57.1)	7	0.66 (0.11–3.88)	0.644
OXC + VPA	6 (85.7)	1 (14.3)	7	0.09 (0.01–0.86)	0.036
GBP	2 (40.0)	3 (60.0)	5	0.88 (0.13–5.77)	0.891

Odds ratios (ORs) and 95% confidence intervals (CIs) and *p* values for seizure freedom from the multilevel logistic regression model adjusted for the order of medications.
CBZ, carbamazepine; GBP, gabapentin; OXC, oxcarbazepine; LEV, levetiracetam; LTG, lamotrigine; PHT, phenytoin; TPM, topiramate; VPA, valproic acid.

possibility of seizure freedom with the first ASM (7). The follow-up time for patients with either persistent seizures or becoming seizure-free after the third or later ASMs was significantly longer compared with those responding to the second ASM (6.0 years, 4.7 years, and 2.6 years, respectively), which is explained by the treatment guidelines in Finland where patients are followed up in a specialist center until 1-year seizure freedom is reached.

We did not detect significant differences in seizure freedom related to sex or etiology, which may be due to the limited number of patients in our cohort.

It has been proposed that when the first ASM fails due to lack of efficacy, add-on therapy should be initiated immediately because it is more effective than its application after the second ASM failure, possibly due to the concept of seizures begetting

TABLE 7 Efficacy of antiseizure medications by different groups based on mechanism of action.

ASM group	Seizure freedom		OR (95% CI)	*p*
	No, *n* (%)	Yes, *n* (%)		
1	152 (35.5)	276 (64.5)	1.00 (reference group)	
2	6 (85.7)	1 (14.3)	0.04 (0.001–1.78)	0.098
3	6 (46.2)	7 (53.9)	0.61 (0.09–4.33)	0.624
4	28 (31.8)	60 (68.2)	1.28 (0.49–3.35)	0.620
1 + 2	14 (87.5)	2 (12.5)	0.03 (0.001–1.21)	0.063
1 + 1	14 (70.0)	6 (30.0)	0.35 (0.06–1.90)	0.223
1 + 3	19 (59.4)	13 (40.6)	0.26 (0.03–2.14)	0.211
1 + 4	20 (66.7)	10 (33.3)	0.27 (0.04–2.00)	0.199
3 + 4	8 (88.9)	1 (11.1)	0.01 (0.00003–2.50)	0.101
2 + 2	1	0		
2 + 3	1	0		
4 + 4	1	0		
1 + 1 + 2	3 (75.0)	1 (25.0)		
1 + 1 + 3	2	0		
1 + 1 + 4	3	0		
1 + 2 + 3	2	0		
1 + 2 + 4	7	0		
1 + 3 + 3	1	0		
1 + 3 + 4	1	0		
1 + 4 + 4	1	0		
2 + 2 + 4	1	0		
2 + 3 + 4	1	0		
3 + 3 + 4	0	1		
1 + 1 + 2 + 4	1	0		
1 + 2 + 4 + 4	2	0		
2 + 3 + 4 + 4	0	1		

Odds ratios (ORs) and 95% confidence intervals (CIs) and *p* values for seizure freedom from the multilevel logistic regression model adjusted for the order of medications. ASM, antiseizure medication.
Group 1: modulation of voltage-gated sodium channels.
- phenytoin, carbamazepine, oxcarbazepine, lamotrigine.
Group 2: enhancement of GABA-mediated inhibitory neurotransmission.
- benzodiazepine, tiagabine, clobazam, clonazepam, phenobarbital.
Group 3: modulation of neurotransmitter release via a presynaptic action.
- levetiracetam, gabapentin, pregabalin.
Group 4: multiple mechanisms of action.
- valproic acid, topiramate.

seizures, that is, secondary epileptogenesis (9). However, our study found no differences in efficacy when add-on therapy was used after the first ASM failed. This finding may be explained by a bias from the treating physician, who may have chosen substitution for patients who were estimated to have a better prognosis, and add-on therapy was offered to patients who were thought to have a worse prognosis in achieving seizure freedom. This bias may explain why patients in the add-on strategy tended to be younger than those in the substitution strategy.

When analyzing the efficacy of different ASMs, the highest seizure freedom rate was achieved with CBZ (65.9%) either in monotherapy or polytherapy in focal epilepsy without significant difference compared with other ASMs, where seizure-freedom rates ranged from 11.8% (clobazam) to 55.8% (OXC); only tiagabine had a significantly lower seizure freedom rate (6.7%). The low proportion of FIAS in our cohort may also be due to the lack of recognition of these seizures (16). This result may also explain why VPA had favorable efficacy in our study because it had good efficacy in FBTCS but was suboptimal in FAS and FIAS compared with CBZ (17). The favorable efficacy of VPA likely reflects physicians' preference to initiate VPA in older patients who generally have better responses to ASM.

TABLE 8 Reasons for discontinuation in focal epilepsy based on the entire history of antiseizure medication.

	Lack of efficacy	Side effects	Other reason	Total
Oxcarbazepine	32	38	3	73
Carbamazepine	8	11	1	20
Valproic acid	9	8	2	19
Lamotrigine	4	7	0	11
Phenytoin	4	4	3	11
Topiramate	4	2	1	7
Tiagabine	5	1	1	7
Clobazam	1	4	2	7
Gabapentin	4	1	0	5
Levetiracetam	2	2	0	4

At the group level with regard to the MOA, in monotherapy, ASMs with multiple MOA or with modulation of voltage-gated sodium channels had the highest seizure freedom rates (67.4 and 64.5%, respectively) compared with ASMs modulating neurotransmitter release *via* a presynaptic action (53.9%) without a significant difference. Conversely, ASMs that enhanced GABA-mediated inhibitory neurotransmission had the lowest seizure freedom rate (14.3%; $p = 0.098$). This is in line with an earlier study reporting that none of the patients who received a combination of a sodium channel blocker and GABAergic agent became seizure-free (8).

Lack of efficacy (45%) and side effects (47%) were the most common reasons for discontinuation of the initial and subsequent ASMs. CBZ had the highest rate of discontinuation owing to side effects when used in monotherapy and polytherapy. Treatment with CBZ is associated with a higher risk of discontinuation than treatment with LTG, LEV, or VPA in elderly individuals (18).

Owing to the retrospective study design, selection bias is a potential limitation of the present study. A modest sample size reduced the power required to determine the effect of combined ASMs. We were unable to document the possible underreporting of seizures. Our cohort also consisted of patients from an era when newer ASMs were non–existent or not widely used. However, CBZ, OXC, and VPA are currently chosen as first-line ASMs for focal epilepsy in Finland owing to the reimbursement policy, and many newer ASMs are reimbursed only when used as an add-on therapy but not as a substitution. However, new ASMs have not improved the probability of seizure freedom (12). On the other hand, there is a paucity of studies that have been performed recently analyzing in more detail the efficacy of subsequent ASM regimens including more newer generation ASMs. Therefore, a new study with a similar approach to our study but from a more recent period would be much warranted. Especially there is preliminary evidence of higher seizure freedom rates with cenobamate compared with older drugs (19). A major contribution to timely referral for epilepsy surgery was based on the official ILAE definition of DRE as a failure of two appropriate drug trials introduced in early 2010 (3). Because of our study design, an initial seizure freedom rate of at least 1 year (time to first remission) was used; however, long-term seizure freedom rates were not available. The proportion of relapsing-remitting courses of epilepsy was estimated as 16–52% depending on the patient population (20). Owing to the reasonably long follow-up time, some patients may have become seizure-free due to the natural disease course, regardless of medication. Finally, we did not have information available about psychiatric comorbidities or the number of pre-treatment seizures limiting the analysis of all possible relevant factors.

One of the key issues about the present study is how well the results from our single center can be generalized to other regions and patient populations? First, we have only included patients from adult neurology department (i.e., patients aged 16 years or more); which also explains why there are so few patients with generalized epilepsy because in the majority of those patients the onset of epilepsy is <16 years. On the other hand, our center covers a well-defined geographical area and is practically population-based. Moreover, our patient population does not represent a typical DRE population, because in order to be included in the original study population the patients needed to be newly diagnosed and the development of DRE was one of the outcomes of the study.

Our study provides new data for the prediction of seizure freedom in the adult population, providing a more positive outlook than previous studies. The results of our study support the feasibility and applicability of the ILAE concept of an adequate ASM trial, with further emphasis on the prognostic significance of the first adequate ASM trial and the failure of two ASMs as a definition of DRE.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements'.

Author contributions

JP and JS conceived and designed the study plan. JS and HH drafted the manuscript. JR performed the statistical analyses and aided in manuscript writing. All authors read and reviewed the manuscript and approved the final version.

Conflict of interest

Author JP has participated in clinical trials for Eisai, UCB, and Bial; received research grants from Eisai, Medtronic, UCB, and Liva-Nova; received speaker honoraria from LivaNova, Eisai, Medtronic, Orion Pharma, and UCB; received support for travel to congresses from LivaNova, Eisai, Medtronic, and UCB; and participated in advisory boards for Arvelle, Novartis, LivaNova, Eisai, Medtronic, UCB, and Pfizer.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Effect of clinical features on antiseizure medication doses in patients with newly diagnosed epilepsy

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Objective: We evaluate the effect of distinct clinical features on anti-seizure medication (ASM) doses in seizure-free and not seizure-free patients aged ≥16 years with new-onset epilepsy.

Materials and methods: This study included 459 patients with a validated diagnosis of epilepsy. The most prescribed ASMs were oxcarbazepine (OXC; $n = 307$), followed by valproic acid (VPA; $n = 115$), carbamazepine (CBZ; $n = 81$), and lamotrigine (LTG; $n = 67$). The seizure freedom rate with their first or subsequent ASM was 88.0%. A retrospective analysis of patient records was performed to determine any association between doses of ASMs and patient characteristics.

Results: The median OXC dose in seizure-free patients aged >60 years was 600 mg compared to 900 mg in younger patients. When controlling for age but not in an unadjusted model, the median dose of OXC was lower (300 mg, $p = 0.018$) for seizure-free patients compared to non-seizure-free patients, and the median dose of OXC was also 300 mg lower among older patients aged >60 years ($p < 0.001$). The median OXC doses for men aged ≤60 years were 300 mg higher than for women aged >60 years (900 mg vs. 600 mg, $p = 0.021$). The median dose of VPA was 400 mg higher in men than in women ($p < 0.001$) and 400 mg higher in not seizure-free patients compared to seizure-free patients only when adjusting for sex ($p < 0.001$). Higher median doses for CBZ were registered with FAS compared with FBTCS (difference in median doses of 200 mg; $p = 0.017$).

Conclusion: Significant OXC dose differences were detected between age groups, whereas VPA dosing was different in men and women. Moreover, CBZ doses were dependent on some seizure types. These data allow for the individualization of the initial target dosing based on key clinical characteristics.

KEYWORDS

antiseizure medication, newly diagnosed epilepsy, seizure freedom, treatment outcomes, oxcarbazepine, valproic acid, carbamazepine

1. Introduction

Several clinical features have been recognized as prognostic factors for achieving seizure freedom in patients with newly diagnosed epilepsy. The response to the first antiseizure medication (ASM) trial is of paramount importance, as most patients achieving seizure freedom respond to the initial adequate ASM trial defined by the International

League Against Epilepsy guidelines (1). We recently identified favorable prognostic factors for seizure freedom on the first ASM trial, including male sex, unknown etiology, no epileptiform activity on electroencephalography (EEG), and presenting seizure types of focal to bilateral tonic-clonic seizures (FBTCS) or focal aware seizures (FAS) (2). Subsequently, we assessed the same prognostic factors on the second or following ASM trials in another study, which found that an age >60 years and absence of epileptiform activity on EEG were favorable prognostic features of seizure freedom (3). These features associated with a favorable prognosis of seizure freedom may also be of importance in determining appropriate doses of a given ASM to achieve seizure freedom, an aspect seldom explored.

There is a changing landscape regarding the age distribution of new-onset epilepsy, emphasizing the need for more granular knowledge of ASM responses based on different age categories. Throughout the last four decades in Finland, the incidence of epilepsy in individuals aged <65 years has been mostly stable, but there has been a nearly 5-fold increase in the rate of new-onset epilepsy in the older population (4). Changes in the prevalence of epilepsy across age groups have important implications for the choice of ASM because different age groups may exhibit different responses to therapy and dose-response characteristics (5). Older patients have a higher serum ASM concentration than younger adults for the same administered dose; thus, the ASM dose must be carefully selected when treating older patients (6). However, no formal clinical practice guidelines exist for patients aged >60 years with new-onset epilepsy (7).

Furthermore, there is emerging data regarding the effect of other clinical features on ASM doses achieving favorable clinical outcomes. In a recent study, the mean doses of most ASMs used in monotherapy were lower in women than in men among adult patients with epilepsy (8). However, there is a paucity of clinical data regarding the effect of sex on the dosing of different ASMs. Moreover, there is even a larger gap in knowledge on the effect of etiology, seizure types, or EEG characteristics on ASM dosing in patients responding to ASM therapy with seizure freedom (9).

This study aimed to evaluate the ASM dosing both in seizure-free and not seizure-free patients aged ≥16 years with newly diagnosed epilepsy based on clinical features, including age, sex, presenting seizure type, etiology, and EEG findings.

2. Materials and methods

The population sampled comprised 584 patients aged ≥16 years who were referred to the Tampere University Hospital between 1 January 1995 and 31 December 2005, following a diagnosis of new-onset epilepsy. All patients were retrospectively followed up until 31 December 2006 until 1 year of seizure freedom was achieved, or until patient death. The medical records of patients, including clinic visits and clinical information, were retrospectively examined, and the demographic information of all patients was collected. Neuroimaging, particularly computed tomography or magnetic resonance imaging, was performed and evaluated by neuroradiologists to screen for underlying structural abnormalities. The evaluation of etiology was based mainly on imaging results and clinical history. The detailed clinical characteristics of all 459 patients with validated newly diagnosed epilepsy who were included in this study cohort are presented in our previous studies (2, 3).

For all patients diagnosed with epilepsy, ASM therapy was initiated according to local standard clinical practice at the time of data collection. Patients were followed up in the epilepsy clinic according to routine clinical practice. At the follow-up visit, clinical information and responses to ASM therapy (either monotherapy or polytherapy) were recorded. The ASM doses were adjusted according to efficacy and tolerability at the discretion of the treating physician.

Data were analyzed using Stata version 17.0 for Windows (College Station, TX: StataCorp LLC). Doses are described as medians with interquartile ranges. We examined the relationships between seizure freedom (patients who did not become seizure-free as a reference group) and doses using a bootstrapped median regression model. Unadjusted models (column "Model 1" in Table 2) and models adjusted for age at the date of diagnosis, sex, seizure type, EEG, and etiology (Model 2 in Table 2, all models in Tables 3–7) were constructed. We used 200 bootstrap replications to obtain an estimate of the variance-covariance matrix of the estimators (standard errors).

We also examined the joint effect of age at the date of diagnosis and sex on the dose of oxcarbazepine (OXC), valproic acid (VPA), and carbamazepine (CBZ) by fitting a bootstrapped median regression model. The joint variable was categorized into four groups: 1 = male ≤60 years (reference group), 2 = female >60 years, 3 = male >60 years, and 4 = female ≤60 years.

In this retrospective study, there was no contact with patients, and information was collected from the patient register of the Tampere University Hospital. This study does not require ethics committee approval, according to the Finnish Law on Research. Following Finnish guidelines, this study was approved by the head of the Tampere University Science Center.

3. Results

The study cohort comprised 251 (54.7%) male patients and 208 (45.3%) female patients. The median age at diagnosis was 45 years; 76.9% (353/459) of patients were aged ≤60 years, whereas 23.1% (106/459) were aged >60 years. The seizure freedom rate with the first or subsequent ASM was 88.0% (404/459). A total of 308 patients (75.9% of all patients achieving seizure freedom) became seizure-free following the administration of the first ASM regimen; 59 of 151 patients (14.5% of all patients achieving seizure freedom) became seizure-free following the administration of the second ASM regimen; and 37 patients became seizure-free after the third to fifth ASM regimens when all ASM trials were counted. The most prescribed ASMs were OXC (307, 66.9%), followed by VPA (115 25.1%), CBZ (81, 17.6%), and lamotrigine (LTG, 67 [14.5%]) (Table 1). Among the patients who achieved 1-year seizure freedom in the entire cohort, 10.1% (41/404) were on combination therapy.

Based on the unadjusted median regression model, no differences in median doses of OXC or other ASMs between seizure-free and not seizure-free patients with focal epilepsy receiving mono- or polytherapy were found (Table 2, Model 1). However, after controlling for age, the median dose of OXC was

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TABLE 1 Clinical features categorized based on ASM response.

	All patients	Seizure-free after the first ASM trial	Seizure-free after the second or subsequent ASM regimens	Persistent seizures
n	459	308	96	55
Sex, *n* (%)				
Female	208 (45.3)	125 (40.6)	54 (56.2)	29 (52.7)
Male	251 (54.7)	183 (59.4)	42 (43.8)	26 (47.3)
Age at the date of diagnosis, *n* (%)				
≤60 years	353 (76.9)	237 (76.9)	69 (71.9)	47 (85.5)
>60 years	106 (23.1)	71 (23.1)	27 (28.1)	8 (14.5)
Etiology, *n* (%)				
Structural				
Benign tumor	19 (4.1)	10 (3.2)	6 (6.3)	3 (5.5)
Hippocampal sclerosis	3 (0.7)	1 (0.3)	2 (2.1)	0
Malformation of cortical development	11 (2.4)	5 (1.6)	3 (3.1)	3 (5.5)
Malignant tumor	21 (4.6)	10 (3.2)	6 (6.3)	5 (9.1)
Other hippocampal pathology	12 (2.6)	8 (2.6)	1 (1.0)	3 (5.5)
Perinatal injury	5 (1.1)	4 (1.3)	1 (1.0)	0
Traumatic brain injury	27 (5.9)	19 (6.2)	3 (3.1)	5 (9.1)
Vascular lesion	113 (24.6)	69 (22.4)	27 (28.1)	17 (30.9)
Vascular malformation	30 (6.5)	21 (6.8)	7 (7.3)	2 (3.6)
Genetic	25 (5.4)	18 (5.8)	7 (7.3)	0
Infectious	15 (3.3)	9 (2.9)	3 (3.1)	3 (5.5)
Unknown	178 (38.8)	134 (43.5)	30 (31.3)	14 (25.5)
Epilepsy type, *n* (%)				
Focal	434 (94.6)	290 (94.2)	89 (92.7)	55 (100)
Generalized	25 (5.4)	18 (5.8)	7 (7.3)	0
Type of first seizure, *n* (%)				
FBTCS	320 (69.7)	222 (72.1)	63 (65.6)	35 (63.6)
FAS	75 (16.3)	50 (16.2)	15 (15.6)	10 (18.2)
FIAS	40 (8.7)	19 (6.2)	11 (11.5)	10 (18.2)
GTCS	15 (3.3)	12 (3.9)	3 (3.1)	0
Myoclonic	9 (2.0)	5 (1.6)	4 (4.2)	0
EEG, *n* (%)				
Normal	188 (41.0)	137 (44.5)	36 (37.5)	15 (27.3)
Epileptiform activity	103 (22.4)	61 (19.8)	26 (27.1)	16 (29.1)
Focal slowing	66 (14.4)	46 (14.9)	12 (12.5)	8 (14.5)
Unspecific	52 (11.3)	34 (11.0)	7 (7.3)	11 (20.0)
No EEG	50 (10.9)	30 (9.7)	15 (15.6)	5 (9.1)
ASM				
Benzodiazepine, *n* (%)	2 (0.4)	0	0	2 (3.6)
Carbamazepine, *n* (%)	81 (17.6)	54 (17.5)	18 (18.8)	9 (16.4)

(Continued)

TABLE 1 (Continued)

	All patients	Seizure-free after the first ASM trial	Seizure-free after the second or subsequent ASM regimens	Persistent seizures
Clobazam, *n* (%)	11 (2.4)	0	4 (4.2)	7 (12.7)
Clonazepam, *n* (%)	8 (1.7)	1 (0.3)	4 (4.2)	3 (5.5)
Gabapentin, *n* (%)	19 (4.1)	1 (0.3)	9 (9.4)	9 (16.4)
Lamotrigine, *n* (%)	67 (14.6)	12 (3.9)	35 (36.5)	20 (36.4)
Levetiracetam, *n* (%)	43 (9.4)	4 (1.3)	22 (22.9)	17 (30.9)
Oxcarbazepine, *n* (%)	307 (66.9)	184 (59.7)	74 (77.1)	49 (89.1)
Phenobarbital, *n* (%)	1 (0.2)	0	0	1 (1.8)
Phenytoin, *n* (%)	27 (5.9)	8 (2.6)	15 (15.6)	4 (7.3)
Pregabalin, *n* (%)	2 (0.4)	0	0	2 (3.6)
Tiagabine, *n* (%)	14 (3.1)	0	8 (8.3)	6 (10.9)
Topiramate, *n* (%)	31 (6.8)	2 (6.5)	15 (15.6)	14 (25.5)
Valproic acid, *n* (%)	115 (25.1)	51 (16.6)	47 (49.0)	17 (30.9)

FBTCS, focal to bilateral tonic-clonic seizures; FAS, focal aware seizures; FIAS, focal impaired awareness seizures; GTCS, generalized tonic-clonic seizures; EEG, electroencephalography; ASM, anti-seizure medication.

significantly lower (300 mg, $p = 0.018$) for seizure-free patients compared to not seizure-free patients (Table 2, Model 2). Moreover, there was also a significant relationship between age and dose of OXC; the median dose of OXC was 300 mg lower among older patients aged >60 years than among their younger counterparts ($p < 0.001$). Finally, the median OXC dose in seizure-free patients aged >60 years was 600 mg compared to 900 mg in younger patients. There were no significant differences in other ASMs.

In a similar analysis adjusted for sex, no difference was found in median doses of OXC between men and women or between seizure-free and not seizure-free patients (Model 1 in Table 3). However, when adding age to the model, a significant relationship between OXC dose and seizure-free and not seizure-free patients was found (the median dose was 300 mg less in seizure-free patients; $p = 0.032$). Conversely, for VPA using the same model, there was a significant relationship: the median dose of VPA was 400 mg higher in men than in women ($p < 0.001$) and, also, 400 mg higher in not seizure-free patients compared to seizure-free patients ($p < 0.001$). The latter finding remained when adding age as an adjustment (Model 2 in Table 3). The median VPA dose in seizure-free women was 750 mg, compared to 1,000 mg in men. There were no significant differences in medians between sexes in other ASMs (Table 3).

When combining age and sex categories into four different combinations (male ≤60 years, male >60 years, female ≤60 years, female >60 years), the median OXC doses for men aged ≤60 years was 300 mg higher than for women >60 years (900 mg vs. 600 mg, $p = 0.021$). When applying the same analysis for VPA, significant findings emerged with women in both age groups with 400 mg lower median doses compared with men ≤60 years (600 mg vs. 1,000 mg).

There were no significant differences in the doses of OXC according to seizure type (Table 4). In Model 2, where the outcome was defined as ASM dose and exposure variables were seizure freedom and seizure type, significantly higher median doses for CBZ were registered with FAS compared with FBTCS (difference in median doses of 200 mg; $p = 0.017$).

The CBZ median dose was 200 mg higher among patients with unspecific activity in EEG compared to patients with normal EEG ($p = 0.031$). In contrast, the median VPA dose was 400 mg lower in patients with unspecific activity in EEG compared to patients with normal EEG ($p = 0.006$). The median doses of other ASMs with focal epilepsy were not significantly influenced by EEG characteristics (Table 5). The median doses of ASMs were not influenced by etiology (Table 6).

Among all patients with focal epilepsy using OXC in monotherapy on either the first ASM regimen or first substitution, in an estimate comparing OXC doses between seizure-free and not seizure-free patients applying five models separately adjusted for sex, age, seizure type, EEG, and etiology, no significant findings emerged (Table 7).

In the 17 patients with generalized epilepsy who achieved seizure freedom, the median dose of VPA was 900 mg in monotherapy or polytherapy. The doses of VPA were not significantly different between women and men (950 mg vs. 900 mg).

4. Discussion

The present study provides new insights into the median ASM doses based on clinical features and patient characteristics. Due to the distribution of ASM in our study, we were able to provide meaningful analysis results mainly for OXC, VPA, and CBZ. Significant OXC dose differences were detected between age groups, whereas VPA dosing was different in men and women. Moreover, CBZ doses were dependent on some seizure types and EEG findings.

TABLE 2 Antiseizure medication doses (median and interquartile range) in either mono- or polytherapy in categories of age in patients with focal epilepsy.

		Age ≤60 years		Age >60 years		Model 1	Model 2	
	szf	*n*	Median (IQR)	*n*	Median (IQR)	Est. (p)[a]	Est. (p)[b]	Est. (p)[c]
Oxcarbazepine	Yes	178	900 (600)	34	600 (300)	0 (1.000)	−300 (0.018)	−300 (<0.001)
	No	71	1,200 (900)	22	600 (300)			
Carbamazepine	Yes	43	400 (200)	15	400 (200)	−200 (0.058)	−200 (0.070)	0 (1.000)
	No	17	750 (400)	5	400 (200)			
Valproic acid	Yes	34	1,000 (400)	30	900 (400)	0 (1.000)	−100 (0.616)	−100 (0.483)
	No	20	1,100 (950)	10	1,000 (800)			
Lamotrigine	Yes	27	200 (300)	2	138 (125)	−100 (0.075)	−100 (0.161)	0 (1.000)
	No	29	300 (200)	3	300 (400)			
Phenytoin	Yes	3	200 (300)	13	250 (100)	−50 (0.382)	−50 (0.555)	0 (1.000)
	No	5	300 (100)	6	250 (200)			
Levetiracetam	Yes	14	1,000 (1.000)	3	1,000 (0)	−500 (0.278)	−500 (0.299)	0 (1.000)
	No	19	1,500 (1,500)	3	1,000 (700)			
Topiramate	Yes	8	300 (225)	2	175 (150)	0 (1.000)	50 (0.635)	−50 (0.631)
	No	18	275 (200)	1	200			
Gabapentin	Yes	4	2,600 (800)	3	900 (400)	200 (0.770)	400 (0.397)	−1,200 (0.026)
	No	10	1,900 (800)	2	1,500 (600)			

Other antiseizure medications were used in less than five patients.

szf, seizure freedom; IQR, interquartile range; n, number; Coef., estimate from the median regression model; p, significance; na, convergence not achieved.

Model 1: outcome = antiseizure medication dose, exposure variable = seizure freedom.

Model 2: outcome = antiseizure medication dose, exposure variables = seizure freedom and age.

[a]estimate and significance of the seizure freedom (ref. = no) from model 1.

[b]estimate and significance of the seizure freedom (ref. = no) from model 2.

[c]estimate and significance of the age (ref. = ≤60) from model 2.

Age was the main factor influencing ASM doses in this study. Patients aged ≤60 years needed higher doses of OXC to achieve seizure freedom compared with older patients, whereas the doses of other ASMs showed no statistically significant differences. However, in our study, the median dose of VPA for patients achieving seizure freedom was 1,000 mg for those younger than 60 years and 900 mg for those over 60 years. This finding is in line with a previously published study showing that 83.3% of older patients became seizure-free with a mean VPA monotherapy dose of 626 mg (10). In contrast, in a cohort of younger (mean age of 33 years) focal epilepsy patients with a seizure freedom rate of 62%, an average dose of 1,066 mg of VPA was required (11).

In our previous studies examining the percentage of seizure-free patients, age did not have an effect on patients achieving seizure freedom on their first ASM regimen (2), whereas in patients with failed achievement of seizure freedom on their first ASM regimen, an age >60 years was a favorable prognostic factor for seizure freedom with subsequent ASM regimens (3). However, it is unclear if decisions to modify doses were based only on the achievement of seizure freedom or on caution over age-related exposure and adverse events with ASMs in this study. The median dose of OXC (600 mg) was slightly lower in patients >60 years with focal epilepsy than in a previously published older cohort (874 mg) (12). In another study, seizure freedom was achieved with a lower mean daily dose of OXC in older individuals (900 mg/day) compared to mean doses of 1,200 mg/day in the whole cohort (13). Similarly, in our study, the median difference in OXC dose was 300 mg between older women and younger men. Age-related differences can partly be explained by drug disposition and elimination. A comparative pharmacokinetic study of OXC in older (age, 60–82 years) vs. young (age, 18–32 years) healthy volunteers showed that the mean concentrations of the OXC metabolite (monohydroxy derivative) were higher in the former population than in the latter population (14). OXC has been shown to have a good safety profile among older patients, which is consistent with the safety outcomes and adverse event rates noted in the general population. However, the concomitant use of drugs in this age group (polypharmacy) and pre-existing chronic conditions and comorbidities may influence drug safety and adverse event rates (15). The rate of hyponatremia linked to OXC therapy is higher in older patients, which may be an important consideration for dose adjustment and therapeutic monitoring (16).

Epilepsy management in older patients should consider a range of factors linked to the efficacy and safety outcomes of ASMs in this context (17), including diagnosed epileptic syndrome, patient sex, comorbidities, concomitant medications, tolerability, and safety of ASM, while ensuring compatibility with local guidelines. Similarly, the decision to increase or decrease the doses of ASM should be guided by these factors to reflect an individualized assessment process (18, 19), which also denotes that patient age also plays a

TABLE 3 Antiseizure medication doses (median and interquartile range) in either mono- or polytherapy according to sex in patients with focal epilepsy.

		Women		Men		Model 1		Model 2
	szf	*n*	Median (IQR)	*n*	Median (IQR)	Est. (p)[a]	Est. (p)[b]	Est. (p)[c]
Oxcarbazepine	Yes	90	900 (600)	122	900 (300)	0 (1.000)	0 (1.000)	−300 (0.032)
	No	51	900 (750)	42	1,425 (900)			
Carbamazepine	Yes	25	400 (200)	33	400 (200)	−200 (0.065)	0 (1.000)	−200 (0.057)
	No	12	600 (400)	10	650 (400)			
Valproic acid	Yes	22	750 (400)	42	1,000 (400)	−400 (<0.001)	400 (<0.001)	−400 (0.002)
	No	18	950 (400)	12	1,800 (500)			
Lamotrigine	Yes	17	200 (200)	12	150 (200)	−100 (0.188)	0 (1.000)	−100 (0.174)
	No	19	200 (350)	13	350 (100)			
Phenytoin	Yes	10	225 (100)	6	250 (100)	−100 (0.111)	−50 (0.420)	−50 (0.528)
	No	6	350 (150)	5	300 (100)			
Levetiracetam	Yes	8	1,000 (1,500)	9	1,000 (0)	−500 (0.201)	0 (1.000)	−500 (0.253)
	No	11	2,000 (1,500)	11	1,000 (1,500)			
Topiramate	Yes	2	250 (300)	8	225 (225)	50 (0.583)	−100 (0.229)	100 (0.294)
	No	9	300 (200)	10	200 (250)			
Gabapentin	Yes	4	1,450 (1,750)	3	2,400 (1,600)	400 (0.520)	800 (0.071)	400 (0.349)
	No	5	1,200 (4,009)	7	2,000 (600)			

Other antiseizure medications were used in less than five patients.

szf, seizure freedom; IQR, interquartile range; n, number; Est., estimate from the median regression model; p, significance.

Model 1: outcome = antiseizure medication dose, exposure variables = seizure freedom and sex.

Model 2: outcome = antiseizure medication dose, exposure variables = seizure freedom, sex, and age.

[a]estimate and significance of the seizure freedom (ref. = no) from model 1.

[b]estimate and significance of the sex (ref. = female) from model 1.

[c]estimate and significance of the seizure freedom (ref. = no) from model 2.

significant role in influencing health outcomes during the ASM treatment process (20, 21).

In our previous publication, addressing the effect of sex on seizure outcomes in the same patient population, men with focal epilepsy were more likely to achieve seizure freedom than their female counterparts on their first ASM (2) but not with subsequent ASM regimens (3). In a recent Taiwanese study not taking seizure outcomes into consideration, the mean doses of OXC in monotherapy were 641 and 614 mg for men and women, respectively ($p = 0.024$). The authors speculated that this could be attributable to the fact that men typically weigh more than women (8). There is no clear evidence that sex differences influence the efficacy of OXC therapy among patients with focal epilepsy (22). Therefore, the reasons underlying this observation are unclear, potentially reflecting differences in patient risk profiles or other factors that were not investigated in this study. While the adjustment of OXC dose may be based on weight in children (23), there is no evidence that weight needs to be considered in adults, excluding the possibility of anthropometric differences between male and female patients accounting for variations in OXC dosing (24). OXC is known to be a weak inducer of CYP3A4, which plays a role in estrogen metabolism and may reduce the efficacy of oral contraceptive pills if used at high doses (24). However, it is unlikely that prescribers avoided higher doses of OXC to avoid drug-drug interactions in women taking oral contraceptive pills since the mean dose of OXC was higher among women who did not become seizure-free than among those who did. Seizure freedom may be achieved with a lower dose of OXC in women with focal epilepsy. In our study, female patients with focal epilepsy required lower doses of VPA to achieve seizure freedom. This is in line with a previous finding that the mean doses of VPA in monotherapy were 1,139 mg and 969 mg for men and women, respectively ($p < 0.001$) (8). Further studies to explore the influence of sex on ASM prescription in this population are warranted.

It was also noted that the CBZ median dose was significantly higher with FAS compared with FBTCS, which is consistent with our previous finding that patients with FBTCS as the presenting seizure type are more likely to achieve seizure freedom (2). There is no evidence in the literature to suggest the variable efficacy of ASM for achieving seizure freedom in different seizure types in patients with focal epilepsy (25). However, further research to confirm the potential for variation, as noted in this study, and explore the implications of drug dose optimizations is warranted. In the present study, some significant differences in median doses between patients with normal and unspecific EEG findings were detected; however, there were no statistically significant differences in seizure freedom rate, and these findings are difficult to interpret in a clinical context. There were no differences in ASM dosing regarding etiology.

This study has some limitations. First, the data were collected from a distinct geographical region and were retrospective in nature, potentially limiting the generalizability and reliability of the dataset. Furthermore, the analysis of patients who achieved seizure freedom on ASM therapy was further restricted by a lack

TABLE 4 Antiseizure medication doses (median and interquartile range) in either mono- or polytherapy according to seizure type in patients with focal epilepsy.

		Seizure-free		Not seizure-free		Model		
	sz type	*n*	Median (IQR)	*n*	Median (IQR)	Est. (p)[a]	Est. (p)[b]	Est. (p)[c]
Oxcarbazepine	FBTCS	157	900 (600)	63	900 (900)	0 (1.000)	0 (1.000)	300 (0.115)
	FAS	40	900 (600)	18	900 (600)			
	FIAS	15	1,200 (600)	12	1,275 (900)			
Carbamazepine	FBTCS	47	400 (200)	13	600 (400)	−200 (0.082)	200 (0.017)	0 (1.000)
	FAS	9	600 (100)	5	600 (400)			
	FIAS	2	400 (0)	4	725 (125)			
Valproic acid	FBTCS	48	900 (400)	20	1,000 (550)	−100 (0.576)	100 (0.656)	100 (0.718)
	FAS	10	1,000 (600)	4	1,200 (1,450)			
	FIAS	6	800 (400)	6	1,500 (600)			
Lamotrigine	FBTCS	21	200 (200)	21	300 (300)	−100 (0.074)	200 (0.248)	0 (1.00)
	FAS	4	500 (200)	4	200 (150)			
	FIAS	4	175 (175)	7	400 (300)			
Phenytoin	FBTCS	14	200 (100)	7	250 (200)	−50 (0.385)	100 (0.103)	100 (0.116)
	FAS	1	300	2	350 (100)			
	FIAS	1	300	2	350 (100)			
Levetiracetam	FBTCS	11	1,000 (1,000)	16	1,000 (750)	0 (1.000)	2,000 (0.090)	1,000 (0.138)
	FAS	1	3,000	1	1,000			
	FIAS	5	1,000 (0)	5	3,000 (500)			
Topiramate	FBTCS	7	250 (250)	10	250 (250)	−50 (0.583)	−50 (0.572)	0 (1.000)
	FAS	1	200	3	250 (100)			
	FIAS	2	250 (300)	6	250 (200)			
Gabapentin	FBTCS	4	2,400 (1,550)	7	1,800 (800)	0 (1.000)	−800 (0.063)	400 (0.342)
	FAS	2	1,000 (400)	2	1,000 (400)			
	FIAS	1	2,400	3	2,400 (1,000)			

Other antiseizure medications were used in fewer than five patients.
szf, seizure freedom; IQR, interquartile range; n, number; Est., estimate from the median regression model; p, significance.
Model: outcome = antiseizure medication dose, exposure variables = seizure freedom and first seizure type.
[a]estimate and significance of the seizure freedom (ref. = no).
[b]estimate and significance of the first seizure type (FAS vs. FBTCS).
[c]estimate and significance of the first seizure type (FIAS vs. FBTCS).

of available data on all concomitant medications, making possible drug-drug interactions unknown. Additionally, we did not have information about comorbidities, adherence to medication, or lifestyle factors that may have influenced dose decisions. We did not analyze separately whether a given ASM was discontinued due to a lack of efficacy or due to tolerability issues for each subanalysis to maintain conciseness and clarity.

The analysis of ASM doses in patients with generalized epilepsy was limited by the small sample size and decreasing statistical power for the key outcomes of the study. The lack of serum level measurements is also a limitation of our study methodology. However, according to Finnish guidelines, ASM concentration measurements have not been routinely recommended due to their large intra- and interindividual variability and undetermined clinical significance, especially for OXC (26).

Finally, our cohort comprised patients initiating their ASM treatment between 1995 and 2005 prior to the widespread use or availability of newer ASMs, including only a restricted number of patients using LTG or LEV. However, due to the reimbursement policy, CBZ, OXC, or VPA are currently chosen as first-line ASMs for focal epilepsy in Finland (26) and are still widely used globally (8).

There have also been developments in the fields of neuroimaging and neurophysiology, but their effect has been greater for the management of drug-resistant epilepsy than for the initial diagnosis. Furthermore, all epilepsy diagnoses were re-evaluated using the new criteria for the definition of epilepsy (2). Owing to our study design, an initial seizure freedom rate of at least 1 year was used; however, long-term seizure freedom rates should be evaluated in the future to enhance the clinical relevance of these findings.

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TABLE 5 Antiseizure medication doses (median and interquartile range) in either mono- or polytherapy in categories of EEG in patients with focal epilepsy.

		Normal		Epileptiform activity			Unspecific changes	
	szf	*n*	Median (IQR)	*n*		Median (IQR)	*n*	Median (IQR)
Oxcarbazepine	Yes	95	900 (600)	42		900 (600)	21	900 (450)
	No	29	900 (1,200)	24		975 (900)	15	1,200 (900)
Carbamazepine	Yes	30	400 (200)	9		600 (400)	4	600 (100)
	No	7	800 (200)	8		400 (250)	2	900 (300)
Valproic acid	Yes	26	1,000 (400)	15		900 (400)	8	600 (750)
	No	10	1,250 (800)	9		1,500 (800)	3	1,000 (400)
Lamotrigine	Yes	15	200 (300)	5		200 (0)	4	175 (75)
	No	12	250 (325)	10		400 (200)	8	200 (150)
Phenytoin	Yes	5	200 (50)	1		200	2	500 (600)
	No	1	400	8		275 (200)	0	
Levetiracetam	Yes	1	3,000	8		1,000 (1,000)	2	1,000
	No	8	1,000 (250)	7		2,000 (2,000)	4	1,500 (1,000)
Topiramate	Yes	4	225 (125)	2		250 (300)	1	150
	No	6	275 (200)	8		200 (200)	2	400 (0)
Gabapentin	Yes	2	1,600 (800)	0			0	
	No	2	2,600 (400)	3	1,933 (416)	1,800 (800)	1	1,800
					Focal slowing		No EEG	
					n	Median (IQR)	*n*	Median (IQR)
Oxcarbazepine	Yes			34		900 (600)	20	825 (450)
	No			15		1,200 (600)	10	750 (1,200)
Carbamazepine	Yes			7		400 (200)	8	450 (200)
	No			2		500 (200)	3	800 (800)
Valproic acid	Yes			7		1,000 (600)	8	1,000 (500)
	No			4		750 (900)	4	600 (550)
Lamotrigine	Yes			2		350 (300)	3	200 (425)
	No			1		100	1	200
Phenytoin	Yes			4		250 (100)	4	275 (75)
	No			1		300	1	300
Levetiracetam	Yes			4		1,000 (750)	2	1,500 (1,000)
	No			3		3,000 (2,000)	0	
Topiramate	Yes			3		400 (300)	0	
	No			1		200	0	
Gabapentin	Yes			3		2,400 (1,900)	2	2,000 (2,400)
	No			3		1,800 (800)	3	1,200 (1,600)

Other antiseizure medications were used in less than five patients.
szf, seizure freedom; IQR, interquartile range; n, number.

TABLE 6 Antiseizure medication doses (median and interquartile range) in either mono- or polytherapy according to etiology in patients with focal epilepsy.

		Structural/Infectious		Unknown		Model	
	szf	*n*	Median (IQR)	*n*	Median (IQR)	Est. (p)[a]	Est. (p)[b]
Oxcarbazepine	Yes	116	900 (600)	96	900 (600)	0 (1.000)	0 (1.000)
	No	66	900 (1,200)	27	900 (900)		
Carbamazepine	Yes	36	400 (200)	22	400 (200)	−200 (0.068)	0 (1.000)
	No	14	650 (400)	8	600 (400)		
Valproic acid	Yes	35	1,000 (600)	29	900 (400)	−100 (0.542)	100 (0.383)
	No	22	1,300 (900)	8	1,000 (250)		
Lamotrigine	Yes	14	200 (300)	15	200 (300)	−100 (0.094)	0 (1.000)
	No	19	200 (200)	13	300 (300)		
Phenytoin	Yes	13	200 (100)	3	250 (100)	−100 (0.064)	−100 (0.055)
	No	9	300 (100)	2	400 (0)		
Levetiracetam	Yes	12	1,000 (1,000)	5	1,000 (0)	−500 (0.290)	0 (1.000)
	No	14	1,250 (1,500)	8	1,250 (1,250)		
Topiramate	Yes	8	300 (275)	2	225 (50)	0 (1.000)	50 (0.605)
	No	12	325 (225)	7	200 (100)		
Gabapentin	Yes	6	1,800 (1,900)	1	2,000	600 (0.458)	400 (0.609)
	No	12	1,800 (1,000)	0			

Other antiseizure medications are used in less than five patients.
szf, seizure freedom; IQR, interquartile range; n, number; Est., estimate from the median regression model; p, significance.
Model: outcome = antiseizure medication dose, exposure variables = seizure freedom and etiology.
[a]estimate and significance of the seizure freedom (ref. = no).
[b]estimate and significance of the etiology (ref. = unknown).

TABLE 7 Oxcarbazepine doses according to clinical features (median and interquartile range) in monotherapy as either the first antiseizure medication or first substitution in patients with focal epilepsy.

	Seizure-free		Not seizure-free		
	n	Median (IQR)	*n*	Median (IQR)	Est. (p)[a]
Sex					0 (1.000)
Male	114	900 (300)	22	900 (600)	
Female	79	900 (300)	37	750 (300)	
Age of diagnosis					0 (1.000)
≤60 years	161	900 (600)	40	900 (600)	
>60 years	32	600 (300)	19	600 (300)	
Seizure type					0 (1.000)
FBTCS	142	900 (450)	42	600 (300)	
FAS	39	900 (600)	13	900 (0)	
FIAS	12	900 (450)	4	750 (300)	
EEG					0 (1.000)
Normal	88	900 (450)	21	900 (300)	
Epileptiform activity	35	900 (600)	14	675 (300)	
Unspecific activity	21	900 (450)	8	750 (600)	
Focal slowing	32	900 (600)	9	900 (300)	
Etiology					0 (1.000)
Structural	98	900 (600)	39	900 (300)	
Infectious	5	1,500 (750)	2	900 (600)	
Unknown	90	900 (600)	18	900 (300)	

IQR, interquartile range; FBTCS, focal to bilateral tonic-clonic seizures; FAS, focal aware seizures; FIAS, focal impaired awareness seizures; EEG, electroencephalography.
[a]estimate and significance of the seizure freedom (ref. = no), five models separately adjusted for sex, age, seizure type, EEG, and etiology.

This study demonstrated that the doses of ASMs associated with seizure freedom in patients with epilepsy were influenced by age for OXC and by sex for VPA. The largest dose differences were observed between men aged ≤60 years and women aged >60 years. Significant dose differences were inconsistent across different ASMs, and further research is needed to clarify the effects of age and sex on ASM efficacy and prescription practices due to limitations inherent to the retrospective design of our study.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

JP and JS conceived and designed the study plan. JS and HH drafted the manuscript. JR performed the statistical analyses and aided in manuscript writing. All authors read and reviewed the manuscript and approved the final version.

Conflict of interest

JP has participated in clinical trials for Eisai, UCB, and Bial, received research grants from Eisai, Medtronic, UCB, and LivaNova, received speaker honoraria from Angelini Pharma, LivaNova, Eisai, Medtronic, Orion Pharma, and UCB, received support for travel to congresses from LivaNova, Eisai, Medtronic, and UCB, and participated in advisory boards for Angelini Pharma, Jazz Pharma, Novartis, LivaNova, Eisai, Medtronic, UCB, and Pfizer.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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PUBLICATION IV

Prescribed Antiseizure Medication Doses and Their Relation to Defined Daily Doses for Achieving Seizure Freedom in Newly Diagnosed Patients with Epilepsy; Focus on Oxcarbazepine

Hersi H, Raitanen J, Saarinen JT, Peltola J.

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ORIGINAL ARTICLE

Prescribed antiseizure medication doses and their relation to defined daily doses for achieving seizure freedom in newly diagnosed patients with epilepsy

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Abstract

Objectives: To investigate the antiseizure medication (ASM) doses required to achieve seizure freedom and their correlation with the World Health Organization's defined daily doses (DDDs) in patients aged 16 years or older with newly diagnosed epilepsy.

Methods: The study included 459 patients with a validated diagnosis of new-onset epilepsy. Patient records were retrospectively analyzed to determine the ASM doses in patients with or without seizure freedom during follow-up. The DDD of the relevant ASM was then retrieved.

Results: The seizure-freedom rate with first and subsequent ASMs was 88% (404/459 patients) during the follow-up. The mean prescribed doses (PDDs) and PDD/DDD ratio of the most commonly used ASMs, ie, oxcarbazepine (OXC), carbamazepine (CBZ), and valproic acid (VPA), differed significantly between seizure-free and non-seizure-free status (992 mg and 0.99 vs 1132 mg and 1.13; 547 mg and 0.55 vs 659 mg and 0.66; and 953 mg and 0.64 vs 1260 mg and 0.84, respectively). The effect of the OXC dose as the first failed ASM on the possibility of achieving seizure freedom was significant (Fisher's exact test, $p = 0.002$). Thirty-four of 43 patients (79%) in which an OXC dose of ≤900 mg failed became seizure-free, as compared with 24 of 54 patients (44%) with a failed OXC dose >900 mg.

Significance: The present study provides new insights into the doses of the commonly used ASMs such as OXC, CBZ, and VPA that can lead to seizure freedom as monotherapy or as combination therapy. The higher PDD/DDD ratio of OXC (0.99) than that of CBZ or VPA renders a generalized PDD/DDD comparison highly problematic.

KEYWORDS

antiseizure medication, defined daily dose, newly diagnosed epilepsy, oxcarbazepine, seizure freedom, treatment outcomes

1 | INTRODUCTION

Using antiseizure medications (ASMs) to treat epilepsy in newly diagnosed patients requires careful consideration of patients' risk factors and drug-dosing requirements, based on age and additional factors, with seizure freedom as the ultimate goal.[1] As new ASMs emerge, the potential for rational prescription of ASMs by physicians has become increasingly challenging.[2] Furthermore, if seizure freedom is not obtained with the first ASM, the proliferation of possibilities for subsequent trials of ASMs, either as monotherapy or combination therapy, further complicates the potential for safe and effective practice.[3]

To compare drug consumption between different periods and/or regions, the World Health Organization (WHO), in 1996, launched a methodology for defining daily doses, which refer to the assumed average maintenance dose per day of a drug used for its main indication in adults.[4] The application of defined daily doses (DDDs) by medical professionals allows the measurement of changes over time when using a particular drug and for the evaluation of the effectiveness of different classes of drugs used in patients. DDDs have been assigned to ASMs that are used in combination therapies. While the DDD represents a unit of drug consumption, it often reflects the dosage in the context of monotherapy.[4] For example, ASM utilization in Israel was reported as DDD/1,000 inhabitants per day for a given drug,[5] and another recent study registered the prescribed drug doses (PDDs) as well as the PDD/DDD ratio for the evaluation of ASM prescription patterns and dosing.[6] Additionally, the DDD concept has been used to represent the total ASM load to allow for comparison with the ever-increasing number of ASMs in combination therapy.[7] Furthermore, the DDD has been applied to estimate the population-attributable risk of negative outcomes of drug treatment for various indications, such as hip fractures associated with diazepam or anti-depressant use.[8,9]

Importantly, after the release of the International League Against Epilepsy (ILAE) guidelines for the definition of drug-resistant epilepsy,[10] the DDD has been used to operationalize an adequate dose for ASM trials. Based on one study, it has been suggested that a PDD value that is 75% of the DDD may be sufficient for achieving seizure freedom and therefore could be applied as a measure of an adequate ASM trial in this context.[11] Using a 75% threshold as a measure for achieving seizure freedom was supported by a cross-sectional study.[12]

It is difficult to define the clinically effective dose range for each individual ASM rigidly. This is further confounded by the setting in which the ASM is used (eg, monotherapy or polytherapy). Moreover, dose optimization is a slow and complex process involving both subjective and objective factors including individual physician's own clinical evaluation based on personal experience as well as specific patient-related aspects such as epilepsy type and comorbidities. To ensure generalizability from a given ASM to another, an easier reference may be made to the DDD.[10] Due to the potential discrepancies between doses used in combined therapy and DDDs derived from monotherapy contexts, monitoring PDDs and comparing them with DDDs can have implications for doses used to achieve optimal outcomes in patients with epilepsy.[13] To complicate matters further, there is some evidence that certain duotherapies, such as lamotrigine (LTG) combined with valproic acid (VPA), may work synergistically to provide superior seizure control than achieved with each drug independently. In a previous study, it was noted that the mean daily doses of combined LTG–VPA were significantly lower in patients with improved seizure frequency than in those who received monotherapy.[14] These data about LTG–VPA highlight the importance of both pharmacokinetic[15] and pharmacodynamic interactions.[16] Therefore, the variability of doses for a single ASM using polytherapy, depending on other ASMs, may complicate comparisons with both monotherapy and combination therapy doses of the drugs, causing further heterogeneity when using DDD as a unit of ASM load measurement.

The main purpose of this study was to evaluate the required ASM doses for achieving seizure freedom in monotherapy or polytherapy and their correlation with the WHO's DDD in patients aged 16 years or older with newly diagnosed epilepsy. No previous study has investigated

Key Points

- The seizure-freedom rate with first-line and subsequent ASMs was 88%
- We defined the mean PDDs and PDD/DDD ratios of the most commonly used ASMs in both 1-year seizure-free and non-seizure-free patients
- A dose of ≤900 mg OXC as first-line ASM predicted seizure-freedom with any subsequent ASM
- The PDD/DDD ratio for seizure-free patients was 0.99 OXC whereas the ratio was 0.55 for CBZ and 0.64 for VPA
- The mean dose of LTG for achieving seizure freedom was 189 mg when used as first-line monotherapy or 97 mg in combination therapy with VPA

the DDDs in the context of polytherapy or the PDD/DDD ratio of various ASMs.

2 | METHODS

A total of 584 patients aged 16 years or older were referred to the Tampere University Hospital between January 1, 1995, and December 31, 2005, following a diagnosis of new-onset epilepsy. All individuals were retrospectively followed-up until they had been seizure-free for at least 1 year; until December 31, 2006; or until death. Medical records were retrospectively examined. The study cohort comprised 459 patients with validated newly diagnosed epilepsy, with the epilepsy type and etiology as described in detail in our previous publications.[17,18] ASM therapy was initiated according to standard clinical practice during that period. If seizure freedom was not achieved with the initial dose, the dose of the first ASM was increased or substitution/add-on ASMs were initiated at the treating physician's discretion, reflecting decision-making in a real-world context. ASM doses were adjusted according to the dictated clinical circumstances, with particular attention given to efficacy and tolerability.

In epilepsy, the DDD for different ASMs are as follows: diazepam 10 mg; carbamazepine (CBZ), 1000 mg; clobazam, 20 mg; clonazepam, 8 mg; gabapentin, 1800 mg; LTG 300 mg, levetiracetam (LEV) 1000 mg; oxcarbazepine (OXC), 1000 mg; phenytoin, 300 mg; phenobarbital, 100 mg; pregabalin, 300 mg; topiramate, 300 mg; tiagabine, 30 mg; and VPA, 1500 mg.[19]

Absolute dose sizes and ratios of PPD and DDD are described as means with ranges and medians with interquartile ranges. Comparisons between different groups were performed using the Mann–Whitney *U*-test. The data were analyzed using Stata version 16.1 (StataCorp LLC).

In this retrospective study, there was no contact with patients, and information was collected from the patient register of the Tampere University Hospital. This study does not require ethics committee approval according to Finnish Law on Research. Following Finnish guidelines, this study was approved by the head of the Tampere University Science Center.

3 | RESULTS

The clinical characteristics of all 459 patients with validated, newly diagnosed epilepsy, who remained in this study cohort, have been presented in detail in our previous publications.[17,18] The combined seizure-freedom rate with firstfirst and subsequent ASMs was 88.0% (404 of 459), and all patients with generalized epilepsy became seizure-free following the administration of a second or subsequent ASM. Among patients who achieved 1-year seizure freedom in the entire cohort, 10.1% (41 of 404) were on combination therapy. In total, 70 different ASM monotherapies or polytherapies (ASM combinations) were used.[18] In Table 1, the clinical characteristics of patients who became seizure-free with the first or subsequent monotherapy or combination therapy are compared with those of patients who did not achieve seizure freedom. Those ASMs used by less than 40 patients were excluded from this and subsequent Tables and statistical analysis: topiramate ($N=31$), phenytoin ($N=27$), gabapentin ($N=19$), tiagabine ($N=14$), clobazam ($N=11$), clonazepam ($N=8$), diazepam ($N=2$), pregabalin ($N=2$), and phenobarbital ($N=1$).

A comparison of the PDD and PDD/DDD ratio was made for all ASMs used, whether in monotherapy or in combination therapy (Table 2). The results were analyzed for focal epilepsy because of the limited number of patients with generalized epilepsy. OXC, CBZ, and VPA demonstrated statistically significant differences in terms of mean prescribed doses and PDD/DDD ratio between patients with 1-year seizure-free and non-seizure-free status (992 mg and 0.99 vs 1132 mg and 1.13; 547 mg and 0.55 vs 659 mg and 0.66; and 953 mg and 0.64 vs 1260 mg and 0.84), respectively. Remarkably, the PDD/DDD ratio for seizure-free patients was 0.99 OXC whereas the ratio was 0.55 for CBZ and 0.64 for VPA. There was no difference in VPA dosing between seizure-free patients with focal or generalized epilepsy (the mean dose of VPA for seizure-free patients with generalized epilepsy was 924 mg and those not achieving seizure freedom 1,200 mg). The only third-generation ASM widely used in patients with focal epilepsy was LTG.[20] More than 40 patients used LTG, with an absolute mean dose of 248 mg for seizure-free patients and a PDD/DDD ratio of 0.83.

Table 3 summarizes the PPDs and DDDs of the first ASM and first substitution/subsequent monotherapy ASM in all patients with epilepsy. No statistically significant differences in doses were observed, regardless of whether the drugs were used as first-line epilepsy treatment or as a first or subsequent substitution. The doses and PDD/DDD ratios for the most used ASMs (OXC, CBZ, and VPA) were comparable with the doses in Table 2. Only LTG, which was initiated seldom as the first monotherapy, had a lower mean dose and PDD/DDD ratio (189 mg and 0.63, respectively) than in all patients with LTG (including also polytherapy usage).

Table 4 presents the ASM mean PDDs and PDD/DDD ratio analysis in patients with focal epilepsy on polytherapy, demonstrating that patients achieving seizure-freedom with OXC as part of combination therapy had a higher dose of OXC than patients who used it as a

TABLE 1 Clinical characteristics of the study group categorized based on seizure outcomes

	1. All seizure-free patients	1A. Seizure-free after 1st ASM	1B. Seizure-free after 2nd or later monotherapy	1C. Seizure-free with polytherapy	2. Persistent seizures
n	404	308	55	41	55
Sex, *n* (%)					
Female	179 (44.3)	125 (40.6)	33 (60.0)	21 (51.2)	29 (52.7)
Male	225 (55.7)	183 (59.4)	22 (40.0)	20 (48.8)	26 (47.3)
Age at date of diagnosis, med (IQR)	46.0 (31.5)	45.5 (31.0)	52.0 (36.0)	36.0 (31.0)	42.0 (24.0)
Etiology, *n* (%)					
Structural	203 (50.2)	147 (47.5)	31 (56.4)	25 (61.0)	38 (69.1)
Genetic	25 (6.2)	18 (5.8)	1 (1.8)	6 (14.6)	0
Infectious	12 (3.0)	9 (2.9)	2 (3.6)	1 (2.4)	3 (5.5)
Unknown	164 (40.6)	134 (43.5)	21 (38.2)	9 (22.0)	14 (25.5)
Epilepsy type, *n* (%)					
Focal	379 (93.8)	290 (94.2)	54 (98.2)	35 (85.4)	55 (100)
Generalized	25 (6.2)	18 (5.8)	1 (1.8)	6 (14.6)	0
ASM					
Carbamazepine, *n* (%)	72 (17.8)	54 (17.5)	10 (18.2)	8 (19.5)	9 (16.4)
Lamotrigine, *n* (%)	47 (11.6)	12 (3.9)	15 (27.3)	20 (48.8)	20 (36.4)
Levetiracetam, *n* (%)	26 (6.4)	4 (1.3)	4 (7.3)	18 (43.9)	17 (30.9)
Oxcarbazepine, *n* (%)	258 (63.9)	184 (59.7)	44 (80.0)	30 (73.2)	49 (89.1)
Valproic acid, *n* (%)	98 (24.3)	51 (16.6)	34 (61.8)	13 (31.7)	17 (30.9)

Note: Patients achieving seizure freedom during follow-up were further subdivided to those becoming seizure free after first ASM regimen (1A), second or later monotherapy regimen (1B) and with any polytherapy (1C).

Abbreviations: ASM, antiseizure medications; IQR, interquartile range; med, median.

TABLE 2 PDDs of ASMs and PDD/DDD ratio in all patients including mono- and polytherapy based on seizure outcome status

	Seizure-free					Not seizure-free					
		Absolute dose in mg		PDD / DDD			Absolute dose in mg		PDD / DDD		
	n	Mean (sd)	Med (IQR)	Mean (sd)	Med (IQR)	*n*	Mean (sd)	Med (IQR)	Mean (sd)	Med (IQR)	*p*
Focal epilepsy											
OXC	213	992 (402)	900 (600)	0.99 (0.40)	0.90 (0.60)	92	1132 (507)	900 (900)	1.13 (0.51)	0.90 (0.90)	0.047
CBZ	58	547 (258)	400 (200)	0.55 (0.26)	0.40 (0.20)	22	659 (258)	600 (400)	0.66 (0.26)	0.60 (0.40)	0.031
VPA	64	953 (395)	950 (400)	0.64 (0.26)	0.63 (0.27)	30	1260 (658)	1000 (900)	0.84 (0.44)	0.67 (0.60)	0.021
LTG	30	248 (148)	200 (300)	0.83 (0.49)	0.67 (1.00)	31	285 (164)	300 (250)	0.95 (0.55)	1.00 (0.83)	0.343
LEV	17	1441 (827)	1000 (1000)	0.96 (0.55)	0.67 (0.67)	22	1650 (851)	1250 (1500)	1.10 (0.57)	0.83 (1.00)	0.337

Note: p = Mann–Whitney U-test between seizure-free and not seizure-free.

Abbreviations: CBZ, Carbamazepine; DDD, defined daily dose; IQR, interquartile range; LEV, Levetiracetam; LTG, Lamotrigine; med, median; OXC, Oxcarbazepine; PDD, prescribed daily dose; sd, standard deviation; VPA, Valproic acid.

monotherapy: 1,413 mg, with a high-PDD/DDD ratio of 1.41. The mean OXC doses and PDD/DDD ratio were somewhat, but not significantly, higher for non-seizure-free patients (1588 mg, 1.50, respectively). The number of patients taking CBZ or VPA in polytherapy was too low to draw any conclusions. Among the third-generation ASMs, there were sufficient numbers of polytherapy patients using LEV for meaningful analysis: there was no

TABLE 3 PDD ASM doses and PDD/DDD ratio in all patients either achieving seizure freedom or not with the first or subsequent monotherapy

		1st ASM					1st or subsequent substitution					
			Absolute dose in mg		PDD/DDD			Absolute dose in mg		PDD/DDD		
		n	mean (range)	med (IQR)	mean (range)	med (IQR)	*n*	mean (range)	med (IQR)	mean (range)	med (IQR)	*p*
OXC	SF	184	949 (300–2700)	900 (600)	0.95 (0.30–2.70)	0.90 (0.60)	9	900 (600–1500)	900 (0)	0.90 (0.60–1.50)	0.90 (0)	0.861
	NSF	50	867 (300–1800)	900 (300)	0.87 (0.30–1.80)	0.90 (0.30)	9	950 (600–1800)	750 (600)	0.95 (0.60–1.80)	0.75 (0.60)	0.698
CBZ	SF	54	554 (400–1800)	400 (200)	0.55 (0.40–1.80)	0.40 (0.20)	0					-
	NSF	17	562 (400–1050)	400 (300)	0.56 (0.40–1.05)	0.40 (0.30)	2	400 (200–600)	400 (400)	0.40 (0.20–0.60)	0.40 (0.40)	0.573
VPA	SF	50	932 (400–2000)	900 (400)	0.62 (0.27–1.33)	0.60 (0.27)	21	914 (600–1800)	1000 (400)	0.61 (0.40–1.20)	0.67 (0.27)	0.835
	NSF	9	900 (300–1800)	1000 (400)	0.64 (0.20–1.20)	0.67 (0.40)	9	989 (600–1500)	1000 (600)	0.66 (0.40–1.00)	0.67 (0.40)	0.563
LTG	SF	9	189 (100–400)	200 (100)	0.63 (0.33–1.33)	0.67 (0.33)	9	239 (100–400)	200 (100)	0.80 (0.33–1.67)	0.67 (0)	0.279
	NSF	4	213 (50–400)	200 (175)	0.71 (0.17–1.33)	0.67 (0.58)	11	264 (100–500)	200 (200)	0.88 (0.33–1.67)	0.67 (0.67)	0.571
LEV	SF	1	1000 (1000–1000)	1000 (0)	0.67 (0.67–0.67)	0.67 (0)	3	833 (500–1000)	1000 (500)	0.56 (0.33–0.67)	0.67 (0.33)	1.000
	NSF	0					2	1750 (1000–2500)	1750 (1500)	1.17 (0.67–1.67)	1.17 (1.00)	-

Note: p = Mann–Whitney U-test between 1st ASM and 1st or subsequent monotherapy.

Abbreviations: ASM, antiseizure medications; 1st ASM, first ASM regimen; 1st or subsequent substitution, second or later ASM regimen; CBZ, Carbamazepine; DDD, defined daily dose; IQR, interquartile range; LEV, Levetiracetam; LTG, Lamotrigine; med, median; NSF, not seizure-free; OXC, Oxcarbazepine; PDD, prescribed daily dose; SF, seizure-free; VPA, Valproic acid.

significant difference in patients with or without seizure freedom (dose and PDD/DDD ratio: 1615 mg and 1.081 vs 1800 and 1.20, respectively). (Table 4). Overall, 13 patients received LTG in combination with VPA. Of those, 4 became seizure-free with a low dose of LTG (dose and PDD/DDD ratio: 94 mg and 0.31, respectively). Nine patients did not achieve seizure freedom with a mean LTG dose of 303 mg (PDD/DDD ratio: 1.01) (Table 5).

Finally, we analyzed the value of the OXC dose as the first failed monotherapy for predicting the likelihood of achieving seizure freedom with subsequent ASM regimens during the follow-up period. There were 281 patients who used OXC as the first ASM, including 97 who did not achieve seizure freedom with OXC. During the follow-up, 59 of these 97 patients (60.8%) became seizure-free with any subsequent ASM regimen. When addressing the dose of OXC as a failed first ASM categorized into 3 different levels 300–600 mg, 900 mg, or 1,050–2,400 mg with the PDD/DDD ratios up to 0.60 or 0.90 and more than 0.90, the effect of the dose of OXC as the first failed ASM on the possibility of achieving seizure-freedom was significant (Fisher's exact test, $p = 0.002$). Thirty-four of 43 patients (79%) in whom first-line OXC failed to achieve seizure freedom at a dose of 900 mg or lower subsequently became seizure free, as compared with 24 of 54 patients (44%) in whom first-line OXC at a dose of more than 900 mg was unsuccessful (Figure 1).

4 | DISCUSSION

The present study provides new insights into doses for different ASMs, particularly OXC, CBZ, and VPA, as first-line or subsequent monotherapy, as well as in combination therapy, that resulted in seizure freedom in patients with newly diagnosed epilepsy. We identified marked variation in the ratio of the PDD to DDD, which renders a general PDD/DDD comparison highly problematic, particularly for OXC. Finally, we demonstrated that failure of OXC, the most-prescribed ASM, as the first-line monotherapy at a dose of ≤900 mg was predictive of achieving seizure freedom with subsequent ASMs.

We were able to offer a highly representative analysis for OXC given its use as the most commonly selected first-line ASM for focal epilepsy (305 patients in our study). The significant findings included the observation that, in focal epilepsy, a median dose of 900 mg of OXC as monotherapy was registered for seizure freedom, whereas in the polytherapy context, the median dose for seizure freedom was 1500 mg. In previous studies, the OXC dose was variable. In a Chinese study of newly diagnosed focal epilepsy patients, 62 out of 102 patients treated with OXC as the first choice became seizure-free with either 600 or 900 mg

TABLE 4 Seizure outcomes and antiseizure medication doses for all medications used in polytherapy (excluding valproate acid and lamotrigine combination) in patients with focal epilepsy.

	Prescribed dose in mg						PDD/DDD						
	Seizure-free			Not seizure-free			Seizure-free			Not seizure-free			
	n	mean (sd)	med (IQR)	*n*	mean (sd)	med (IQR)	*n*	mean (sd)	med (IQR)	*n*	mean (sd)	med (IQR)	*p*
OXC	19	1413 (462)	1500 (600)	34	1588 (316)	1500 (450)	19	1.41 (0.46)	1.50 (0.60)	34	1.59 (0.32)	1.50 (0.45)	0.322
CBZ	3	533 (115)	600 (200)	5	950 (229)	800 (400)	3	0.53 (0.12)	0.60 (0.20)	5	0.95 (0.23)	0.80 (0.40)	0.036
VPA	3	867 (231)	1000 (400)	7	1300 (698)	1500 (1400)	3	0.58 (0.15)	0.67 (0.27)	7	0.87 (0.47)	1.00 (0.93)	0.490
LTG	7	371 (170)	500 (300)	9	328 (160)	300 (300)	7	1.24 (0.57)	1.67 (1.00)	9	1.09 (0.53)	1.00 (1.00)	0.541
LEV	13	1615 (870)	1000 (1000)	16	1800 (894)	1750 (1750)	13	1.08 (0.58)	0.67 (0.67)	16	1.20 (0.60)	1.17 (1.17)	0.486

Note: *p* = Mann–Whitney *U*-test between seizure-free and not seizure-free.

Abbreviations: CBZ, Carbamazepine; DDD, defined daily doses; IQR, interquartile range; LTG, Lamotrigine; LEV, Levetiracetam; med, median; OXC, Oxcarbazepine; PDD, prescribed drug doses; VPA, Valproic acid.

TABLE 5 Seizure outcomes and antiseizure medication doses for lamotrigine in combination with valproic acid in focal epilepsy

	Absolute dose in mg					PDD/DDD						
	Yes			No		Yes			No			
	n	mean (sd)	med (IQR)	*n*	mean (sd)	med (IQR)	*n*	mean (sd)	med (IQR)	*n*	mean (sd)	med (IQR)	*p*
VPA	4	1325 (822)	1100 (1050)	9	1500 (650)	1500 (800)	4	0.88 (0.55)	0.73 (0.70)	9	1.00 (0.43)	1.00 (0.53)	0.613
LTG	4	94 (43)	88 (63)	9	303 (182)	300 (300)	4	0.31 (0.14)	0.29 (0.21)	9	1.01 (0.61)	1.00 (1.00)	0.053

Note: *p* = Mann–Whitney *U*-test between seizure-free and not seizure-free.

Abbreviations: DDD, defined daily doses; IQR, interquartile range; LTG, lamotrigine; PDD, prescribed drug doses; sd, standard deviation; VPA, valproic acid.

of the drug, whereas only 10% of the patients with OXC were titrated to doses over 900 mg.[21] In our previous study from Tampere, 80% of patients became seizure-free with OXC as the first-line ASM with doses ≤900 mg, whereas 20% of patients achieved seizure-freedom with doses of 1200 mg or 1500 mg.[22]

The 2nd and 3rd most commonly used ASMs in our study were CBZ and VPA, respectively, accounting for 80 and 94 patients, respectively. In patients with focal epilepsy, the mean dose of the ASM for achieving seizure freedom was 547 mg for CBZ and 953 mg for VPA, whereas in patients who did not achieve seizure freedom, the doses were slightly but significantly higher (659 mg and 1260 mg, respectively). These doses were comparable to those previously published.[23] The number of patients treated with CBZ or VPA as part of polytherapy was too small to draw conclusions. Furthermore, the mean dose of LTG for achieving seizure freedom (248 mg) was comparable with previously reported data, with lower doses when used as first-line monotherapy (189 mg) or in combination therapy with VPA (97 mg).[23] The number of patients using third-generation ASMs in our study was too small to allow firm conclusions, particularly regarding monotherapy. However, LEV was the second most-commonly used ASM in polytherapy (29 patients), with a mean daily dose of 1615 mg in patients who became seizure-free and 1800 mg in those who did not become seizure-free.

The PDD/DDD ratios of the most-commonly used ASMs in patients with focal epilepsy in our study varied significantly, with a mean seizure-freedom PDD/DDD ratio of 0.99 for OXC, 0.55 for CBZ, and 0.64 for VPA. For all ASMs, the PDD/DDD ratios were higher when seizure freedom was not achieved. The high-mean PDD/DDD ratio for OXC compared to those for CBZ and VPA signifies that the DDD-based comparison is not valid when OXC is part of the ASM equation. Brodie et al. previously speculated about the outlier status of OXC questioning the WHO-defined DDD for CBZ and OXC, which were both assigned the same DDD (1000 mg/day), since a dose ratio of 1:1.5 for CBZ vs OXC is often assumed in clinical practice and in research.[11] Our study now provides data to support the aforementioned notion. Moreover, in a Hungarian cross-sectional study, the mean PDD/DDD ratio for OXC in seizure-free patients was only slightly lower than that noted in our patients.[12] Additionally, the mean PDD/DDD ratios for achieving seizure freedom with CBZ and VPA in our study were in line with those reported in previous studies.[11,12] The outlier values for OXC also implies that the 75% DDD dose as a definition of an adequate ASM trial cannot be applied to OXC. Conversely, the significance of an OXC dose of ≤900 mg as the first failed monotherapy for predicting an increased possibility of seizure freedom for subsequent ASMs was in line with reported outcomes for other ASMs, such as CBZ, VPA, and LTG.[11]

Pharmacokinetic interactions between ASMs complicate the assessment of dosing further in polytherapy settings in our study. CBZ is strong inducer of cytochrome P450 and glucuronizing enzymes whereas OXC has weaker inducing properties, and a lower propensity to cause interactions mediated by enzyme induction. Conversely, enzyme inhibitors such as VPA result in decreased metabolic clearance of the affected drug, such as LTG and CBZ.[15] Furthermore, different combinations of ASMs may produce either increased (synergism) or decreased (antagonistic) efficacy or tolerability.[16]

Owing to the retrospective study design, selection bias is a potential limitation of this study. Especially, dose optimization is dependent on the complex set of clinical and physician-derived variables which are difficult to operationalize. The small sample size for some ASMs in this cohort limited the potential for statistical analysis of seizure-freedom status. In addition, our cohort consisted

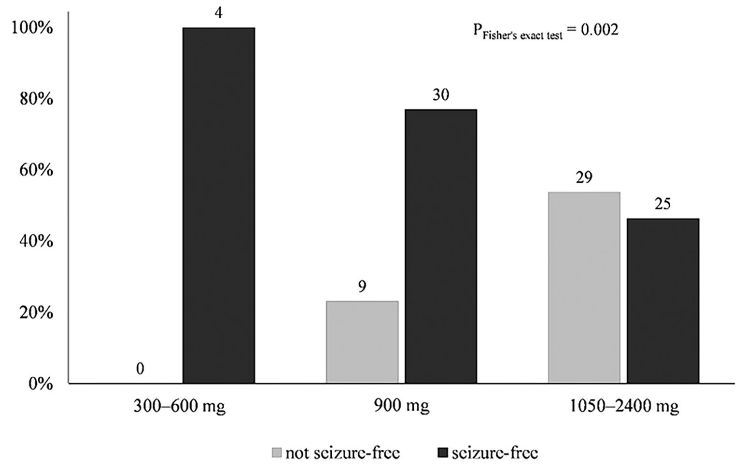

FIGURE 1 The predictive value of OXC dose as the 1st failed monotherapy for possibility of seizure freedom with subsequent ASM regimens.

of patients from an era when newer ASMs were not yet widely used. However, due to the reimbursement policy in Finland, CBZ, OXC, and VPA are currently chosen as the first-line treatment. ASMs for focal epilepsy in Finland and many newer ASMs are reimbursed only when they are used as an add-on therapy, but not as a substitution therapy. Nevertheless, the new ASMs have not yet improved the probabilities of seizure freedom.[24,25] Because of our study design, an initial seizure-freedom rate of at least 1 year was used; however, long-term seizure-freedom rates were not available. We were unable to document possible underreporting of seizures. The low proportion of focal impaired awareness seizures in our cohort may also be due to a lack of recognition of these seizures, as previously described.[26]

In conclusion, the present study provided new insights into the doses of the commonly used ASM, OXC, that leads to seizure freedom in patients with newly diagnosed epilepsy when used as first-line or subsequent monotherapy, as well as when used in combination therapy. We demonstrated marked variation in the ratio of PDDs to DDDs, rendering a generalized PDD/DDD comparison highly problematic, for OXC in particular, but also for LTG as first-line monotherapy or in combination therapy with or without VPA. Finally, for OXC, we demonstrated the value of a dose of ≤900 mg of OXC as first failed monotherapy for predicting achievement of seizure freedom, suggesting a decision-point dose for an adequate trial of OXC for ILAE definition.

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CONFLICT OF INTEREST STATEMENT

H.H., J.T.S., and J.R. report no conflicts of interest. J.P. has participated in clinical trials for Eisai, UCB, and Bial; received research grants from Eisai, Medtronic, UCB, and LivaNova; received speaker honoraria from Angelini Pharma, LivaNova, Eisai, Medtronic, Orion Pharma, and UCB; received support for travel to congresses from LivaNova, Eisai, Medtronic, and UCB; and participated in advisory boards for Angelini Pharma, Jazz Pharma, Novartis, LivaNova, Eisai, Medtronic, UCB, and Pfizer. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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