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Personal view

Translational veterinary epilepsy: A win-win situation for human and veterinary neurology

Marios Charalambous ^{a,*,1}, Andrea Fischer ^{b,1}, Heidrun Potschka ^c, Matthew C. Walker ^d, Robrecht Raedt ^e, Kristl Vonck ^e, Paul Boon ^e, Hannes Lohi ^f, Wolfgang Löscher ^g, Gregory Worrell ^h, Tosso Leeb ⁱ, Andrew McEvoy ^d, Pasquale Striano ^{j,k}, Gerard Kluger ^l, Aristeia S. Galanopoulou ^m, Holger A. Volk ^{a,2}, Sofie F.M Bhatti ^{n,2}

^a *Department of Small Animal Medicine and Surgery, University of Veterinary Medicine Hannover, Hannover 30559, Germany*

^b *Centre for Clinical Veterinary Medicine, Ludwig-Maximilians-University Munich, Munich 80539, Germany*

^c *Institute of Pharmacology, Toxicology and Pharmacy, Ludwig-Maximilians-University, Munich 80539, Germany*

^d *Institute of Neurology, University College London, London WC1N 3JD, UK*

^e *Department of Neurology, 4brain, Ghent University, Ghent 9000, Belgium*

^f *Department of Veterinary Biosciences, Department of Medical and Clinical Genetics, and Folkhälsan Research Center, University of Helsinki, Helsinki 00014, Finland*

^g *Department of Pharmacology, Toxicology, and Pharmacy, University of Veterinary Medicine Hannover, Hannover 30559, Germany*

^h *Department of Neurology, Mayo Clinic, Minnesota 55905, USA*

ⁱ *Institute of Genetics, University of Bern, Bern 3001, Switzerland.*

^j *IRCCS 'G. Gaslini', Genova 16147, Italy*

^k *Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, Italy*

^l *Clinic for Neuropediatrics and Neurorehabilitation, Epilepsy Center for Children and Adolescents, Schoen Clinic Vogtareuth, Vogtareuth 83569, Germany; Research Institute „Rehabilitation- Transition-Palliation“, PMU Salzburg, Salzburg 5020, Austria*

^m *Saul R Korey Department of Neurology, Isabelle Rapin Division of Child Neurology, Dominick P. Purpura Department of Neuroscience, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx NY 10461, USA*

ⁿ *Faculty of Veterinary Medicine, Small Animal Department, Ghent University, Merelbeke 9820, Belgium*

* Corresponding author. Tel.: +49 511 953-6202.

E-mail address: marios.charalambous@tiho-hannover.de (M. Charalambous).

¹ Shared first authorship

² Shared last authorship

Abstract

Epilepsy is a challenging multifactorial disorder with a complex genetic background. Our current understanding of the pathophysiology and treatment of epilepsy has substantially increased due to animal model studies, including canine studies, but additional basic and clinical research is required. Drug-resistant epilepsy is an important problem in both dogs and humans, since seizure freedom is not achieved with the available antiseizure medications. The evaluation and exploration of pharmacological and particularly non-pharmacological therapeutic options need to remain a priority in epilepsy research. Combined efforts and sharing knowledge and expertise between human medical and veterinary neurologists are important for improving the treatment outcomes or even curing epilepsy in dogs. Such interactions could offer an exciting approach to translate the knowledge gained from people and rodents to dogs and vice versa. In this article, a panel of experts discusses the similarities and knowledge gaps in human and animal epileptology, with the aim of establishing a common framework and the basis for future translational epilepsy research.

Keywords: Dog; Human; Nervous system; Seizures; Therapy

Introduction

Epilepsy is one of the most common and challenging chronic neurological disorders in dogs and is characterized by spontaneous recurrent epileptic seizures (Berendt et al., 2015). The prevalence of canine epilepsy varies in different studies between 0.5%-0.82% in non-referral and 1-2.6 % in referral hospital populations, while in specific predisposed breeds higher prevalence rates are reported (Kearsley-Fleet et al., 2013; Heske et al., 2014; Berendt et al., 2015; Hülsmeier et al., 2015; Erlén et al., 2018).

The classification of epilepsy is constantly evolving. Most recently, the International Veterinary Epilepsy Task Force (IVETF) proposed that epilepsy can be differentiated according to its etiology into idiopathic and structural (Berendt et al., 2015). More precisely, idiopathic epilepsy (IE) is considered by the IVETF as an umbrella term that can be subclassified into genetic epilepsy, i.e., when an epilepsy gene is confirmed, suspected genetic epilepsy, i.e., when a breed-related genetic influence or background is suspected, and epilepsy of unknown cause, i.e., when the underlying cause is unknown, and there is no indication of brain pathology (Berendt et al., 2015). Structural epilepsy is caused by an underlying brain pathology (Berendt et al., 2015; De Risio et al., 2015a). Structural epileptogenic lesions may occasionally have genetic etiologies, examples include cortical dysplasia (Machado et al., 2012; Casey et al., 2014), lissencephaly (Greene et al., 1976; Rodríguez-Sánchez et al., 2020) and polymicrogyria (Jurney et al., 2009).

In humans, epilepsy is also a common chronic brain disease accompanied by psychological, cognitive, and social consequences (Fisher et al., 2014). The prevalence and annual incidence of epilepsy are 6.4 cases per 1,000 persons and 67.8 cases per 100,000 persons, respectively, comparable to dogs (Fiest et al., 2017). Although the classification of human epilepsy is similar to that in dogs, the categories have been expanded to include structural, genetic, infectious, metabolic, immune, and unknown groups, with individual epilepsies being able to span more than one category, e.g., metabolic/genetic and genetic/structural (Scheffer et al., 2017). The importance of including infectious, immune-mediated and metabolic epilepsies as individual categories in human epileptology is partly due to their characteristic etiology-specific treatments (Assi et al., 2017).

A group of four veterinary neurologists, four veterinary geneticists and neuroscientists, and eight human epileptologists, all with expertise in animal epilepsy research, held a panel discussion to identify similarities and differences between canine and human epilepsy and determine translational scientific gaps and barriers to enhance veterinary evidence-based medicine. The panel aimed to: (1) summarize the current knowledge about the genetic background of epilepsy; (2) discuss the challenges and opportunities in epilepsy management, with a focus on drug-resistant epilepsy; (3) evaluate the impact of epilepsy on the quality of life of both dogs and humans with epilepsy; and (4) emphasize the importance of translational epilepsy research with the perspective of improving the understanding and management of this multifactorial disorder. The conclusions from the expert panel's meeting orchestrated with the existing literature was the basis for the current publication.

What is the role of genetics in epilepsy?

Pedigree analysis has strongly suggested a genetic influence on canine IE (Hülsmeier et al., 2015). Examples of certain canine breeds that are predisposed to IE include but are not limited to Australian shepherd (Weissl et al., 2012), Belgian shepherd (Famula et al., 1997; Berendt et al., 2008), Border collie (Hülsmeier et al., 2010), Irish wolfhound (Casal et al., 2006), Labrador retriever (Berendt et al., 2002), Petit Basset Griffon Vendeen (Gullov et al., 2011), Finnish Spitz dog (Viitmaa et al., 2013) and Italian Spinone (De Risio et al., 2015b). Further support for a genetic predisposition to IE originates from prevalence studies reporting increased prevalences of IE in many other dog breeds far exceeding the prevalence of epilepsy in the general dog population (summarized in Hülsmeier et al., 2015; Fischer, 2022). Yet, progress in the identification of genes has been quite challenging (Ekenstedt and Oberbauer, 2013).

To date, only a few idiopathic epilepsies with monogenic recessive inheritance have been identified in dogs showing parallels to focal and idiopathic generalized epilepsies in humans in age of seizure onset, seizure types and clinical course, i.e., *DIRAS1-related* generalized myoclonic epilepsy with photosensitivity in young Rhodesian Ridgeback dogs (Wielaender et al., 2017; Wielaender et al., 2018) with similarities to juvenile myoclonic epilepsy in humans (Hirsch et al., 2022) and *LGI2-related* benign juvenile remitting focal epilepsy in the Lagotto Romagnolo dogs with parallels to self-limited focal childhood epilepsies (Seppala et al., 2011; Zuberi et al., 2022). A haplotype in *ADAM23* on chromosome 37 represents a risk factor for adult-onset epilepsy in the Belgian shepherd with weaker associations in several other dog breeds, e.g., Australian shepherds, Kromfohrländers, Labrador retrievers, and Whippets (Seppala et al., 2012; Koskinen et al., 2017). Identification of other important risk loci on chromosome 14 (*RAPGEF5*; Belgian shepherds) and chromosome 4 (Irish wolfhounds) supports the concept of interactions of multiple loci underlying the genetic susceptibility profile in dogs with epilepsy (Seppala et al., 2012; Hayward et al., 2016; Koskinen et al., 2017; Belanger et al., 2020; Belanger et al., 2022). More progress has been made when epilepsy is the predominant clinical manifestation of genetic neurometabolic defects resulting in neonatal encephalopathy or neurodegeneration: *PITRM1*, which represents a severe manifestation of early-onset epilepsy with lethal status epilepticus, mitochondrial dysfunction and neurodegeneration in Parson Russell terriers (Hytonen et al., 2021), *ACADM*, which represents a syndrome of complex focal seizures accompanied by lethargy and elevated medium-chain acyl-CoA dehydrogenase metabolites in the blood and urine in Cavalier King Charles spaniels (Christen et al., 2022), the various neuronal ceroid lipofuscinoses (NCL) genes, and the first canine epilepsy gene, *EPM2B* (*NHLRC1*), responsible for late-onset Lafora disease characterized by tonic-clonic seizures,

myoclonus and progressive behavioural impairment in many canine breeds (Lohi et al., 2005; Hajek et al., 2016).

Over 500 causal and risk gene variants have been identified in humans with epilepsy, substantially more than in dogs (Devinsky et al., 2018). In humans, common epilepsies are rarely monogenic (major effect of a rare gene variant in a single gene responsible for causing the disorder). Polygenic epilepsies (resulting from multiple common gene variants, each with minor or moderate effects, along with environmental factors that influence epilepsy susceptibility) are far more common (Koeleman, 2018). However, a monogenic mode of inheritance can be observed in some familial focal and generalized epilepsies and a monogenic background is common in developmental and epileptic encephalopathies, metabolic disorders and some focal structural epilepsies (Steinlein, 1999). Recent advances have revolutionized genetic testing in human monogenic epilepsies with the ability now to detect the pathogenic variant in almost all cases (Perucca et al., 2020). For polygenic epilepsies, however, this is more challenging, even though the genetic technologies and detections of these epilepsy syndromes have greatly improved (Koeleman, 2018). The advances in identifying pathogenic sequence variants and revealing genetic mechanisms in human epilepsy results from developments in sequencing technologies, computational and novel analytical approaches, large-scale international collaborations (Koeleman, 2018; Perucca et al., 2020), and advances in phenotyping epilepsies (Wirrell et al., 2022). For instance, single-cell RNA sequencing technologies map gene expression at single-cell resolution; this permits the identification of different populations of cells, reveals regulatory interactions between genes, and detects the trajectories of distinct cell lineages in development (Hwang et al., 2018). Single-cell RNA sequencing could also be applied to brain tissue obtained via surgical approaches or even post-mortem from humans with epilepsy,

which might help identify the underlying mechanisms of epilepsy. Recently, gene mosaicism (i.e., ≥ 2 cell lineages with variable genotypes arising from a single zygote) has been increasingly reported in epilepsy-associated genes which provides a new perspective on genetic epilepsy in humans (Stosser et al., 2018; Gecz and Thomas, 2020; Gong et al., 2020; Miller et al., 2020). Extensive international collaborative studies in humans may contribute further towards developing epilepsy genetics (Perucca et al., 2020; Epi25 Collaborative, 2021).

The fact that in dogs only a few monogenic epilepsies, risk haplotypes and concepts have been identified might be attributed to the lack of phenotyping or genotyping resources or to the fact that inheritance in dogs may be more complex than speculated (Ekenstedt et al., 2012; Ekenstedt and Oberbauer, 2013). A genome-wide association study (GWAS) has identified at least 16 risk loci in human epilepsy genetics, using 15,212 cases and 29,677 controls (ILAE, 2018). Such large and well-phenotyped cohorts are not yet available for dogs, and consequently, GWAS for canine epilepsy has not yet been very successful. In addition, the human field has greatly benefitted from progress in whole exome and whole genome sequencing (WES/WGS). Parent-child trio WES enabled the detection of de novo somatic mutation events and substantially impacted our understanding of human childhood epilepsies (Epi4K, 2013). So far, these modern WES/WGS approaches have not been widely applied to dogs but hold considerable promise for the future. Regarding the phenotyping of epilepsy, the complexity and heterogeneity of the disorder and the existence of phenocopies make it challenging to assign a given phenotype to a specific underlying genotype. In humans, systematic efforts have been made to characterize the clinical features and categorize the epilepsies into subgroups and syndromes, which is mainly guided by the specific age of onset, focal versus generalized seizure semiology and electroencephalography (EEG) with additional

information provided by molecular diagnostics. In dogs, even though efforts have been made for an etiologic classification of epilepsy and phenotyping of seizures (e.g., IVETF consensus statements; Berendt et al., 2015; De Risio et al., 2015), there is still a large window for improvement in phenotyping seizures and epilepsies and application of EEG. EEG is a commonly used and important diagnostic tool in human neurology. It can reveal characteristic findings and localize an epileptogenic focus thereby contributing to the classification into focal or generalized epilepsies and the diagnosis of several epilepsy syndromes (Noachtar et al., 2009; Wirrell et al., 2022). However, the panel emphasized the fact that EEG has not become widely available in veterinary medicine for reasons including, but not limited to, low availability, lack of expertise and standardization, as well as technical challenges related to the lack of equipment specifically adapted for dogs, potential need for sedation, and muscle artefacts. Lack of EEG application represents a substantial barrier to the appropriate characterisation of large cohorts of dogs. Despite these challenges, EEG is increasingly used in veterinary research settings (James et al., 2017; Wieleaender et al., 2017; Wieleaender et al., 2018; Parmentier et al., 2020; Ukai et al., 2021). The panel agreed that the introduction of EEG and objective criteria for recognising the phenomenology of a specific epileptic syndrome in veterinary medicine will enhance epilepsy phenotyping in dogs.

The genetic architecture of canine IE and possible modes of inheritance are largely unknown at this time, although existing GWASs in many breeds suggest non-Mendelian modes despite many affected closely related dogs within the pedigrees (Koskinen et al 2017). The panel suggested that the mode of inheritance in dogs might be polygenic and multifactorial with many genetic risk factors of small effect size or canine epilepsies may be caused by relatively few or even single genetic risk factors of large effect size. However, there might be substantial heterogeneity and every dog with epilepsy might have a unique form of

monogenic epilepsy. A combination of different scenarios is possible and would further complicate the inheritance concepts in canine epilepsy. Lastly, the panel highlighted that the genetic influence and predisposition to develop epileptic seizures follows a continuum and is relevant for genetic epilepsies and should also be considered for the evolution of structural epilepsy. For instance, whether or not epilepsy develops after traumatic brain injury may also depend on the individual genetic background, which defines the risk of epilepsy development and affects the outcome. Indeed, recent studies in humans showed that the genetic variation among individuals with traumatic brain injury is relevant for the outcome by altering pre-trauma compensatory mechanisms, secondary injury pathological changes, neuronal repair and plasticity, and neurodegenerative pathways (Davidson et al., 2015; Zeiler et al., 2021). Such an influence might also likely occur in dogs with traumatic brain injury and subsequent epilepsy, however, there is no concrete evidence to support such a concept in dogs to date.

The panel's geneticists made the point that in the near future, it might be possible to identify individual cases of canine epilepsy caused by de novo mutation events. Those could be genetically quite similar to human epilepsy cases. However, there are clear breed predispositions for epilepsy in dogs that point towards breed-specific genetic risk factors; in this perspective, the genetics might differ between humans and dogs. So far, none of these hypothetical breed-specific risk factors has been elucidated at the molecular level. Successful identification of such breed-specific risk factors could enhance comparisons between humans and dogs.

Lastly, the panel agreed that progress in epilepsy genetics in both species has the potential to have a major impact on clinical practice. Identifying a pathogenic genetic variant and genetic risk factors is crucial for humans and dogs with epilepsy, particularly with regard

to clinical management and long-term prognosis as well as individualized treatment plans through targeted genetic or pharmacological precision therapies.

Therapeutics

What is the role of drugs in the management of epilepsy?

Even though there have been substantial advances regarding diagnosis, classification and characterisation of epilepsy in dogs, the management of epileptic seizures often requires long-term and ongoing care. Medical treatment is the cornerstone of management in both canine and human epilepsy. In contrast to humans, where numerous drugs with different mechanisms are available, only few remain at the heart of long-term management of canine IE mainly due to their known efficacy and safety profile, widespread availability, long-standing history, and relatively low cost (Charalambous et al., 2014; Bhatti et al., 2015; Charalambous et al., 2016). Only three antiseizure medications (ASMs), phenobarbital, imepitoin, and potassium bromide, have been approved for canine epilepsy in the EU. In the US, only one ASM (primidone) is approved. However, several other ASMs, such as levetiracetam, zonisamide, felbamate, gabapentin, and topiramate, are used in the management of IE in Europe and North America, particularly as adjunctive therapies to phenobarbital and/or potassium bromide (Bhatti et al., 2015). Levetiracetam is commonly used as a first-line therapy in the US, which is not the case in the EU. In general, according to EU legislation, when ASMs used in veterinary medicine fail to control the seizures adequately, ASMs approved for human epilepsy can be tried as add-on medications. It has been challenging to find suitable ASMs because of inappropriate pharmacokinetics, i.e., elimination half-life that is too short to allow convenient dosing by owners and maintenance of adequate therapeutic serum drug levels (e.g., valproic acid, phenytoin, ethosuximide and carbamazepine; Frey and Löscher, 1985; Picker et al., 1985; Bhatti et al., 2015). In addition, not all ASMs licensed in

human medicine are safe to use in dogs, e.g., lamotrigine (cardiotoxicity) or vigabatrin (neurotoxicity and hemolytic anemia)(Speciale et al., 1991; Weiss et al., 1994; Wong and Lhatoo, 2000; Bhatti et al., 2015). The use of some ASMs may also be costly in dogs.

The panel discussed that adequate combination therapy in dogs is hampered by the fact that the currently licensed drugs, phenobarbital, potassium bromide and imepitoin, all address mainly γ -aminobutyric acid (GABA)ergic neurotransmission, while a combination of drugs with different mechanisms of action is rather considered when treating epilepsy in humans. However, further randomized controlled clinical trials assessing these drugs in different types and stages of epilepsy are necessary for veterinary medicine (Charalambous et al., 2014; Charalambous et al., 2016). An important consideration when conducting therapeutic clinical trials in epilepsy is the placebo effect (i.e., positive response to sham intervention), which can increase the risk of overstatement of results when the study design does not control for this bias. In a previous canine study, 29% of dogs were characterized as responders (i.e., >50% in seizure frequency reduction) to placebo administration (Muñana et al., 2010). In human epilepsy studies, the reported placebo effect ranges between 0%-36% (Cramer et al., 1999; Burneo et al., 2002; Goldenholz et al., 2016). The placebo effect is of great importance in human and canine epilepsy studies and makes the objective assessment of therapeutic agents quite challenging. Furthermore, many of the previous and current open-label drug trials are only 3-4 months long, which could bias the results because of a 'honeymoon'-effect (Volk et al., 2008; Muñana et al., 2010) unless long-term follow-up is provided (Kriechbaumer et al., 2022). The panel agreed that 6 months or longer placebo-controlled trials are critical in evaluating potentially effective therapeutic strategies to account for natural fluctuations of the disease.

What perspectives should be considered when managing drug-resistant epilepsy?

Drug resistance is a critical challenge in both human and canine epilepsy (Parent, 1988; Potschka et al., 2015). Even though true drug resistance is the most likely reason for poor seizure control, pseudoresistance should be first considered to allow valid conclusions about outcome. Pseudoresistance can be related to misdiagnosis of epilepsy (i.e., diagnosis of another disorder, such as paroxysmal movement disorders, as epilepsy), poor client compliance (i.e., failure to follow the appropriate treatment instructions given by the clinician) or inadequate dosages (Potschka et al., 2015). Depending on the reason, pseudoresistance can be excluded via a thorough assessment of the history, re-evaluation of the diagnostic approach or evaluation of the ASM(s)' blood serum levels (Potschka et al., 2015). In veterinary medicine, it has been reported that 75–86% of the canine patients treated with ASMs continue to experience epileptic seizures (Heynold et al., 1997; Berendt et al., 2008; Arrol et al., 2012; Boothe et al., 2012; Packer et al., 2014, 2015; Tipold et al., 2015). While part of this may be attributed to pseudoresistance, approximately 30% of the dogs will remain poorly controlled (< 50% reduction of seizure frequency) despite adequate ASM combination therapy (Schwartz-Porsche et al., 1985; Podell et al., 1995; Trepanier et al., 1998). In human medicine, more than 30 ASMs have been approved by the US Food and Drug Administration and the European Medicines Agency, substantially more than the three ASMs approved for dogs. Yet, drug resistance remains a similar challenge (Chen et al., 2018). In general, approximately 50% of people with epilepsy will achieve seizure control after the first ASM, a further 13% after the second ASM and approximately 36% of patients will manifest multidrug resistance and poor seizure control (Kwan et al., 2010).

The panel agreed that despite the availability of many therapeutic options in humans (in contrast to dogs), the prevalence of drug resistance in both species is reported to be

similar. However, it is crucial to consider the differences in terminology and classification between human and veterinary epileptology before defining drug resistance. According to the International League against Epilepsy (ILAE), drug-resistant epilepsy is defined as the failure of adequate trials of two or more tolerated and appropriately used ASM regimens (whether administered as monotherapies or in combination) to achieve seizure freedom (Kwan et al., 2010; Kwan et al., 2011). Based on the ILAE definition, a high number of dogs with epilepsy would be classified as drug-resistant due to the fact that seizure freedom is only observed in 15-24% of the canine epileptic population treated with ASMs (Heynold et al., 1997; Berendt et al., 2007; Arrol et al., 2012; Packer et al., 2015), which is lower compared to that in humans (46-63%; Kwan and Brodie, 2000). From a medical perspective, achieving seizure freedom in dogs is as important as in humans based on the negative impact of the epileptic seizures, i.e., progressive decline in ASM responsiveness, development of behavioural comorbidities, impairment of the quality of life (QOL), and risk for increased mortality and sudden unexpected death (SUDEP; Balosso et al., 2008; Librizzi et al., 2012; Balosso et al., 2014; Wilcox and Vezzani, 2014). However, from a socioeconomic perspective, the urge for seizure freedom might not be as essential in dogs as in humans. In addition, aiming solely for seizure freedom in dogs might pose risks, such as increased incidence of adverse effects related to multiple ASM therapy and unaffordable costs for the owners (Potschka et al., 2015). On the other hand, owners might not be willing to care for a dog with intractable seizures and might opt for euthanasia. Therefore, the panel agreed that partial therapeutic success (i.e., reduction of seizure frequency and severity compared to baseline and prevention of status epilepticus and cluster seizures, rather than just seizure freedom) is also important in veterinary patients. According to the IVETF, canine drug-resistant epilepsy is defined as ‘a failure of adequate trials of two tolerated, appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve patient-specific therapeutic success’.

Therefore, the panel indicated that failure to achieve seizure freedom despite optimal ASMs dosages and/or serum concentrations has different reasons and consequences in dogs compared to humans.

Overall, in both human and veterinary medicine, the best predictor of drug resistance is two-fold, firstly, the epilepsy severity (number of epileptic seizures, seizure clusters, and status epilepticus), and secondly, the number of ASMs that have been tried and shown to be inadequately effective (Packer et al., 2014; Devinsky et al., 2018). However, considering the different ASMs used in veterinary (limited options, mainly focusing on GABA signalling and, to a less extent, other mechanisms) compared to human medicine (many ASMs targeting diverse mechanisms and with different efficacies for specific epileptic syndromes), the panel argued that the perceived ‘drug-resistance’ in canine seizures might be more dependent upon resistance to GABAergic drugs in particular. Since current ASMs used in veterinary medicine might not always be sufficient to control epileptic seizures (Charalambous et al., 2014; Kriechbaumer et al., 2022) or could lead to safety or tolerability issues (Charalambous et al., 2016), it is necessary to evaluate the efficacy and safety of new pharmacological options via double-blinded randomized controlled clinical trials. The panel agreed that there is still a realistic, though smaller, chance of achieving adequate seizure control or even freedom if additional drugs are added. The panel indicated that this is the current practice in human medicine, and with this approach there may be a decision to withdraw the ASM that is considered the least effective. Withdrawal time points may vary and depend on the time when the therapeutic drug concentrations of the novel add-on drug are achieved as well as the pharmacokinetic profile of the novel add-on treatment, i.e., some drugs (e.g., phenobarbital) depend on serum concentrations and may require subsequent up-titrations, whereas for others (e.g., levetiracetam) the effect may be readily available. In dogs, the overall recommendation

is to add another ASM when the epileptic seizures are not adequately controlled (Bhatti et al., 2015; Potschka et al., 2015; Podell et al., 2016), but the panel mentioned that veterinary practitioners tend not to remove the previous, possibly less effective, ASM. The panel added that the same tendency is observed among human physicians; hence, many ineffective drugs might remain on board in humans with epilepsy. However, the panel concluded that this might be beneficial in some cases of epilepsy, particularly since responses to previous ASMs are sometimes unclear (e.g., lack of history and adequate objective measurements). Lastly, it is possible that even if additional ASMs become available in veterinary medicine in the future, the proportion of dogs that manifest drug-resistant epilepsy may remain the same as it has been observed in humans despite the rapid growth of the number of ASMs over the last 30 years. Hence, the panel expressed that there is a necessity for better pharmacological and non-pharmacological, preferably minimally or non-invasive, therapeutic options for drug-resistant epilepsy in humans and dogs. Such treatments may include dietary therapies, neurostimulation, blood-brain barrier transporter modification or bypass, epilepsy surgery, and potential targeted ‘precision’ or genetic therapies if seizure foci or molecular targets are identified (Devinsky et al., 2018; Jones et al., 2021).

Is dietary management of epilepsy an option?

A large body of evidence supports diet’s efficacy for the treatment of drug-resistant epilepsy in children and adults as well as epileptic encephalopathies (Kossoff et al., 2018; Martin-McGill et al., 2018). While the classic ketogenic diet is considered the most efficient dietary approach, it is also linked to poor tolerability and less compliance. Therefore, in the last decades, this introduced other less stringent ketogenic nutritional therapies such as the medium-chain triglycerides (MCT) diet, modified Atkins diet and low glycemic index diet (Lefevre and Aronson, 2000; Cervenka et al., 2016; Masino et al., 2019).

Dietary modification with MCT showed promising results for reducing seizure frequency as an adjunctive therapeutic strategy in dogs with epilepsy (Law et al., 2015, 2016; Berk et al., 2020; Berk et al., 2019, 2021; Molina et al., 2020; Pilla et al., 2020). These observations mirror results in rodent models and humans (Han et al., 2021). Medium-chain fatty acids (MCFAs) can readily cross the blood-brain barrier (BBB), increase mitochondrial function and brain energy reserves, modify neurotransmitter levels (reduction of excitatory neurotransmitters), and inhibit excitatory glutamatergic α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and mechanistic target of rapamycin complex 1 (Law et al., 2015, 2016; Augustin et al., 2018; Berk et al., 2020; Berk et al., 2019, 2021; Molina et al., 2020; Pilla et al., 2020). Overall, the panel supported the use of ketogenic diets in dogs with epilepsy with the exception of Cavalier King Charles spaniels. In this breed, medium-chain acyl-CoA dehydrogenase deficiency might occur, which leads to impaired metabolism of MCFAs and diminished production of ketone bodies. Given that approximately 7% of Cavalier King Charles spaniels might be homozygous for this mutation, ketogenic diets could be considered in this breed only after performing the genetic test for this disorder (Christen et al., 2022).

In the last few years, the gut-brain axis has received much attention. An emerging number of studies have demonstrated the potential role of gut microbiota composition in humans with epilepsy. Specifically, the microbiota composition was shown to be altered in individuals with epilepsy compared to healthy humans, while differences were reported between drug-resistant and drug-responsive cases (Peng et al., 2018; Gong et al., 2021). These findings might indicate that iatrogenic alteration of the gut microbiota might be a potential tool for better control of epileptic seizures. In dogs, modulating the gut microbiota (e.g., using

fecal transplantation, probiotics) to change brain function offers novel research perspectives and likely promising results, yet research is still at a preliminary stage (Muñana et al., 2020; Garcia-Belenguer et al., 2021; Pilla et al., 2022; Watanangura et al., 2022). However, the panel agreed that ongoing research, at least in humans, still provides conflicting results (Mejia-Granados et al., 2021).

In both dogs and humans, dietary therapy is currently considered part of the multimodal approach to the treatment of epilepsy besides drugs. This additional non-pharmacologic treatment strategy appears relatively easy to implement and, if successful, can help reduce seizure frequency without the need for additional ASMs and tolerability issues related to multidrug therapy.

What is the potential for neurostimulation techniques in the treatment of canine and human epilepsies?

Neurostimulation is an established, mostly palliative treatment option for human patients with drug-resistant focal epilepsy who are not suitable for epilepsy surgery. Neurostimulation therapy is an emerging therapy for generalized epilepsy and has gained interest over the past decades, and several research studies have been conducted on this topic (Lin and Wang, 2017). During neurostimulation, electrical pulses are administered directly to or in the network of neural tissue, generating seizures. The aim is to modify tissue function and neuroplasticity and eventually reach the desired antiseizure effect (Boon et al., 2009; Boon et al., 2018). Animal research has shown positive results following stimulation of nerves, basal and thalamic nuclei, and cerebral cortex (Rutledge et al., 1967; Zabara, 1992; Boon et al., 2018)

The several types of neurostimulation differ regarding their invasiveness, target region of the nervous system, the stimulation method and their application (Vonck and Boon, 2015). Examples of neurostimulation techniques used in humans for epilepsy treatment include deep brain stimulation (DBS; invasive) largely focusing on the anterior nucleus of the thalamus, centromedian nucleus of the thalamus, or the individually-determined epileptogenic focus, vagus nerve stimulation (VNS; invasive) or transcutaneous vagus nerve stimulation (tVNS; non-invasive), trigeminal nerve stimulation (TNS; invasive) or transcutaneous trigeminal nerve stimulation (tTNS; non-invasive) and repetitive transcranial magnetic stimulation (rTMS; non-invasive; Lin and Wang, 2017; Boon et al., 2018). These techniques are generally used in combination with pharmacological therapies in humans (Vonck and Boon, 2015). In contrast to dogs, in humans, there is a remarkable amount of research on neurostimulation for epilepsy, especially for VNS (Vonck and Boon, 2015; Lin and Wang, 2017; Boon et al., 2018). Each technique provides advantages and disadvantages and is considered appropriate for specific individuals and disease characteristics, which are yet to be explored and defined in dogs. The main neurostimulation techniques evaluated for canine epilepsy are VNS (Zabara, 1992; Muñana et al., 2002; Martle et al., 2014; Martle et al., 2015; Martle et al., 2016; Harcourt-Brown and Carter, 2021; Hirashima et al., 2021) and, to a lesser extent, rTMS (Charalambous et al., 2020), and DBS (Zamora et al., 2021).

VNS causes increases in noradrenaline, which can be responsible for the anti-seizure properties of the technique (Raedt et al., 2011; De Taeye et al., 2014; Martle et al., 2015). Overall, up to approximately 60% of humans respond to VNS and this effect enhances over time (Groves et al., 2005; Panebianco et al., 2016). In dogs with epilepsy, VNS was shown to be safe and potentially effective, with a response rate varying between 44% and 89% among studies (Zabara, 1992; Muñana et al., 2002; Martle et al., 2016; Harcourt-Brown and Carter,

2021; Hirashima et al., 2021). However, the technique has not been studied as thoroughly as in humans. Regarding rTMS, this is a non-invasive neurostimulation method, which might affect the neuroplasticity of the brain and synaptic transmission of excitatory neurons and/or inhibitory interneurons (Funke and Benali, 2010; Hoogendam et al., 2010). These effects have been shown to outlast the duration of the stimulation in humans (Carrette et al., 2016), which allows to achieve seizure control for a period after the neurostimulation sessions have been completed. Similarly, in dogs, rTMS is likely effective in reducing seizure frequency with a duration of action of 4 months post-treatment in drug-resistant dogs with epilepsy and with no reported adverse effects. However, future larger-scale studies are vital to confirm this (Charalambous et al., 2020). Repetitive TMS can have various effects on the brain, depending on the stimulation parameters used (Carrette et al., 2016; Charalambous et al., 2020). Therefore, choosing the appropriate parameters on individual basis is crucial for successful long-term treatment. It should be remembered that optimal stimulation parameters can differ depending on anatomical, physiological and disease characteristics.

The anatomical differences between humans and dogs could affect the application of neurostimulation techniques. In dogs, contrary to humans, anatomical variabilities are generally more pronounced. One notable example is the variability of the canine cranium (e.g., thickness, shape) among breeds, which might affect the penetration of the magnetic field into the brain. Therefore, it might be of particular importance for dogs to tailor the stimulation parameters individually for optimal effects (Charalambous et al., 2020). Another example is the application of VNS. Specifically, VNS is applied to the left VN because it innervates the atrioventricular node of the heart; the right VN innervates the sinoatrial node, which may cause severe cardiac complications (Schachter et al., 1998; Nowakowska et al., 2022). In dogs, however, the cardiac branches cannot be excluded from the stimulation due to their

more distal exit from the VN within the thoracic cavity. As a result, the stimulation electrodes are wrapped around the left vagosympathetic trunk (sympathetic and vagal nerves are fused), which may also lead to sympathetic stimulation and cardiac-related complications (Martlé et al. 2016; Nowakowska et al., 2022).

Based on canine epilepsy studies on neurostimulation and deep brain EEG recordings (Muñana et al., 2002; Davis et al., 2011; Long et al., 2014; Martle et al., 2014; Martle et al., 2015; Martle et al., 2016; Charalambous et al., 2020; Zamora et al., 2021; Löscher et al., 2022; Sladky et al., 2022), it has been proposed that human neuromodulation could potentially be studied in canine models (Patterson, 2014). The experts agreed that dogs could provide novel models with advantages compared to rodent models for evaluating and investigating these techniques, even as a first-line approach. However, the fact that dogs need to be anesthetized as well as the costly equipment, lack of expertise, and anatomical variations, make the investigation and application of various neurostimulation devices in veterinary medicine quite challenging up to date.

How can modification or bypass of the blood-brain barrier affect the treatment outcomes in drug-resistant epilepsy?

In drug-resistant epilepsy, BBB transporters such as P-glycoprotein (P-gp), responsible for protecting the brain from molecules arriving from the blood circulation, are upregulated (van Vliet et al., 2004; Hoffmann and Löscher, 2007), which leads to decreased permeability of ASMs through the BBB (Ma et al., 2013; Rojas et al., 2014; Wang et al., 2016). The panel discussed whether downregulating or preventing the overexpression of P-gp could be beneficial in drug-resistant epilepsy, even though this is only one factor of the multifactorial problem of drug resistance among several others. In this aspect, the panel

pointed out that indiscriminate use of P-gp blockers could lead to substantially increased BBB permeability to any molecules, not just ASMs, including toxic and harmful substances for the brain. Anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids could modulate the function of the BBB; COX-2 inhibition appears to prevent seizure-induced upregulation of the BBB efflux transporter P-gp in endothelial cells, but studies showed conflicting results (van Vliet et al., 2004; Angelini et al., 2008; Bauer et al., 2008; Takara et al., 2009; Zibell et al., 2009; Holtman et al., 2010; Jambroszyk et al., 2011; Yan et al., 2012) whereas disease-modifying effects may only be evident in dogs with a high seizure frequency (Fischer et al., 2022).

Lastly, it would be relevant to assess further or use routes of ASM administration that bypass BBB, such as intranasal administration. Intranasal delivery of ASM could induce higher drug concentrations in the brain, avoiding any possible systemic adverse effects. Intranasal administration is an easy, practical and non-invasive method which allows drugs to enter the brain via the nose-brain pathway, thus, partially bypassing the BBB (Illum, 2002, 2004; Talegaonkar and Mishra, 2004; Dhuria et al., 2010; Lochhead and Thorne, 2012; Lochhead et al., 2015; Charalambous et al., 2021). The efficacy and safety of intranasal drug administration has been clinically demonstrated in dogs with status epilepticus (Charalambous et al., 2017; Charalambous et al., 2019). However, anatomical and physiological differences of the nasal cavity in various breeds of dogs, as well as the pharmacokinetic and pharmacodynamic properties of the drug. For example, molecular weight and lipophilicity should be considered for successful nose-to-brain delivery of ASMs (Charalambous et al., 2021).

Epilepsy surgery

Surgery may provide the highest likelihood of eradicating epileptic seizures in human patients with drug-resistant epilepsy. However, extensive presurgical evaluation is required to achieve a favourable outcome. The goal of presurgical evaluation is to identify a focal epilepsy syndrome associated with a lesion (Englot, 2018). This requires the identification of a well-localized epileptogenic zone (EZ) which is concordant with seizure semiology, focal epileptogenic EEG activity and visible brain lesions on structural magnetic resonance imaging (MRI) and/or concordant areas of hypometabolism with positron emission tomography (PET)–MRI. The most frequently identified focal brain lesion amenable to surgery is drug-resistant mesial temporal lobe epilepsy/hippocampal sclerosis in humans, which can be approached by anterior temporal lobectomy (Englot, 2018). Complete resection of this lesion improves the prognosis for successful long-term postoperative epileptic seizure control (Tellez-Zenteno et al., 2005). Furthermore, in pediatric epilepsy surgery centers, there is a high proportion of multilobe resections and hemispherectomy due to malformations of cortical development and Rasmussen's encephalitis. The authors debated whether these techniques are realistic options for dogs in the near future. In this context, the panel agreed that most human patients remain on multi-ASMs therapy following epilepsy surgery, indicating that surgery may only convert drug-resistant into drug-responsive epilepsy rather than curing epilepsy. In dogs, decreased volume and asymmetry of the hippocampus on MRI were observed in dogs with epilepsy and were considered a marker of hippocampal atrophy (Kuwabara et al., 2010; Estey et al., 2017; Czerwik et al., 2018). Future studies should define correlations between MRI findings, seizure semiology and EEG to define the relevance of these findings for drug-resistant epilepsy in dogs (Czerwik et al., 2018).

In veterinary medicine, epilepsy surgery is still immature, considering the presence of non-lesional epilepsies. There are only a few case reports of successful treatment after corpus

callosotomy in veterinary medicine (Asada et al., 2021; Hasegawa et al., 2021). The combined use or fusion of novel imaging and EEG techniques in veterinary medicine might alter the current perspective. Neuroimaging techniques such as PET and subtraction (ictal and interictal) single-photon emission computer tomography (CT) may be helpful for further investigation of the EZ in drug-resistant epilepsies without visible lesions on MRI. However, these techniques are limited by expense and the need for a template (O'Brien et al., 2008). Lastly, experts suggested that dogs can benefit from magnetencephalography (MEG) as this technique is less likely to be influenced by muscle, bone or movement artefacts and, thus, it could be applied in awake dogs. However, as with other advanced neuroimaging techniques, the lack of expertise, appropriate veterinary equipment, and the high costs still pose an important barrier. The future might lie in wearable EEG or MEG devices and non-invasive approaches to the brain (Vivekananda et al., 2020).

Can dogs serve as models for disease-targeting precision therapies?

Since IE has a genetic or suspected genetic cause, targeted and genetic therapies might provide a reasonable cure to epilepsy. Epilepsy may be caused by underlying molecular changes that affect the structure and function of various neuronal networks; understanding of these changes may lead to development of mechanism-targeted treatments for epilepsy. In human medicine, some studies have already evaluated novel compounds which reverse the functional disruption caused by a genetic variant. A notable example is a search for a candidate for precision therapy in epilepsy related to the genetic variants in the *KCNT1* gene, i.e., the gene encoding a potassium channel subunit or the use of statins in *SYNGAP1* (Barcia et al., 2012; Fitzgerald et al., 2019; von Stulpnagel et al., 2020). Factors such as the type of mutation, pathogenic mechanisms (e.g., whether loss of function or gain of function occurs), mutant protein and effect of multiple genes need to be considered for the successful

application of targeted therapies. In addition, developing specific drugs for each affected gene might not be a realistic goal, at least in the current era. However, focus can be given to altering specific molecular pathways affected by the mutant genes. Oligonucleotide-based approaches to target haploinsufficiency and gene therapy approaches are in the developmental pipeline. Such approaches have not been investigated in dogs with epilepsy and may currently be restricted to rare monogenic epilepsies, yet the genetic mutations and precise molecular mechanisms are still under investigation for the majority of dogs with IE. Hence, it would be quite beneficial not only for dogs with epilepsy, but also for human translational research, to focus on the investigation of epilepsy risk variants and molecular pathways in dogs with epilepsy (Devinsky et al., 2018).

How is quality of life affected in epilepsy?

Not only can IE adversely affect the QOL of both dogs and their owners, but it can also reduce the canine life expectancy (Berendt et al., 2007; Asher et al., 2009; Hulsmeyer et al., 2010; Summers et al., 2010; Packer and Volk, 2015; Nettifee et al., 2017). This is likely due to the combined impact of epileptic seizures, potential adverse effects from ASMs, and neurobehavioral comorbidities (Wessmann et al., 2016). In one study, 71% of dogs manifested altered behaviour since the onset of IE, including fear, anxiety, and aggression (Shihab et al., 2011). These changes were also present in ASM-naïve dogs, demonstrating that they do not simply represent adverse pharmacological effects but can potentially share common pathways with IE (Shihab et al., 2011; Watson et al., 2018).

Regarding QOL in humans with epilepsy, seizure freedom, not seizure frequency reduction, is associated with higher QOL (Choi et al., 2014). In individuals with drug-resistant epilepsy, seizure frequency is a poor predictor of QOL (Boylan et al., 2004; Choi et

al., 2014). Other essential determinants of QOL, e.g., the adverse effects of ASM, stress, and physiological, mood and sleep disturbances, might be overlooked by neurologists. Mental health issues, such as depression, are among the best predictors of QOL in individuals with epilepsy (Boylan et al., 2004); subclinical signs of depression can substantially lower QOL (Kanner et al., 2010). This is important, as depressive signs occur in approximately 30% of individuals with epilepsy and $\geq 50\%$ of patients with drug-resistant epilepsy (Boylan et al., 2004). Depression is an important cause of mortality and morbidity and is also linked to decreased adherence to ASMs, seizure control and sleep as well as poor performance on a personal and professional level, all of which can further impair QOL (DiMatteo et al., 2000; Boylan et al., 2004). Other mental dysfunctions, e.g., psychosis and anxiety, may decrease QOL in individuals with epilepsy (Hamid et al., 2014). It has been estimated that suicidal behaviour in humans with epilepsy is three times higher compared to the general population (Fazel et al., 2013; Thurman et al., 2017). Patients with epilepsy and mental health disorders have a thirteen times higher risk to succumb due to suicide or accidents compared to humans with epilepsy but without psychiatric illness (Fazel et al., 2013). Several stress-related factors, emotional and physical stress and other reflex mechanisms (bathing, eating, noise, photostimulation) can trigger seizures and impair QOL (Italiano et al., 2016).

Increased stress levels in humans with epilepsy can impair QOL and correlate with increased seizure frequencies. Stress can influence seizure liability indirectly due to sleep disturbances or poor adherence to ASMs, but stress can also be a direct seizure precipitant and reflect pathophysiology and epileptic networks (McKee and Privitera, 2017).

In dogs, mental disorders might not be easily recognisable or applicable, while they could impair QOL and epileptic seizure control to some extent similar to what occurs in

humans. On the other hand, seizure precipitants and triggers might be easily recognized in dogs. Their recognition can provide insights into the relevance of specific networks and serve as independent descriptors of the epilepsy phenotype; recent examples being photosensitivity and noise as triggers in genetic myoclonic epilepsy of Rhodesian Ridgeback dogs (Wielander et al., 2017) or photosensitive myoclonus in dogs with Lafora disease (Flegel et al., 2021). Stress, for instance, could have the same effect in triggering seizures. Indeed, in one study, stress and sleep deprivation were precipitating factors in dogs with epilepsy (Forsgard et al., 2019). Furthermore, cortisol levels were elevated in the hair and saliva of dogs with epilepsy, which suggested that canine epilepsy can cause chronic stress and potential adrenergic fatigue (Packer et al., 2017; Packer et al., 2019a). Interestingly, a study showed that long-term stress hormone levels were synchronized between dogs and their owners, and the stress levels of owners can affect the stress levels of their dogs and vice-versa (Sundman et al., 2019). Therefore, the panel agreed that it is essential for veterinary clinicians to recognize and treat not only epileptic seizures, but any behavioural comorbidities in dogs with epilepsy, and limit trigger factors, especially stress in both dogs and owners, as these could substantially improve canine seizure control and both canine and human QOL (Watson et al., 2018; Packer et al., 2019b).

Animal translational models

Epilepsy in dogs offers a rich foundation for translational research in various animal species. Apart from rodents and other animals, dogs and cats with naturally occurring epilepsy have been recruited to investigate ASMs and other non-pharmacological treatments (Löscher et al., 1985; Patterson, 2014; Szabo et al., 2017; Kitz et al., 2017). Canine epilepsy shares strong clinical (Chandler, 2006; Wielander et al., 2017), electrophysiological (Berendt et al., 1999; Davis et al., 2011), and pharmacological (Volk et al., 2008) similarities with

human epilepsy and has also been proposed as a large animal translational model for investigating new therapeutic options in human epilepsy (Löscher et al., 1985; Löscher, 1997; Karlsson and Lindblad-Toh, 2008; Nowend et al., 2011; Rowell et al., 2011; Potschka et al., 2013; Patterson, 2014;). In addition, the similarities between human and canine epilepsy regarding natural occurrence as well as response and resistance to treatment, make the canine model promising for assessing new treatment options such as neurostimulation or other non-pharmacological therapies (Löscher, 2022).

The naturally-occurring character of canine epilepsy is of particular importance for therapeutic studies, for several reasons, including: (1) costs (lower expenses are needed to conduct pharmacological trials in dogs); (2) practical considerations (application and assessment of novel epilepsy-related devices are generally easier in dogs); and (3) dog owner considerations (owners might be more willing to consent to therapies that carry high risks or have not been proven yet to be effective or safe as a last resort before euthanasia; Löscher, 2022). It is important to consider that canine translational studies are a win-win situation, not only providing potential benefits for human medicine, but also enhancing the treatment and QOL of dogs. For instance, a notable example is the ASM imepitoin, which was first developed for human epilepsy. Still, after conducting several studies, it was proven safe, effective, and approved for treating dogs with epilepsy. Dogs are also widely used in pharmacological research, which can further accelerate the applicability of the canine model for discovering new therapeutic options. A characteristic example is the establishment of VNS in humans, which was initially based on canine studies (Zabara, 1992; Löscher, 2022).

Research studies have compared data regarding epilepsy mechanisms from animal models and post-mortem human brains as well as data from intracranial EEG recordings

obtained during presurgical evaluation; this cross-validation between human and animal data was vital, because it provided a deeper insight into the understanding of the mechanisms underlying epileptogenesis, which could eventually aid advanced treatment options (Devinsky et al., 2018). Furthermore, dogs provide exciting models for further investigations of epilepsy phenotypes, including reflex epilepsy and the combination of movement disorders and epilepsy as described in *SCN2A* and *PRRT2* in humans (von Stulpnagel et al., 2020). In humans, multimodal investigations of cerebral function (Italiano et al., 2016) indicate that ictogenic mechanisms in reflex epilepsies largely depend on the excitation of functional anatomic networks normally serving highly complex physiological processes that are genetically determined or regulated in humans and animals. Lastly, the panel agreed that biobanks with high-quality biological samples from canine brain tissue should be established in the future. This will allow neurologists to gain new insights into epileptic brain morphology and underlying causes. A notable example is cortical dysplasia (malformation of cortical development often due to somatic genetic mutations), a common cause of lesional focal epilepsy in humans and may be amenable to surgical resection. Reports of cortical malformations are quite limited in dogs with epilepsy (Machado et al., 2012; Casey et al., 2014; Herkommer et al., 2020). The panel considered that such malformations might be underdiagnosed in the veterinary field due to limitations in medical imaging (e.g., low-field MRI) and a lack of standardized post-mortem examinations of canine epileptic brains (Matiasek et al., 2015). Identifying malformations of cortical origin might change the general perspective towards the prognosis and treatment of canine epilepsy as it occurs in humans.

Lastly, the canine model for epilepsy studies has not been widely utilized. Several reasons might contribute to this including: (1) the lack of scientific awareness about the translational canine model; (2) the considerable differences regarding drug elimination

between humans and dogs; (3) the less systematic and analytic classification of epilepsies in dogs; (4) the lack of routine EEG recording, and, in many cases; and (5) the lack of knowledge regarding the etiology of canine epilepsy (Patterson, 2014; Löscher, 2022).

Conclusions

Epilepsy, particularly drug-resistant epilepsy, is a complex multifactorial disorder with a complex genetic background requiring additional basic and clinical research. Our current understanding of the pathophysiology and treatment of epilepsy has substantially profited from animal models, including dogs. Drug-resistant epilepsy is an important problem in both dogs and humans, since these cases do not benefit from the available ASMs. Therefore, the evaluation and exploration of pharmacological and non-pharmacological therapeutic options need to remain a priority in epilepsy research. Combined efforts and sharing of knowledge and expertise between human medical and veterinary neurologists is important for improving the treatment outcomes or even curing epilepsy in dogs. Interaction and knowledge exchange between veterinary and human epilepsy experts also offers an exciting approach. This serves the goal of better diagnosing and treating all aspects of canine epilepsy and translating the knowledge gained from people and rodents to dogs and vice versa.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Highlights

- Drug-resistant epilepsy is a challenging multifactorial disorder with poor outcome
- Exploration of non-pharmacological therapeutic options remains a research priority
- Collaboration between human medical and veterinary neurologists is essential
- Establishment of a common framework is needed to improve treatment outcomes
- Translational research offers an exciting approach in human and canine epileptology