UPDATE ON CANINE EPILEPSY: TREATMENT ADVANCEMENTS

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discuss therapy methods for this common idiopathic condition in dogs, including drug administration, as well as neurobehaviour and nutritional influences

Summary

Canine epilepsy – characterised by recurrent epileptic seizures (more than two seizures at least 48 hours apart), unremarkable interictal neurological examination and routine diagnostic tests – can be defined as “idiopathic epilepsy”. Idiopathic epilepsy should not be seen as one single disease, but rather a variety of brain diseases in which the lesion was not identified on routine diagnostics. It is likely idiopathic epilepsy represents a complex interplay between genetic predisposition and intrinsic and extrinsic environmental factors. Therefore, it is not surprising dogs with idiopathic epilepsy will vary in their response to treatment.

In the past year, many articles have been published about canine epilepsy – especially about drug treatment. This review article will not solely focus on first line antiepileptic drug treatment, but discuss what can be expected from an antiepileptic drug in terms of efficacy, treatment of co-morbidities such as neurobehavioural disorders, and the impact of epilepsy and treatment on quality of life. Furthermore, the influence of diet on canine epilepsy will be discussed in greater

detail.

PRESUMPTIVE idiopathic epilepsy remains the most common reported chronic neurological disorder in general practice in the UK, with an estimated prevalence of 0.6 per cent (Kearsley-Fleet et al, 2013). Considering there are 9.4 million dogs in the UK, around 55,000 dogs will be affected and might require chronic treatment.

Depending on the investigated population, up to three-quarters of dogs with idiopathic epilepsy will continue to experience seizures (Heynold et al, 1997; Arrol et al, 2012) and around one-third will remain poorly controlled (defined as a less than 50 per cent reduction in seizure frequency), despite suitable treatment with the former standard antiepileptic drugs (AEDs) phenobarbital and/or potassium bromide (KBr; Trepanier et al, 1998; Schwartz-Porsche et al, 1985; Podell and Fenner, 1993).

Dogs with recurrent seizures – especially if poorly controlled – have an increased risk of developing behaviour changes, reduced quality of life (QoL) and early death (Shihab et al, 2011; Berendt et al, 2007b; Chang et al, 2006; Wessmann et al, 2012). Seizures can be unpredictable and uncontrollable, and, therefore, do not only affect the pet's welfare and QoL, but also the QoL of the dog's owner (Chang et al, 2006; Wessmann et al, 2012; Lord and Podell, 1999).

In the past, the development of new antiepileptic treatment has focused mainly on reducing the likelihood of seizures. However, few trials have focused on achieving complete cessation of seizures as their main outcome measure.

In human medicine, the best improvement in QoL for human patients with recurrent seizures is achieved when treatment leads to remission (seizure freedom; Poochikian-Sarkissian et al, 2008; Birbeck et al, 2002; Kwan et al, 2010). Most epilepsy trials have defined success as a reduction of seizure frequency of at least 50 per cent. However, a reduction of seizure frequency by more than 50 per cent may still entail a high seizure frequency in some animals, which negatively impacts on the pet's and owner's QoL (Chang et al, 2006; Wessmann et al, 2012).

In a survey by Wessmann and colleagues (2012) many owners (30 per cent) felt only complete seizure-free status was acceptable, while slightly fewer thought one seizure every six months (16 per cent) or one seizure every three to six months (21 per cent) was tolerable. Historically, veterinary epilepsy trials have also largely neglected the impact of seizures and degree of side effects on the animal's overall QoL. In the aforementioned survey, around half of pet owners stated they thought their dog's and their own QoL was negatively affected by the adverse effect profile of the current standard AEDs used in veterinary medicine.

Owners regard QoL of their pet as an important consideration in determining overall treatment success (Chang et al, 2006; Lord and Podell, 1999). Some studies in veterinary medicine have considered seizure freedom (Boothe et al, 2012; Muñana et al, 2012) and QoL (Muñana et al, 2012) as an important outcome measure, setting new standards for veterinary AED treatment trials.

Seizure remission – can this be achieved?

Seizure remission with or without medication has been reported in dogs with idiopathic epilepsy, revealing canine epilepsy is not always a lifetime condition. Studies of remission rates are sparse.

A study of Danish Labrador retrievers with idiopathic epilepsy showed a remission rate of 24 per cent, with only six per cent of the seizure-free dogs studied receiving antiepileptic treatment (druginduced remission; Berendt et al, 2002). In a further study from the same group, the spontaneous and druginduced remission rate was 15 per cent (Berendt et al, 2007a). The authors of these studies classified an animal to have achieved remission if it was free of seizures for two or three years.

In a Swiss study of epileptic Labrador retrievers, which were followed for an average period of 4.8 years, 30 per cent of phenobarbital-treated epileptic dogs came into remission (Heynold et al, 1997). Following a group of dogs with juvenile epilepsy (epilepsy started in dogs less than one year of age) being referred to a UK specialist hospital, 22 per cent became seizure free (80 per cent of them not receiving any medication at follow-up; Arrol et al, 2012).

The highest remission rate was described in a US study in a general practice population, where the efficacy of phenobarbital was compared with KBr as a first-line treatment in a blinded randomised trial. Complete seizure remission was achieved in 85 per cent and 52 per cent, respectively, of treated dogs (Boothe et al, 2012). This group reported a higher seizure remission rate than other former studies and this could be due to their follow-up time being shorter, at only six months (Volk and Penderis, 2013).

Apart from demographics, there will be differences between the populations studied – for example, general practice versus referral hospital populations. Large-scale epidemiological studies are needed to estimate the prevalence of seizure remission rate more accurately, so owners can be advised correctly.

Clinical risk factors predicting response

As idiopathic epilepsy is not the same disease in each epileptic patient, what are the known clinical risk factors responding adequately to AEDs? There is some evidence in rodent models that early treatment increases the likelihood of remission in certain types of epilepsy (Blumenfeld et al, 2008). Traditionally, human patients are treated with a standard AED depending on the seizure type immediately after their first seizure and this has been thought to increase the probability of

achieving seizure freedom.

Data from developing countries has questioned if early treatment is the best predictor for outcome. Patients in developing countries have no easy access to AEDs and, despite different time points of treatment initiation, have similar remission rates than patients in the Western world (Placencia et al, 1993). AEDs suppress seizure activity, but few reports could show they can also modify the development of epilepsy (antiepileptogenic) and/or are disease modifying.

When to start treatment is also debated in veterinary medicine. Some advise to start treatment after the dog has had a second seizure. Some owners are, however, reluctant to start treatment then, as they are worried about the side effects of the traditional AEDs. This concern is echoed in one study looking at QoL of epileptic dogs, where AED side effects was one of the top reasons cited by around one-third of owners for a decreased QoL in their dogs (Chang et al, 2006).

As clinicians we need to inform the owners of the benefits gained from using AEDs and the potential side effects they might cause. It is always a balance between tolerability and efficacy. Saying this, the main limiting factor for early AED treatment has been the side effect profile.

There have been some suggestions that the new AED imepitoin might have a better side effect profile; however, this can only be robustly demonstrated if owners are more willing to start this drug earlier, to see if this is associated with better long-term results. However, early initiation of treatment has not been associated with improved treatment outcome.

The aforementioned Swiss study in Labrador retrievers showed dogs in remission received medication a longer period of time after their first

seizure than those dogs that continued to seizure (Heynold et al, 1997). These findings need to be seen in the light of the normal clinical situation; that dogs presenting with a more severe seizure phenotype will receive treatment earlier, so these results may be biased. Future prospective studies need to determine the influence of early treatment on outcome.

There are other factors that might predict better drug responsiveness and treatment outcome (Kwan and Brodie, 2000; Hülsmeyer et al, 2010; Weissl et al, 2012; Löscher and Brandt, 2010; Heynold et al, 1997). The most consistent finding is that treatment outcome is worse when humans or animals experience a high “seizure density” – for example, a high seizure frequency before treatment, the presence of cluster seizures and/or status epilepticus.

Several studies in human medicine have shown a high number of seizures prior to treatment is a poor prognostic indicator for seizure control (Kwan and Brodie, 2000; Sillanpää, 1993). Rodent studies have confirmed high seizure frequency in the early phase of epilepsy is a strong predictor for the development of pharmacoresistance epilepsy (Löscher and Brandt, 2010). Dogs that develop pharmacoresistance epilepsy have also been reported to have a higher number of

seizures prior to initiation of treatment (Heynold et al, 1997) and an initially higher seizure frequency (Hülsmeyer et al, 2010).

There continues to be a debate as to whether high seizure frequency and its association with pharmacoresistant epilepsy might be secondary to a kindling effect (“each seizure begs another seizure”; Reynolds, 1995).

However, as not every dog with idiopathic epilepsy deteriorates, and time to treatment has not been determined to be a good risk factor for the development of pharmacoresistant epilepsy, it is more likely high seizure frequency is a cause of the underlying pathophysiology (Kwan and Brodie, 2000; Berg and Shinnar, 1997). Future studies will hopefully determine different treatment protocols for different seizure phenotypes.

Certain breeds have been suggested to have a higher number of animals presenting with cluster seizures, such as the border collie, German shepherd dog, Staffordshire bull terrier and Labrador retriever. Since 1971, it has been known male dogs with idiopathic epilepsy seizure more than female dogs (Bielfelt et al, 1971).

A study found male dogs were more frequently reported to have cluster seizures than female dogs (Monteiro et al, 2012). Furthermore, two UK studies showed male dogs are over-represented in studies of idiopathic epilepsy (Short et al, 2011; Kearsley-Fleet et al, 2013). It might, therefore, be that being male and from a certain breed could be associated with a poorer treatment outcome. Dogs with cluster seizures might require more aggressive treatment regimens from the beginning and future studies are also indicated to investigate which seizure phenotype responds best to which treatment regimen.

In general, the authors would recommend if an animal is presented with a “high risk” signalment that has formerly been associated with pharmacoresistant epilepsy, and/or if a patient is presented with cluster seizures or a high seizure frequency, this patient is more closely monitored until adequate response is achieved.

Neurobehavioural changes and epilepsy

For some time it has been known human patients with epilepsy have a higher chance of developing neurobehavioural disorders and vice versa. This bi-directional relationship has also been reported in rodent epilepsy models, so that nowadays drug screening does not only involve measurement of the efficacy in terms of seizure control, but also the impact of the new drug on behaviour changes secondary to epilepsy.

Our group has formerly shown that drug-naïve dogs can develop behaviour changes such as fear/anxiety and defensive aggression (Shihab et al, 2011). Dogs treated with phenobarbital and/or KBr also had changes in fear/anxiety, but no longer showed changes in defensive aggression.

They did, however, show other behavioural changes, which were most likely secondary to the sedative effect of the AED.

Interestingly, the new AED imepitoin has potential anxiolytic effects (Rundfeldt and Löscher, 2014) and in the future it will be seen if this can help improve the fear/anxiety changes seen with idiopathic epilepsy.

When treating epileptic patients for seizures, the clinician needs to also consider that animals with idiopathic epilepsy might develop or have neurobehavioural changes.

Influence of diet on seizure control

A myriad of anecdotal reports have suggested the importance of diets, such as the ketogenic diet (KD), hypoallergenic diet, fatty acid supplementation and raw meaty bones diet, as new or alternative treatment strategies for canine epilepsy (Collins, 1994). However, there remains a lack of conclusive supporting or opposing data in veterinary medicine and peer-reviewed literature.

The KD, consisting of high fat, low protein and low carbohydrate dietary intake, was first introduced for use in human childhood epilepsy when common antiepileptic drugs were not readily available (Bough and Rho, 2007). Although the popularity of the KD has dropped due to the development of new antiepileptic drugs, the diet is still being used in difficult-to-handle or pharmacoresistant epilepsy cases in humans.

The anticonvulsant effectiveness of the KD, such as reduction in seizure frequency, severity of seizure and length of seizure, has been reported in both human patients and rodent epilepsy models (Keene, 2006; Thavendiranathan et al, 2000). Although the exact mechanisms resulting in the antiepileptic effects remain elusive, proposed mechanisms include involvement in and/or alterations in brain energy metabolism, inhibitory and excitatory neurotransmitters, ketone bodies, fatty acids and AED metabolism.

The antiepileptic properties of the KD have led to its proposal as a treatment option for canine epilepsy. However, due to differences in metabolism between dogs and humans, inducing ketosis in dogs using the original KD is much more difficult, thus explaining the lack of research and published data in this area so far (Puchowicz et al, 2000). Only one abstract describes the use of a KD in dogs with pharmacoresistant idiopathic epilepsy (Patterson et al, 2005). The ketone serum concentration was far lower than what would be expected in children. The ketone serum concentration was increased in dogs on the KD diet compared to control, but there was no difference in seizure frequency between the groups.

The proposed hypoallergenic diet was derived by the assumption that possible “triggers” to an epileptic seizure, such as toxins and allergens, should be avoided (Collins, 1994). Again, this idea stemmed from human studies, which reported more than 50 per cent incidence of epileptic patients

who also have allergic diseases.

A pilot study was carried out to investigate a similar phenomenon in dogs (Lujan et al, 2004). In this study, seven out of eight AED resistant dogs were found to also have skin or gastrointestinal allergies. After the introduction of an exclusion diet, seven dogs showed reduction in seizure levels. However, there have not been supporting data published since this trial other than advocates of anecdotal reports.

Another proposed dietary treatment option includes fatty acid supplementation. In one human epilepsy study, supplementation of omega-3 fatty acids resulted in both reduced seizure frequency and strength of epileptic seizures (Schlanger et al, 2002). In a case study of drug-resistant epilepsy in dogs, omega-3 fatty acid supplementation resulted in an 85 per cent reduction in seizure frequency (Scorza et al, 2009).

A larger study involving omega-3 supplementation incorporated in a blinded, placebo-controlled trial in 15 dogs showed inconclusive results (Matthews et al, 2012). However, it is reported that one dog showed significant reduction in seizure frequency and others had an improved behavioural outcome.

The raw meaty bone diet has also been advocated as a potential diet for dogs suffering from epilepsy. The rationale for such diets includes theories such as dietary deficiencies and grain content in commercial products causing or triggering epileptic seizures (Collins, 1994). Although many have claimed success with such diet, no scientific study has been performed to verify the hypothesis.

Although there have been different proposals for dietary therapeutic options in canine epilepsy, backed by anecdotal and/or scientific evidence, there is lack of conclusive results and data.

However, the collective evidence shown to date strongly suggests a link between diet and epilepsy. More research involving diet trials in canine epilepsy models are needed to elucidate the mechanisms in question.

Antiepileptic drugs

Until last year phenobarbital and KBr were the main products used for epilepsy treatment in the UK. Phenobarbital was mainly used as first line treatment. KBr is most often used as a second line AED in dogs (should not be given to cats); however, some veterinarians have used KBr as a first line treatment in dogs suffering from a hepatopathy.

A study compared the efficacy and tolerability of phenobarbital with KBr as a first line treatment and complete seizure freedom was achieved in 85 per cent and 52 per cent respectively of treated dogs for a six-month period (Boothe et al, 2012). Phenobarbital’s side effect profile was thought to be

superior to KBr's. Last year, imepitoin was licensed for the treatment of idiopathic epilepsy in dogs, which shows similar efficacy to phenobarbital, but might have a more favourable side effect profile (Rundfeldt and Löscher, 2014). It appears to have a similarly rapid onset of efficacy than phenobarbital, but lacks phenobarbital's liver enzyme induction and therefore reaches a stable steady state quicker. Imepitoin might also have, apart from the antiepileptic and anxiolytic effect, and could potentially be beneficial for those patients that have also a neurobehavioural co-morbidity.

We now have the possibility to adapt drug treatment if clinically severe and significant side effects occur on an AED. However, "never change a winning team" – there is no need to change AED if the animal is well controlled. If you need to change medication, never stop an AED immediately to avoid "withdrawal seizures".

It is usually safe to reduce the AED by 20 per cent each month, at the same time starting the patient on the new AED. If you need to change the drug more aggressively because of life-threatening side effects then the patient needs to be hospitalised for closer monitoring.

When considering treatment of epileptic dogs, also consider clinical risk factors, owner and dog's QoL, side effect profile, neurobehavioural changes and the influence of diet on treatment outcome. Considering all these factors will provide the clinician with a toolset to individualise treatment for each patient to maximise patients' welfare and QoL.

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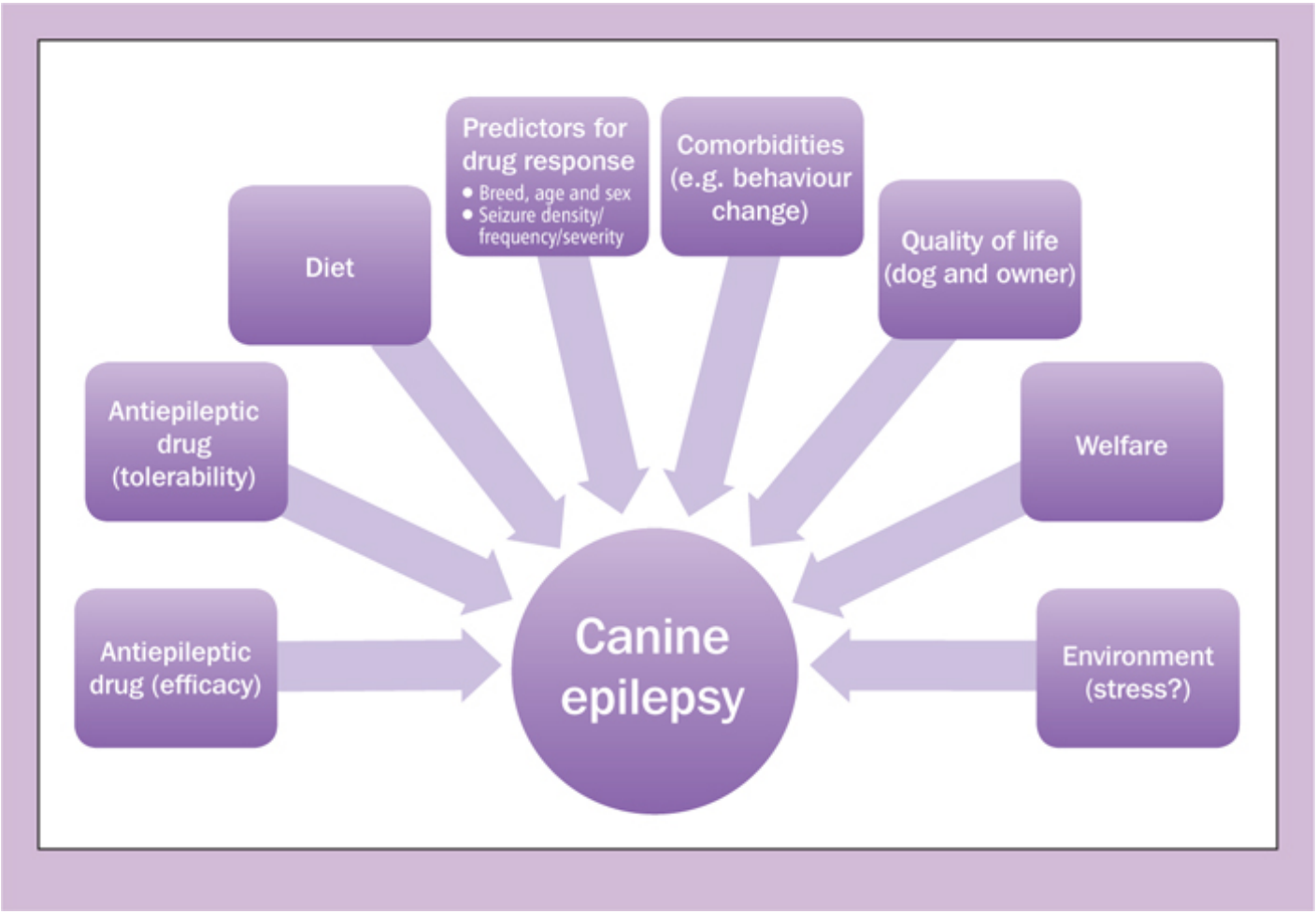
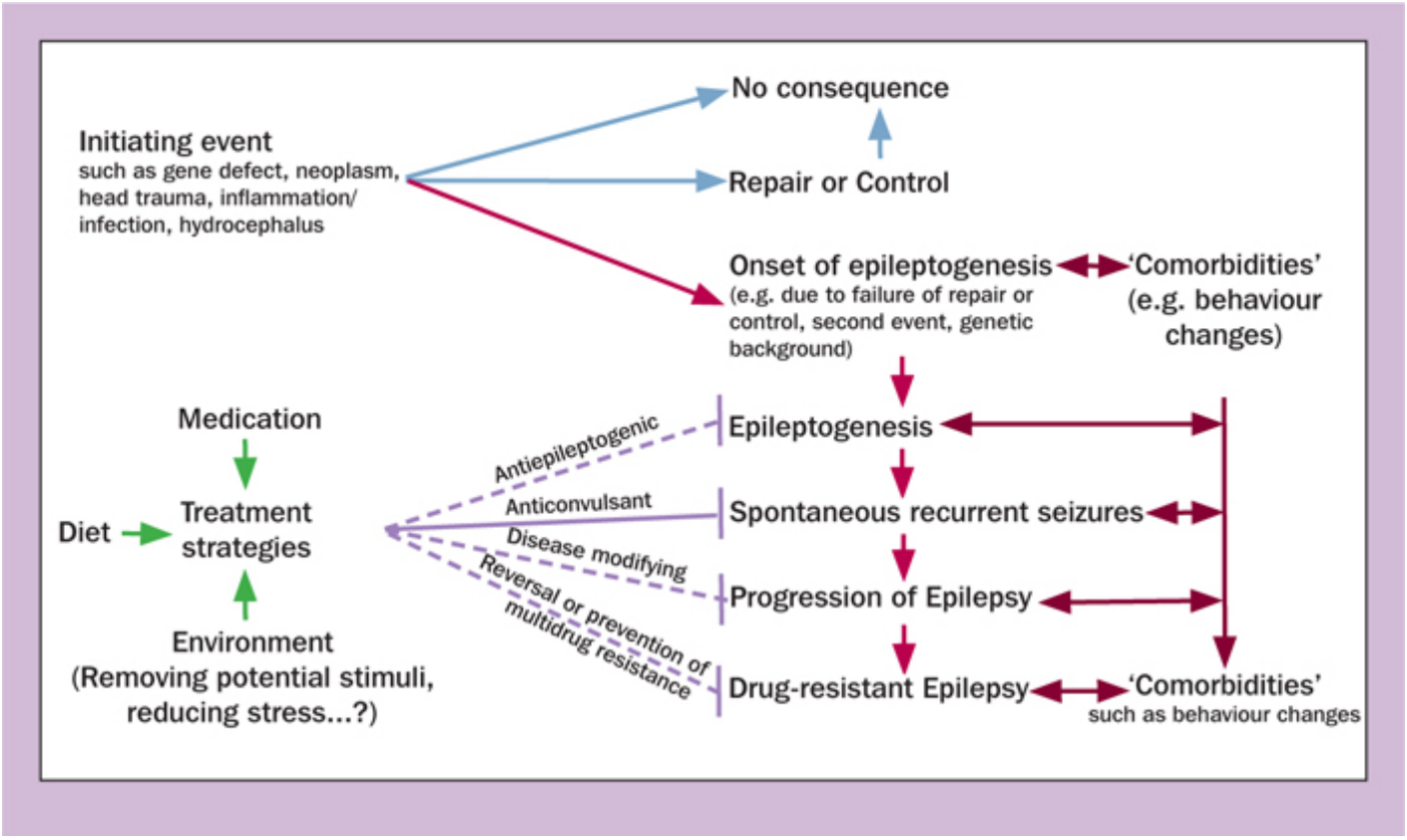
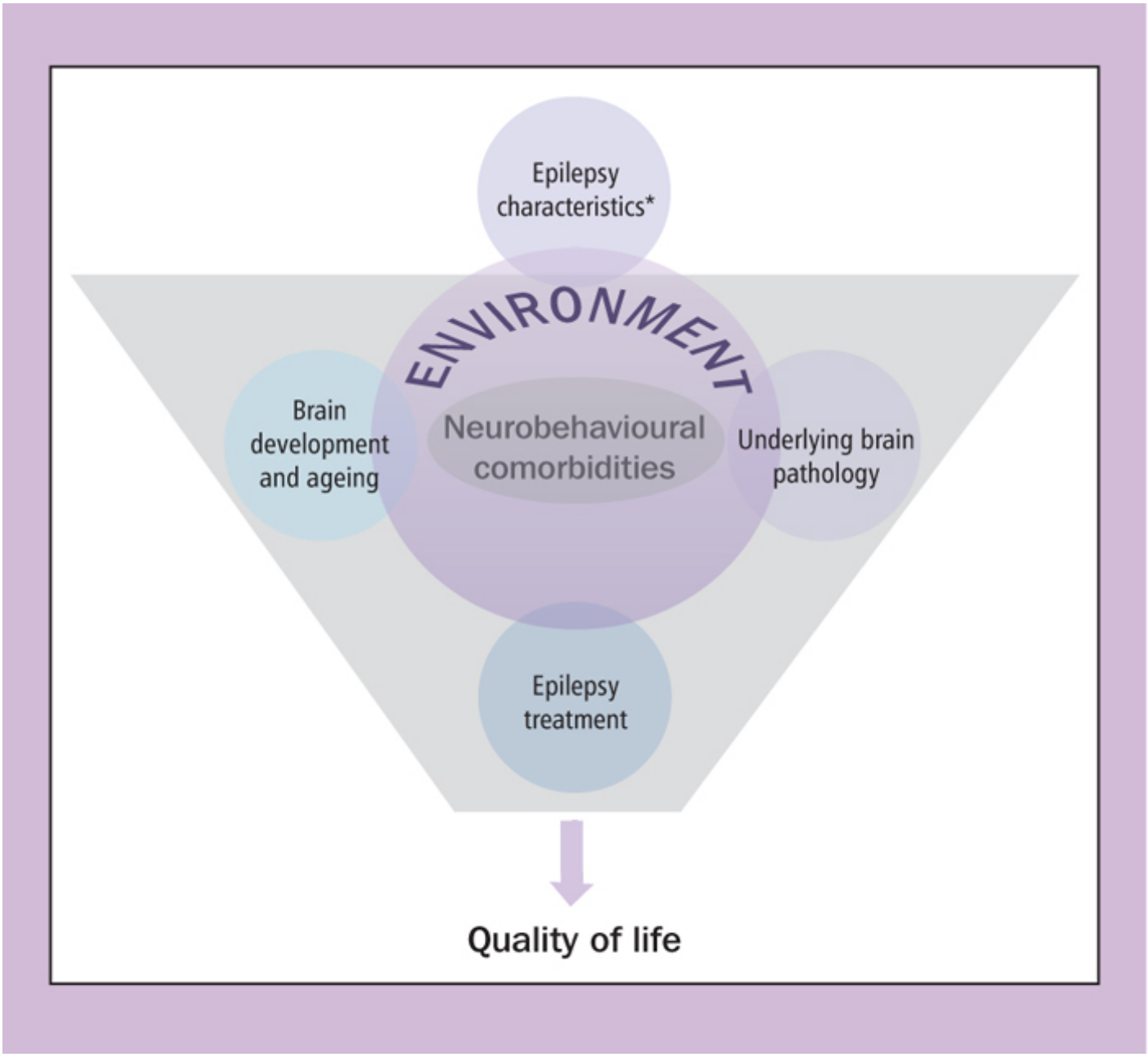


Factors to consider for the management of canine epilepsy.



Targets of therapeutic interventions. While the majority of therapeutics used in veterinary medicine have good anticonvulsant effects, none have reliably been shown to have antiepileptogenic (that is, to delay the development of epilepsy) or disease modifying effects. Comorbidities are also common in dogs with epilepsy – for example, neurobehavioural changes such as fear and aggression (figure is modified from Löscher, 2002).



Mediators of neurobehavioural comorbidities of epilepsy. A schematic drawing shows the potential interplay of major mediators of neurobehavioural comorbidities of epilepsy and how this can affect quality of life of the animal. Potential mediators include brain development and ageing, underlying brain pathology, epilepsy treatment and epilepsy characteristics such as seizure frequency,

epilepsy duration and response to treatment (figure is modified from Lin et al, 2012).