Epilepsy beyond seizures: a review of the impact of idiopathic epilepsy on canine quality of life

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Abstract

Idiopathic epilepsy (IE) is one of the most common chronic neurological conditions in the dog; estimated to affect 0.6%-0.75% of dogs. Owners of dogs with IE have previously indicated that their dog's quality of life (QoL) is of greatest importance to them above their seizure frequency; however, much of the research into canine IE to date has focussed on seizure frequency, and how to reduce it via anti-epileptic drug treatment. In humans, the impact of epilepsy upon QoL has been widely studied, exploring its impact on physical health, but also the psychological health and cognitive capabilities of affected individuals. This paper reviews the existing literature on canine IE, identifying potential threats to QoL, drawing parallels from human epilepsy research. We suggest that canine IE poses threats to both quality and quantity of life, with treatment interventions posing a fine balance of potential benefits and harms to the patient. At present, little is known about the neurobehavioural, emotional and cognitive effects of IE upon affected dogs, with further studies needed to establish the extent to which unknown QoL-inhibiting comorbidities exist in the dog, to avoid their undertreatment. More in-depth studies are required to objectively quantify the effects of IE on QoL

Keywords: Canine, epilepsy, seizure, welfare, behaviour, longevity, quality of life

Epilepsy and Quality of Life

Idiopathic epilepsy (IE) is defined as epilepsy of predominantly genetic or presumed genetic origin and in which there are no gross neuroanatomical or neuropathological abnormalities nor other relevant underlying diseases causing seizure activity (Shorvon 2014). IE is the most common chronic neurological condition in domestic dogs, and although the true prevalence is unknown, it has been estimated to be 0.6% – 0.75% in the general canine population (Heske and others 2014; Kearsley-Fleet and others 2013). Age of onset is most commonly between 6 months and 6 years (Armaşu and others 2014) and the condition is lifelong, in some cases requiring constant medication. Owners of dogs with IE have previously indicated that their dog's quality of life (QoL) is of greatest importance to them above their seizure frequency (Chang and others 2006a); however, much of the research into canine IE to date has focussed on seizure frequency, and how to reduce it via anti-epileptic drug (AED) treatment e.g. (Dewey and others 2009; Dowling 1994; Pearce 1990) with little consideration of QoL until recent years, which has been heavily focussed on the owner's QoL (Chang and others 2006b; Wessmann and others 2014). In humans, the impact of epilepsy upon QoL has been widely studied, exploring the holistic impact of epilepsy on physical health, but also the psychological health and cognitive capabilities of affected individuals (Elger and others 2004). Indeed, QoL scoring systems for people with epilepsy cover a broad range of topics. For example, the Quality of Life in Epilepsy (QOLIE-89) inventory (Devinsky and others 1995), summarised in Table 1, comprises diverse topics, some of relevance to canine IE (e.g. 'medication effects), while others are human-centric (e.g. 'work/driving/social). These impacts on QoL are not simply those that impact physical and mental directly, but also indirect effects that decrease opportunities to participate in activities that promote QoL.

Previously, the impact of IE on canine welfare has been judged as mild-moderate, with a general illness severity index score of 4-10 out of 16 (Asher and others 2009; Summers and others 2010). This comprised a prognosis score of 2-3/4, treatment 2-3/4, complications 0-2 and behaviour 0-2. As that review was an overarching assessment of all disorders considered to be inherited in dogs, justification of each score was not provided. This review will consider the potential impact of IE on canine welfare, QoL, and highlight areas of epilepsy-related QoL compromise in humans that require further study in canine patients. Issues of both quality of life (threats to emotional state) and quantity of life (threats to longevity) will be considered as they are both of importance to companion animal owners. An overview of areas reviewed is depicted in Figure 1.

Are seizures *per se* a welfare problem?

The most salient feature of IE, and target of treatment is the epileptic seizure. Human epilepsy research has the advantage that many epilepsy patients can vocally self-report their experiences, and the effect a seizure has upon them. To date, no studies have objectively measured the impact of a seizure event on the affective state of a dog (e.g. through physiological or behavioural analysis such as cognitive bias testing, which has detected negative emotional states in dogs previously (Harding and others 2004; Mendl and others 2010)). As such, estimating the mental effects at present is limited to behavioural observations (which are often anecdotal rather than systematically studied), and considering comparable effects in humans. The welfare impact of a seizure may depend on the seizure type and severity due to variability in the dog's awareness of the event, and the capacity for physical harm. In addition, each phase of the seizure (prodrome, ictal and post-ictal phases) may have a different impact on the mental state of the dog, although all three phases do not occur in all seizures.

Prodrome

In some dogs, seizures are be preceded by a prodromal phase, a long-term change in disposition and indicator of forthcoming seizures, occurring over hours to days. Signs may include abnormal behaviours such as anxiety, restlessness, irritation, and attention-seeking (Skerritt 1988). Owners may be able to identify these behaviours as predictors of seizure activity. Whether dogs can learn to predict the onset of a seizure, and experience negative anticipation during this phase is not known; however, retrograde amnesia may occur after a generalised seizure due to loss of consciousness impairing normal brain processes, disrupting the encoding and storage of information (Butler and Zeman 2008). The behavioural signs of the prodromal phase are in line with this being a negative affective experience, with anxiety and mood changes also reported in people with epilepsy during this phase, including tension, uneasiness or, alternatively, sadness, apathy and indifference (Scaramelli and others 2009).

Ictal phase

Seizures can be generalised i.e. affecting both cerebral hemispheres or focal, where the abnormal electrical activity is limited to a specific area or areas of the brain. Focal seizures occur when abnormal electrical activity arises in a specific area of the brain, resulting in divergent clinical signs dependent on the function of the area involved. Focal seizures have been reported in dogs with IE (Berendt and others 2009; Licht and others 2007; Patterson and others 2005; Patterson and others 2003), as well as symptomatic epilepsy. Focal seizures can occur with or without a reduction in consciousness. Prior to the revised classification, focal seizures were categorised in humans based on consciousness status, with consciousness maintained with *simple* focal seizures, and consciousness impaired in *complex* focal seizures (with the patient self-reporting their consciousness state post-seizure) (Berg and others 2010). In dogs, as vocal self-report is not possible, assessments of consciousness are dependent upon observers

assessments, which are often unreliable (Packer and others 2015a). Focal motor, sensory, autonomic, or psychic behavioural signs can occur (Berendt and others 2004). Focal motor seizures often occur as localised motor phenomena, such as rhythmic twitching of an extremity and abnormal rhythmic blinking, during which the dog is often presumed to be conscious. Focal seizures with a parasympathetic component may present as vomiting, hypersalivation, or dilation of the pupils, while focal seizures with a sensory of psychic component often manifest as behavioural changes, including anxious behaviours, restlessness, pacing, and seeking out their owner (Berendt and others 2004). The latter may have been described in humans as usually dominated by unpleasant or frightening sensations, including unexplained feelings of fear and apprehension (Ali and others 2012; Lennox and Lennox 1960). It is possible that in rare cases, certain types of seizure may be painful. Among human epilepsy patients with somatosensory seizures, whereby the seizure arises from sensory areas in the parietal lobe, pain was found in 23.6% of seizures (Mauguiere and Courjon 1978). In one study of 858 human epilepsy patients, 2.8% (n=24) had experienced painful seizures (Young and Blume 1983), and in a further study, 1.4% (n=8) of 573 epilepsy patients (Siegel and others 1999). In these cases, involvement of the primary somatosensory cortex in the parietal lobe was again suspected rather than conscious awareness of painful involuntary motor movements during the seizure (Young and Blume 1983). Pain from headaches has also been associated with seizures as a preictal, ictal or postictal phenomenon, which is often neglected due to the dramatic neurological manifestations of the seizure (Dainese and others 2011)

Focal seizures can develop into generalised seizures, by spreading through subcortical structures to involve the entire brain, termed ‘focal seizure with secondary generalisation’. The initial localisation of signs during the focal seizure (which may be very brief) is followed by a generalised seizure, with the focal seizure potentially missed by an observer. Generalised seizures are characterised by bilateral involvement (both sides of body) indicating that both cerebral hemispheres are involved. Generalised seizures are seen predominantly as tonic (stiffening), clonic (jerking), or tonic-clonic seizures; however, myoclonic seizures can occur (with sporadic jerks affecting both sides of the body) and non-convulsive generalised seizures, termed atonic seizures, or ‘drop attacks’(where a sudden loss of muscle tone causes collapse). During generalised seizures, it is widely accepted that total amnesia and loss of consciousness occur in humans (Goldensohn and others 1984). Although we cannot truly know the experience of a dog during a seizure, dogs are also thought to be unconscious and thus unaware of the event during a generalised seizure and thus protected from mental distress (except in myoclonic seizures). During this phase, dogs are at risk of physical injury due to uncontrolled motor movements, including uncontrolled chewing leading to tongue injuries.

Status epilepticus

During the ictal phase dogs are at risk of status epilepticus (SE), a prolonged seizure classed as a neurological emergency due to high mortality rates of up to 25% (Bateman and Parent 1998), and a significantly shorter survival time than dogs with IE that have not experienced SE (Saito and others 2001). A poor outcome (death or euthanasia) is significantly associated with loss of seizure control after 6 hours of hospitalisation (Bateman and Parent 1998). Definitions of SE vary, and include (i) a continuous epileptic seizure lasting longer than (i) five or (ii) ten minutes, (iii) up to 30 minutes or longer, or (iv) two seizures with incomplete recovery of consciousness interictally, with (i) and (iv) used most commonly in veterinary medicine (Bateman and Parent 1998; Patterson 2014; Saito and others 2001; Zimmermann and others 2009). In a hospital population of dogs with SE, over one third of dogs with SE (37.5%) had IE (Zimmermann and others 2009). SE occurs in two stage, the first characterised by generalised tonic-clonic seizures and an increase in autonomic activity, followed after approximately thirty minutes by hypotension, hypoglycaemia, hyperthermia, hypoxia, decreased cerebral blood flow, cerebral oedema and increased intracranial pressure. The sustained muscle contractions during SE, along with impaired ventilation can cause lactic acidosis, hyperkalaemia, hypercarbia and severe myoglobinuria, which may result in impaired renal function (Platt and McDonnell 2000). SE requires prompt treatment to control the seizure, with prolonged seizure activity leading to the development of circuits in the brain allowing the seizure to become self-sustaining (Manno 2003). In humans, SE has consistently been associated with long-term cognitive problems, and widespread neuronal cell loss in the brain (Wasterlain and others 1993). In rat models of epilepsy, SE in adult rats results in long-term disturbances in learning and memory, and increases susceptibility to further seizures (Cilio and others 2003). Longitudinal follow-up of canine SE cases are needed to provide insights into the physical and mental effects of SE in dogs, and whether they are physically and/or mentally compromised after these events.

Seizure severity

Seizures between and within dogs may vary greatly in severity, including duration and intensity of ictal signs. Associations have been found between seizure severity and QoL in human patients, with correlations between QoL and cognitive function, social functioning and the degree the patient worries about seizures (Harden and others 2007). Further human studies have found that seizure severity is negatively associated with QoL score (Gromov and others 2005), and that this effect is independent of seizure frequency (which may otherwise confound this result) (Bautista and Tannahill Glen 2009). Objective measures of seizure severity have not yet been devised in canine IE patients, or the effect of severity on QoL studied.

Post ictal phase

During the postictal phase, the brain regains normal function, with this phase lasting from minutes to hours. The dog may appear tired, ataxic and disorientated. In humans, muscles may be sore after a generalised seizure due to the accumulation of lactic acid during the seizure (Orringer and others 1977). Dogs may also be thirsty and hungry in this period, and show behavioural signs such as aggression, hyperexcitability and fearful behaviours such as hiding, and seeking their owner's attention, which may indicate a state of distress. As in humans (Sadeh and others 1983), some dogs appear to be blind during this phase, which although transient has the potential to cause confusion and distress.

Cluster seizures

Time between seizures often varies markedly both within and between dogs. Some dogs with IE experience cluster seizures (CS), defined as two or more seizures within a 24-hour period in which the patient regains consciousness between seizures (Patterson 2014; Thomas 2010), with reports of 38% (Short and others 2011) to 77% of dogs with epilepsy experiencing CS depending on the population investigated (Fredso and others 2014; Monteiro and others 2012). CS likely reduces quality and quantity of life, as dogs with a history of CS are less likely to achieve seizure-freedom following treatment (Packer and others 2014), experience a decreased survival time (Arrol and others 2012; Berendt and others 2007; Monteiro and others 2012; Saito and others 2001) and an increased likelihood of euthanasia (Fredso and others 2014) compared to dogs with single seizure episodes. Dogs may not fully recover from a preceding ictal period before another begins; however, further research is needed to determine the effect of temporally dense seizures compared to single seizures on canine welfare.

Inter-ictal phase

In veterinary medicine, much of the focus on the diagnosis and treatment of canine IE has focused on the seizures themselves, with research into the inter-ictal period relatively neglected. In contrast, in human epilepsy, much attention is upon the detection and treatment of inter-ictal changes and comorbidities. Although dogs with IE appear 'neurologically normal' between seizures (i.e. they have an unremarkable neurological examination) (Skerritt 1988), a recent study indicates that similarly to people with epilepsy, behavioural changes may be present in these dogs (Shihab and others 2011). Inter-ictal changes in behaviour, emotion and cognition that may affect QoL will now be considered in people with epilepsy, with evidence from canine IE described where available.

Neurobehavioural impact of epilepsy

The prevalence of psychiatric disorders in people with epilepsy is higher than in either the general population or patients with other chronic medical diseases (Boro and Haut 2003; Gaitatzis and others

2004; Kobau and others 2006), with the most common disorders being depression and anxiety disorders, followed by psychoses and attention-deficit disorders (Boro and Haut 2003; Dunn and Austin 1999; LaFrance Jr. and others 2008; Prueter and Norra 2005; Seminario and others 2009). A bidirectional relationship between epilepsy and psychiatric disorders such as depression has been considered, with potentially common operant pathogenic mechanisms in the disorders that facilitate the occurrence of one in the presence of the other (Kanner 2003). This is supported by people with epilepsy being at greater risk of developing depressive disorders, but patients with depressive disorders also being at higher risk of epilepsy (Forsgren and Nystrom 1999). As such, epilepsy can be considered a more general brain disorder, which is not limited to seizure activity.

Anxiety and depression

In a study of health-related QoL (HRQoL) in people with epilepsy, inter-ictal anxiety and depression were found to have adverse effects on HRQoL, with their effects greater than those of seizure frequency, severity and chronicity (Johnson and others 2004). In addition, although co-morbidity was observed between anxiety and depression, their negative effects on HRQoL were found to be independent of one another (Johnson and others 2004). Despite the high prevalence of depression and anxiety in people with epilepsy, these and other psychiatric disorders are thought to be underrecognised and undertreated in both children and adults with epilepsy (Ettinger and others 1998; Gilliam and Kanner 2002; Kanner and Palec 2000; O'Donoghue and others 1999; Wiegartz and others 1999).

To date, few studies have considered the possibility of psychiatric co-morbidities in dogs with IE. In one study, at least one behaviour had changed since the onset of IE in 71% of all dogs studied (Shihab and others 2011). Dogs with IE showed behavioural changes including excessive fear/anxiety, abnormal perception (e.g. barking without apparent cause), abnormal reactivity, attachment disorder, demented behaviour, apathetic behaviour and aggression (Shihab and others 2011). Some of these changes were present in dogs who were not receiving AEDs, demonstrating they are not merely a treatment side effect. The authors considered the increases in anxiety and defensive aggression comparable to anxiety disorders seen in people with epilepsy (LaFrance Jr. and others 2008). After the onset of IE, dogs in this population began to act more anxiously or fearfully when approached by unfamiliar dogs or people, when in unfamiliar surroundings, or when faced with sudden or unpredicted movements. They acted more aggressively when being handled, when approached by other dogs or unfamiliar people, or when strangers passed by the house. These effects have the potential to adversely affect QoL due to the induction of chronic negative emotional states, and impairment of social interactions with conspecifics and/or humans.

Psychoses

Psychoses are the third most common psychiatric comorbidity in people with epilepsy, and can be accompanied by hallucinations, delusions, reduced connection to reality, and impaired thought [36]. Although lack of self-report in dogs impairs our ability to detect psychosis, behaviours that may indicate these signs can be observed. A hallucination is defined as sensory perception in the absence of external stimuli, and in dogs this may manifest as barking without apparent cause, chasing shadows or light spots, aimless pacing, and staring into space. These signs of abnormal perception were detected in dogs following the onset of epilepsy (Shihab and others 2011), and if dogs are conscious during these episodes, then they could induce fear and distress, and could lead to further behavioural problems if reinforced by the owner (e.g. through increased attention or attempted punishment to stop the behaviour). Hallucinations may be challenging to differentiate from sensory focal seizures, and whether they occur in dogs requires further study.

Attention-deficit/hyperactivity disorder

Finally, attention-deficit/hyperactivity disorder (ADHD) is the fourth most common psychiatric co-morbidity of epilepsy, with around one third of epilepsy patients diagnosed with ADHD (Thome-Souza and others 2004). In a recent large community-based survey, ADHD symptoms were self-reported in nearly one of five adults with epilepsy, which was associated with are increased psychosocial morbidity and lowered QoL (Ettinger and others 2015). Hallmarks of ADHD e.g. easy distraction and slow learning have also been demonstrated in a strain of epilepsy-model laboratory rats in various behavioural paradigms, with a disinhibited or impulsive behavioural style (Anisman and McIntyre 2002). In a recent single breed study of Lagotto Romagnolo dogs with a history of Benign Familial Juvenile Epilepsy (BFJE), an epilepsy syndrome in which dogs often experience spontaneous seizure remission before 13 weeks of age, dogs with BFJE (n=25) showed significantly higher scores on the behavioural factors 'Inattention' and 'Excitability/Impulsivity' than did the control group of Lagotto Romagnolo dogs without BFJE (Jokinen and others 2015). Recent data indicates that the three most prominent behavioural domains of dogs with IE were excitability, chasability and attachment/attention seeking, mirroring behavioural traits of humans with epilepsy and ADHD in a variety of breeds (Packer and others, Submitted). In contrast, the 'trainability' behavioural domain was relatively low, with two thirds of owners reporting that their dog is 'always' easily distracted by interesting sights, sounds and smells. These signs may lead to punishment from owners to stop these undesirable behaviours, and have an impact on their cognitive abilities due to poor attention skills.

Cognitive impact of epilepsy

Cognition is broadly defined as the ways in which an individual takes in information about the world through the senses, processes, retains and decides to act on it, which includes perception, learning, memory and decision making (Shettleworth 2001). There is a predisposition to cognitive deficits in

people with epilepsy; however, to the authors' knowledge, this has not yet been studied in dogs with epilepsy. Epilepsy *per se* has been found to induce or exacerbate underlying cognitive impairments, with a variety of factors contributing to these deficits, including the seizure type and age of onset (Motamedi and Meador 2003). The degree of compromise is diverse, with IEs having a milder deterioration than symptomatic epilepsy (Elger and others 2004). Intellectual abilities of people with IE are usually in the normal range, but lower than the general population (Mirsky and others 2001). Compared to healthy siblings, children with IE have a reduced memory performance and psychomotor speed despite normal intelligence (Bailet and Turk 2000). The main area of compromise for people with IE is thought to be attention-related, with patients impaired in visual and auditory sustained attention (Mirsky and others 2001), and have been reported across all seizure types in children with IE (Bhise and others 2010). These problems with attention are frequently observed in IE, irrespective of the intellectual level of the patient (Williams 2003). If present in dogs, impaired attention may result in reduced 'trainability' i.e. the ability to learn new commands from their owner. Although this may not have a direct impact on QoL, the consequences of this inability to sustain attention may result in the perpetuation of undesirable behaviours and inappropriate punishment from owners.

The presence of neurobehavioural abnormalities in dogs with IE is poorly studied at present, and thus strategies to avoid their development, or ameliorate their effect if present is unknown. Identifying dogs at risk of these changes is a priority, and may be linked with drug response, with drug-resistant rats having greater behaviour changes than drug-responsive rats (Gastens and others 2008). Further study into the causal mechanisms underlying the association between epilepsy and neurobehavioural changes is needed, as common mechanistic pathways may underlie these problems, and offer a common therapeutic pathway.

Treatment

Due to the threat of seizure activity to both quality and quantity of life, canine IE therapy is aimed at reducing seizure frequency. In veterinary medicine, a positive response to therapy is defined as a $\geq 50\%$ reduction in seizure frequency (Muñana 2013). This is the definition of AED efficacy in the majority of canine epilepsy studies (Dewey and others 2009; Dewey and others 2004; Muñana and others 2012a; Muñana and others 2012b; Platt and others 2006; Volk and others 2008; von Klopmann and others 2007). This may be a problematic outcome measure as a $\geq$50% reduction in an initially high seizure frequency may still result in an unacceptably high seizure frequency outcome. This may not be a satisfactory outcome for the carers (the owners), with nearly one third considering only complete seizure freedom as an acceptable outcome (Wessmann and others 2012).

QoL is decreased in people with epilepsy by poor seizure control and increased seizure severity (Johnson and others 2004), and as such, in human medicine the best improvements in QoL for epilepsy patients are achieved when treatment leads to remission (seizure freedom) (Birbeck and others 2002; Kwan and others 2010; Poochikian-Sarkissian and others 2008). Indeed, in one study no significant change in QoL was found after treatment for subjects that did *not* achieve seizure freedom (Birbeck and others 2002). Unfortunately, in veterinary medicine more than two thirds of dogs with epilepsy will continue to have seizures long-term (Arrol and others 2012; Berendt and others 2007; Berendt and others 2002; Heynold and others 1997; Packer and others 2015b) and around 20-30% will remain poorly controlled (<50% reduction of seizure frequency) despite adequate treatment with phenobarbitone (PB) and/or potassium bromide (KBr) (Podell and Fenner 1993; Schwartz-Porsche and others 1985; Trepanier and others 1998). Remission with or without medication has been observed in canine epilepsy cases, demonstrating that epilepsy in dogs is not *necessarily* a lifelong condition. Remission rates vary between studies and population studied, from as low as 14-15% (Berendt and others 2007; Packer and others 2014) to as high as 85% (Boothe and others 2012). As complete control of seizures is rare in dogs with IE, clinicians and owners goals for therapy are often based on minimising seizure frequency and severity (by titrating animals to the maximum tolerated dose), whilst minimising side effects of AEDs.

Effects of anti-epileptic drugs

Known effects

Side effects of AEDs have a high potential for reducing QoL of the patients they are administered to, as they must be taken continuously (on a daily basis) to be effective, and thus effects may be chronic. In people with epilepsy, increases in AED side effects are significantly negatively associated with self-reported QoL, more so than seizure frequency (Gilliam 2002). Although the range of AEDs used to treat IE in dogs differs from those used in humans, a variety of side effects have been reported that are considered to have a major contribution to the QoL of dogs with IE, including polyphagia, polydipsia, weight gain, polyuria, increased sleeping, ataxia, restlessness, pruritus, vomiting and diarrhoea (Wessmann and others 2014). The side effects of AEDs can predispose affected dogs to obesity, due to the combined effects of enhanced appetite (polyphagia) and reduced activity (sedation). Obesity may impede a dog's ability to behave normally and predispose them to obesity-related diseases (German 2006). Obesity has also been found to have a significant negative impact upon QoL of dogs with other neurological disorders (Rutherford and others 2012)/ Behavioural side effects of AEDs may also occur, with increases in abnormal reactivity (anxiety with unpredicted movements or with sudden or loud noises), attachment disorder (signs of separation anxiety), demented behaviour (reduced ability to recognize family members or familiar people, aimless pacing or wandering), and apathetic behaviour (reduced interest in activities, agitation if not allowed to sleep) observed in dogs with IE receiving

AEDs, but not drug-naïve dogs (Shihab and others 2011). Future studies of AED efficacy should ensure behavioural side effects are adequately reported alongside physical side effects, due to their potential impact on QoL.

In many cases, side effects are present at their greatest intensity in the first 2-4 weeks of treatment, and subside after this period once serum levels reach a steady state (Boothe and others 2012; Podell 1998; Schwartz-Porsche and others 1985). In some dogs, side effects are permanent (Dewey 2006), with chronic effects observed particularly in dogs receiving polytherapy (more than one AED) rather than monotherapy. Dogs receiving three AEDs have been found to have a lower QoL than those on less than 3 AEDs (Wessmann and others Submitted). Accordingly, for dogs with a low seizure frequency, the impact of AED side effects on QoL may be greater than the seizures themselves, and thus careful consideration must be given over the necessity of medication.

Complications

In addition to these known effects that can be explained by the known pharmacological properties of the drug (Zaccara and others 2007), reactions that are not dose related, are independent of the known mechanism of action of the drug can occur which may pose a threat to life, and require discontinuation of treatment (Zaccara and others 2007). Phenobarbital (PB) also has been associated with idiosyncratic adverse drug reactions, including haematological abnormalities (PBIHA, 'phenobarbital induced haematological abnormalities') such as neutropenia, anaemia and thrombocytopenia (Behne and Engelhardt 2010; Jacobs and others 1998; Khoutorsky and Bruchim 2008; Thrift and others 2010; Vargo and others 2007; Von Klopmann and others 2006; Weiss 2005; Weiss and Smith 2002). The prevalence of these abnormalities is variable, with estimates of 4.2%-22% (Bersan and others 2014; Haböck and Pakozdy 2012). Although up to a fifth of dogs may be affected, the effects of PBIHA on the animal may be minimal; for example, in a case series of 37 PB treated dogs, 8 dogs showed PBIHA (22%), but only 2 of these (5%) were clinically significant (Haböck and Pakozdy 2012). As such, PBIHA may only be welfare relevant in the most severely affected cases, where PB should be discontinued and another AED added (Bersan and others 2014).

Long-term PB treatment has also been associated with hepatotoxicity in several studies which appear to be dose dependent (Bunch and others 1982; Dayrell-Hart and others 1991; Gaskill and others 2005; Muller and others 2000). Dogs with PB-induced hepatoxicity may exhibit a poor body condition, ascites, low serum albumin and blood urea nitrogen concentrations, moderately increases serum bilirubin concentrations, and abnormally high fasting and post-prandial bile acid concentrations (March and others 2004). As such bile acids should be monitored periodically, and PB should be avoided in patients with hepatic dysfunction. Superficial necrolytic dermatitis has been reported in dogs treated with PB chronically (March and others 2004). This condition commonly causes painful footpad lesions

resulting in lethargy, inactivity and reluctance to walk, and carries a poor prognosis, with dogs euthanased on average 12 weeks after diagnosis (March and others 2004). The prevalence of this disorder in PB-treated dogs is not known. Finally, dogs with epilepsy have been demonstrated to be at risk of acute pancreatitis (Hess and others 1999) which can cause vomiting, diarrhoea, anorexia, abdominal pain and death. This association has since been attributed to long-term treatment with PB and potassium bromide (KBr) (Gaskill and Cribb 2000), where the prevalence of suspected pancreatitis associated with KBr/phenobarbital combination therapy was at least 10%, compared with 0.3% with PB monotherapy.

Ethical considerations

The ethics of epilepsy treatment is complex, with a fine balance of the potential benefits of AEDs versus potential harms. This balance varies between dogs, and over an individual's disease course. Factors that may influence this balance may include the initial seizure frequency, response to AEDs, and the number of AEDs required to provide adequate seizure control. In addition to the side effects described above, there may be iatrogenic consequences of treating epilepsy, that is, unintentional adverse effects that may occur as a by-product of diagnosis and treatment, even when used appropriately (Yeates 2012). As IE is a diagnosis of exclusion, a variety of diagnostic tests may be carried out including blood tests requiring venipuncture that may be uncomfortable and distressing to the individual, as well as invasive diagnostics requiring general anaesthesia (cerebrospinal fluid analysis and MRI of the brain) that carry a small risk of death (Brodbelt 2009). Hospitalisation to carry out these tests may be aversive to the dog, and has been associated with an increase heart rate (Väisänen and others 2005) and cortisol levels (Van Vonderen and others 1998). As dogs with epilepsy may show increases in fear/anxiety, hospitalisation may be particularly stressful, and restraint and punishment of these dogs should be avoided as they may increase fear-related behaviours (Herron and others 2009; Rosado and others 2009). Once AED treatment has been initiated, regular monitoring of serum drug concentrations (PB and KBr), and blood tests (haematology/serum biochemistry) are required, with periodic checks every 3-6 months, dependent upon AED and the dog's response to it. These visits may be aversive to the dog, with veterinary practice visits increasing heart rate and blood pressure (Kallet and others 1997), cortisol (Van Vonderen and others 1998), and fear-related behaviours (Döring and others 2009). As epilepsy is a chronic condition, efforts should be made to ensure these visits are positive, as dogs with only positive previous experiences in veterinary surgeries were significantly less 'fearful' than dogs that had a previous negative experience (Döring and others 2009).

Quantity of life

Canine epilepsy has the potential to substantially reduce quantity of life. The median longevity of 102,609 owned dogs attending first opinion veterinary practices was 12.0 years (IQR 8.9–14.2) (O'Neill and others 2013). In contrast, the median age at death of dogs with epilepsy was 7.0 years in two separate studies (Berendt and others 2007; Proschowsky and others 2003). In single breed studies, the life expectancy for Irish Wolfhounds is shortened by almost 2 years in epileptic dogs compared with seizure-free relatives (Casal and others 2006); however, the lifespan of Belgian Shepherds with epilepsy was not significantly shortened, despite being the predominant cause of death (Gulløv and others 2012). Within a mixed population of dogs with epilepsy, those that died or were euthanased because of epilepsy had a shorter lifespan than those euthanased due to other causes (4 years vs. 12 years) (Berendt and others 2007). After diagnosis, the median number of years that a dog lived with epilepsy was 2.3 years (Berendt and others 2007). That study was in both pure and mixed bred dogs, and in a single breed population of Border Collies, similar results were observed, with a median survival time after first seizure of 2.07 years (Hülsmeyer and others 2010). The majority of deaths of dogs with epilepsy are epilepsy related, with more than 60% of Irish Wolfhounds (Casal and others 2006) and 70% of Belgian Shepherds with epilepsy dying of epilepsy-related reasons (Gulløv and others 2012).

Few risk factors for lifespan have been identified for dogs with epilepsy; however, in one study, bitches lived longer with epilepsy compared with males (Berendt and others 2007), and in a study of Australian Shepherds, poor seizure control and a high initial seizure frequency (≥ 10 seizure days/6 months after seizure onset) were associated with reduced survival time (Weissl and others 2012). Intact Belgian Shepherd dogs with IE have also been found to have an increased risk of being euthanased because of IE compared to neutered dogs with IE (Berendt and others 2008), which the authors attributed to a reduced seizure frequency in neutered dogs.

SUDEP (sudden unexpected death in epilepsy) is defined as "sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in epilepsy, with or without evidence of a seizure and excluding documented status epilepticus" (Annegers 1997) and is a well-known risk to life (Lindsten and others 2000). Incidence rates vary between populations, but reach 10 in 1000 human patients (Téllez-Zenteno and others 2005), with risk factors including poor seizure control, nocturnal seizures, young age and being male (Opeskin and Berkovic 2003). Cases of presumed SUDEP have been reported in dogs (Berendt and others 2007; Gulløv and others 2012); however, further investigation of risk factors and its prevalence are needed.

Conclusions

In conclusion, IE is a prevalent disorder in the canine population, with the potential to have a chronic negative effect on affected dog's QoL, as well as significantly reducing quantity of life. As Summarised

in Table 2, all of the Five Freedoms have the potential to be comprised by epilepsy and its treatment (Farm Animal Welfare Council 1992). Although seizures may be the most salient feature of canine epilepsy, inspiration should be sought from the field of human epilepsy, where the epilepsy patient's QoL is viewed more holistically, considering all impacts on both their physical and mental health beyond simply seizure frequency. It is clear that further research is required to gain a fuller understanding of the extent to which dogs are affected by co-morbidities of epilepsy e.g. psychiatric disorders, which should be a focus of future study to ensure that they are not under-treated. Although seizure freedom may be the holy grail of both canine and human epilepsy treatment, clinicians and owners should not lose sight of the potential harms of treatment, and always keep this fine balance in favour of the dog's quality of life.

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Figure 1 Threats to Quality of Life in dogs with idiopathic epilepsy

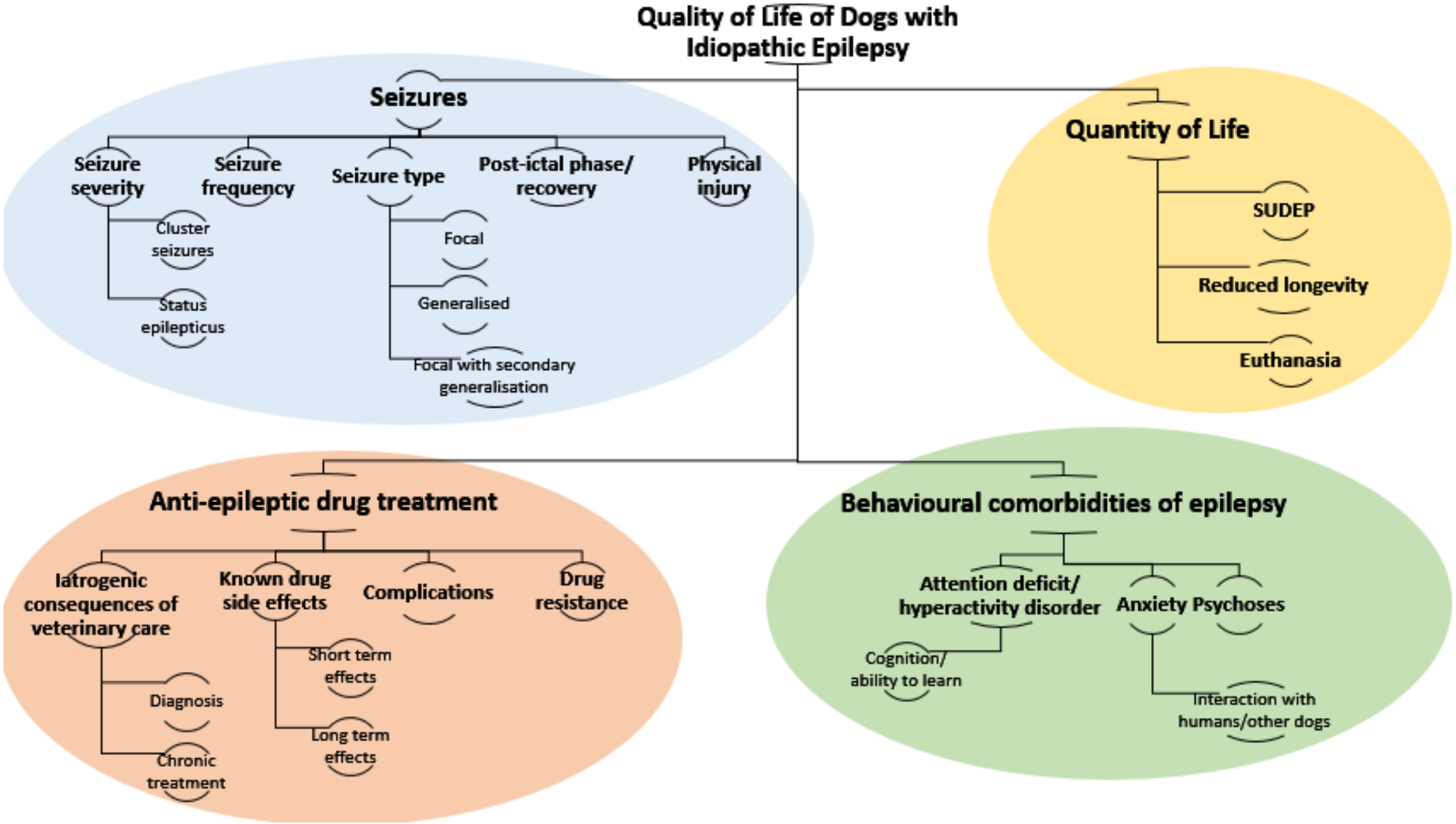

Table 1. Scales and items that compromise the Quality of Life in Epilepsy (QOLIE-89) inventory, an instrument to measure health-related quality of life (HRQOL) in people with epilepsy

Scale	Item	General description
Epilepsy-targeted	Seizure worry	Fear and worry about having a seizure
	Medication effects	Physical and mental effects of AEDs
	Health discouragement	Feelings of discouragement regarding epilepsy
	Work/driving/social	Degree of which epilepsy impedes 'normal' life
Cognitive	Language	Effect of epilepsy on ability to communicate with others
	Attention/concentration	Ability to concentrate and organise complicated activities
	Memory	Effect of epilepsy on memory function
Mental health	Emotional wellbeing	Frequency of experiencing positive and negative emotions
	Role limitation: emotional	Extent that emotional problems e.g. anxiety limit daily life
	Social isolation	Frequency of feelings of isolation and being 'left out'
	Social support	Quality of supportive interactions with family and/or friends
	Energy/fatigue	Frequency of feeling low on energy or tired
Physical health	Health perceptions	Perception of current and future health, and health risks
	Physical function	Frequency of epilepsy preventing physical activities
	Role limitations: physical	Extent that physical problems limit daily life
	Pain	Severity of bodily pain and degree it interferes with daily life

Table 2 Potential impact of epilepsy and anti-epileptic drug treatment upon the Five Freedoms (Farm Animal Welfare Council, 1992)

Five Freedoms Framework	Potential impact of epilepsy upon freedom	Potential impact of anti-epileptic drugs upon freedom
Freedom from hunger and thirst	Postictal hunger	Polyphagia, polydipsia due to antiepileptic drug treatment such as phenobarbital and/or potassium bromide treatment
Freedom from discomfort	Venipuncture for blood tests required for diagnosis of IE	Venipuncture for blood serum monitoring
Freedom from pain, injury and disease	Injury sustained during uncontrolled motor movements of generalised seizure activity; Brain damage from prolonged seizure activity (status epilepticus); Pain of seizures in somatosensory cortex	Physical side effects including polyuria (which may lead to incontinence), ataxia, pruritus, vomiting, diarrhoea; Increased risk of obesity resulting from polyphagia and lethargy; Increased risk of hepatotoxicity, pancreatitis, superficial necrolytic dermatitis and haematological abnormalities
Freedom to behave normally	Increased fear/anxiety, defensive aggression and abnormal perception; potential impact of behavioural abnormalities upon ability to interact normally with conspecifics and/or humans	Increased fear/anxiety, abnormal perception, abnormal reactivity attachment disorder, demented behaviour and apathetic behaviour; potential impact of behavioural abnormalities upon ability to interact normally with conspecifics and/or humans Side effects of lethargy and restlessness
Freedom from fear and distress	Increased fear/anxiety; Focal seizures with a psychic behavioural component in which consciousness is maintained; Anxiety during the prodromal and/or postictal phase; Repeated veterinary visits and hospitalisation including venepuncture and separation from owner	Increased fear/anxiety; Repeated veterinary visits including venepuncture for drug serum monitoring