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Packer, R. M. A. and Volk, H. A. (2015) 'Epilepsy beyond seizures: a review of the impact of epilepsy and its comorbidities on health-related quality of life in dogs', *Veterinary Record*, 177(12), 306-315.

The final version is available online via <http://dx.doi.org/10.1136/vr.103360>.

The full details of the published version of the article are as follows:

TITLE: Epilepsy beyond seizures: a review of the impact of epilepsy and its comorbidities on health-related quality of life in dogs

AUTHORS: Packer, R. M. A. and Volk, H. A.

JOURNAL TITLE: *Veterinary Record*

VOLUME/EDITION: 177/12

PUBLISHER: BMJ Publishing Group

PUBLICATION DATE: September 2015

DOI: 10.1136/vr.103360

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

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1 **Abstract**

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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

## 35 **Epilepsy and Quality of Life**

36

37 Idiopathic epilepsy (IE) is defined as epilepsy of predominantly genetic or presumed genetic origin and  
38 in which there are no gross neuroanatomical or neuropathological abnormalities nor other relevant  
39 underlying diseases causing seizure activity (Shorvon 2014). IE is the most common chronic  
40 neurological condition in domestic dogs, and although the true prevalence is unknown, it has been  
41 estimated to be 0.6% – 0.75% in the general canine population (Heske and others 2014; Kearsley-Fleet  
42 and others 2013). Age of onset is most commonly between 6 months and 6 years (Armaşu and others  
43 2014) and the condition is lifelong, in some cases requiring constant medication. Owners of dogs with  
44 IE have previously indicated that their dog’s quality of life (QoL) is of greatest importance to them  
45 above their seizure frequency (Chang and others 2006a); however, much of the research into canine IE  
46 to date has focussed on seizure frequency, and how to reduce it via anti-epileptic drug (AED) treatment  
47 e.g. (Dewey and others 2009; Dowling 1994; Pearce 1990) with little consideration of QoL until recent  
48 years, which has been heavily focussed on the owner’s QoL (Chang and others 2006b; Wessmann and  
49 others 2014). In humans, the impact of epilepsy upon QoL has been widely studied, exploring the  
50 holistic impact of epilepsy on physical health, but also the psychological health and cognitive  
51 capabilities of affected individuals (Elger and others 2004). Indeed, QoL scoring systems for people  
52 with epilepsy cover a broad range of topics. For example, the Quality of Life in Epilepsy (QOLIE-89)  
53 inventory (Devinsky and others 1995), summarised in Table 1, comprises diverse topics, some of  
54 relevance to canine IE (e.g. ‘medication effects), while others are human-centric (e.g.  
55 ‘work/driving/social). These impacts on QoL are not simply those that impact physical and mental  
56 directly, but also indirect effects that decrease opportunities to participate in activities that promote  
57 QoL.

58

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

68

69

70 **Are seizures *per se* a welfare problem?**

71

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

83

84 ***Prodrome***

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

95

96 ***Ictal phase***

97 Seizures can be generalised i.e. affecting both cerebral hemispheres or focal, where the abnormal  
98 electrical activity is limited to a specific area or areas of the brain. Focal seizures occur when abnormal  
99 electrical activity arises in a specific area of the brain, resulting in divergent clinical signs dependent on  
100 the function of the area involved. Focal seizures have been reported in dogs with IE (Berendt and others  
101 2009; Licht and others 2007; Patterson and others 2005; Patterson and others 2003), as well as  
102 symptomatic epilepsy. Focal seizures can occur with or without a reduction in consciousness. Prior to  
103 the revised classification, focal seizures were categorised in humans based on consciousness status, with  
104 consciousness maintained with *simple* focal seizures, and consciousness impaired in *complex* focal  
105 seizures (with the patient self-reporting their consciousness state post-seizure) (Berg and others 2010).  
106 In dogs, as vocal self-report is not possible, assessments of consciousness are dependent upon observers

107 assessments, which are often unreliable (Packer and others 2015a). Focal motor, sensory, autonomic,  
108 or psychic behavioural signs can occur (Berendt and others 2004). Focal motor seizures often occur as  
109 localised motor phenomena, such as rhythmic twitching of an extremity and abnormal rhythmic  
110 blinking, during which the dog is often presumed to be conscious. Focal seizures with a parasympathetic  
111 component may present as vomiting, hypersalivation, or dilation of the pupils, while focal seizures with  
112 a sensory or psychic component often manifest as behavioural changes, including anxious behaviours,  
113 restlessness, pacing, and seeking out their owner (Berendt and others 2004). The latter may have been  
114 described in humans as usually dominated by unpleasant or frightening sensations, including  
115 unexplained feelings of fear and apprehension (Ali and others 2012; Lennox and Lennox 1960). It is  
116 possible that in rare cases, certain types of seizure may be painful. Among human epilepsy patients with  
117 somatosensory seizures, whereby the seizure arises from sensory areas in the parietal lobe, pain was  
118 found in 23.6% of seizures (Mauguiere and Courjon 1978). In one study of 858 human epilepsy patients,  
119 2.8% (n=24) had experienced painful seizures (Young and Blume 1983), and in a further study, 1.4%  
120 (n=8) of 573 epilepsy patients (Siegel and others 1999). In these cases, involvement of the primary  
121 somatosensory cortex in the parietal lobe was again suspected rather than conscious awareness of  
122 painful involuntary motor movements during the seizure (Young and Blume 1983). Pain from  
123 headaches has also been associated with seizures as a preictal, ictal or postictal phenomenon, which is  
124 often neglected due to the dramatic neurological manifestations of the seizure (Dainese and others 2011)

125  
126 Focal seizures can develop into generalised seizures, by spreading through subcortical structures to  
127 involve the entire brain, termed ‘focal seizure with secondary generalisation’. The initial localisation of  
128 signs during the focal seizure (which may be very brief) is followed by a generalised seizure, with the  
129 focal seizure potentially missed by an observer. Generalised seizures are characterised by bilateral  
130 involvement (both sides of body) indicating that both cerebral hemispheres are involved. Generalised  
131 seizures are seen predominantly as tonic (stiffening), clonic (jerking), or tonic-clonic seizures; however,  
132 myoclonic seizures can occur (with sporadic jerks affecting both sides of the body) and non-convulsive  
133 generalised seizures, termed atonic seizures, or ‘drop attacks’(where a sudden loss of muscle tone  
134 causes collapse). During generalised seizures, it is widely accepted that total amnesia and loss of  
135 consciousness occur in humans (Goldensohn and others 1984). Although we cannot truly know the  
136 experience of a dog during a seizure, dogs are also thought to be unconscious and thus unaware of the  
137 event during a generalised seizure and thus protected from mental distress (except in myoclonic  
138 seizures). During this phase, dogs are at risk of physical injury due to uncontrolled motor movements,  
139 including uncontrolled chewing leading to tongue injuries.

140

141 *Status epilepticus*

142

143 During the ictal phase dogs are at risk of status epilepticus (SE), a prolonged seizure classed as a  
144 neurological emergency due to high mortality rates of up to 25% (Bateman and Parent 1998), and a  
145 significantly shorter survival time than dogs with IE that have not experienced SE (Saito and others  
146 2001). A poor outcome (death or euthanasia) is significantly associated with loss of seizure control after  
147 6 hours of hospitalisation (Bateman and Parent 1998). Definitions of SE vary, and include (i) a  
148 continuous epileptic seizure lasting longer than (i) five or (ii) ten minutes, (iii) up to 30 minutes or  
149 longer, or (iv) two seizures with incomplete recovery of consciousness interictally, with (i) and (iv)  
150 used most commonly in veterinary medicine (Bateman and Parent 1998; Patterson 2014; Saito and  
151 others 2001; Zimmermann and others 2009). In a hospital population of dogs with SE, over one third  
152 of dogs with SE (37.5%) had IE (Zimmermann and others 2009). SE occurs in two stage, the first  
153 characterised by generalised tonic-clonic seizures and an increase in autonomic activity, followed after  
154 approximately thirty minutes by hypotension, hypoglycaemia, hyperthermia, hypoxia, decreased  
155 cerebral blood flow, cerebral oedema and increased intracranial pressure. The sustained muscle  
156 contractions during SE, along with impaired ventilation can cause lactic acidosis, hyperkalaemia,  
157 hypercarbia and severe myoglobinuria, which may result in impaired renal function (Platt and  
158 McDonnell 2000). SE requires prompt treatment to control the seizure, with prolonged seizure activity  
159 leading to the development of circuits in the brain allowing the seizure to become self-sustaining  
160 (Manno 2003). In humans, SE has consistently been associated with long-term cognitive problems, and  
161 widespread neuronal cell loss in the brain (Wasterlain and others 1993). In rat models of epilepsy, SE  
162 in adult rats results in long-term disturbances in learning and memory, and increases susceptibility to  
163 further seizures (Cilio and others 2003). Longitudinal follow-up of canine SE cases are needed to  
164 provide insights into the physical and mental effects of SE in dogs, and whether they are physically  
165 and/or mentally compromised after these events.

166

### 167 **Seizure severity**

168

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

177

### 178 *Post ictal phase*

179

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

187

### 188 **Cluster seizures**

189

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

201

### 202 ***Inter-ictal phase***

203

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

212

### 213 **Neurobehavioural impact of epilepsy**

214

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



217 2004; Kobau and others 2006), with the most common disorders being depression and anxiety disorders,  
218 followed by psychoses and attention-deficit disorders (Boro and Haut 2003; Dunn and Austin 1999;  
219 LaFrance Jr. and others 2008; Prueter and Norra 2005; Seminario and others 2009). A bidirectional  
220 relationship between epilepsy and psychiatric disorders such as depression has been considered, with  
221 potentially common operant pathogenic mechanisms in the disorders that facilitate the occurrence of  
222 one in the presence of the other (Kanner 2003). This is supported by people with epilepsy being at  
223 greater risk of developing depressive disorders, but patients with depressive disorders also being at  
224 higher risk of epilepsy (Forsgren and Nystrom 1999). As such, epilepsy can be considered a more  
225 general brain disorder, which is not limited to seizure activity.

226

### 227 *Anxiety and depression*

228

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

237

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

252

### 253 *Psychoses*

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

265

### 266 *Attention-deficit/hyperactivity disorder*

267 Finally, attention-deficit/hyperactivity disorder (ADHD) is the fourth most common psychiatric co-  
268 morbidity of epilepsy, with around one third of epilepsy patients diagnosed with ADHD (Thome-Souza  
269 and others 2004). In a recent large community-based survey, ADHD symptoms were self-reported in  
270 nearly one of five adults with epilepsy, which was associated with increased psychosocial morbidity  
271 and lowered QoL (Ettinger and others 2015). Hallmarks of ADHD e.g. easy distraction and slow  
272 learning have also been demonstrated in a strain of epilepsy-model laboratory rats in various  
273 behavioural paradigms, with a disinhibited or impulsive behavioural style (Anisman and McIntyre  
274 2002). In a recent single breed study of Lagotto Romagnolo dogs with a history of Benign Familial  
275 Juvenile Epilepsy (BFJE), an epilepsy syndrome in which dogs often experience spontaneous seizure  
276 remission before 13 weeks of age, dogs with BFJE (n=25) showed significantly higher scores on the  
277 behavioural factors ‘Inattention’ and ‘Excitability/Impulsivity’ than did the control group of Lagotto  
278 Romagnolo dogs without BFJE (Jokinen and others 2015). Recent data indicates that the three most  
279 prominent behavioural domains of dogs with IE were excitability, chasability and attachment/attention  
280 seeking, mirroring behavioural traits of humans with epilepsy and ADHD in a variety of breeds (Packer  
281 and others, Submitted). In contrast, the ‘trainability’ behavioural domain was relatively low, with two  
282 thirds of owners reporting that their dog is ‘always’ easily distracted by interesting sights, sounds and  
283 smells. These signs may lead to punishment from owners to stop these undesirable behaviours, and have  
284 an impact on their cognitive abilities due to poor attention skills.

285

### 286 **Cognitive impact of epilepsy**

287

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

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

306

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

314

## 315 **Treatment**

316

317 Due to the threat of seizure activity to both quality and quantity of life, canine IE therapy is aimed at  
318 reducing seizure frequency. In veterinary medicine, a positive response to therapy is defined as a  $\geq 50\%$   
319 reduction in seizure frequency (Muñana 2013). This is the definition of AED efficacy in the majority  
320 of canine epilepsy studies (Dewey and others 2009; Dewey and others 2004; Muñana and others 2012a;  
321 Muñana and others 2012b; Platt and others 2006; Volk and others 2008; von Klopmann and others  
322 2007). This may be a problematic outcome measure as a  $\geq 50\%$  reduction in an initially high seizure  
323 frequency may still result in an unacceptably high seizure frequency outcome. This may not be a  
324 satisfactory outcome for the carers (the owners), with nearly one third considering only complete seizure  
325 freedom as an acceptable outcome (Wessmann and others 2012).

326

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

344

#### 345 **Effects of anti-epileptic drugs**

346

##### 347 *Known effects*

348 Side effects of AEDs have a high potential for reducing QoL of the patients they are administered to,  
349 as they must be taken continuously (on a daily basis) to be effective, and thus effects may be chronic.  
350 In people with epilepsy, increases in AED side effects are significantly negatively associated with self-  
351 reported QoL, more so than seizure frequency (Gilliam 2002). Although the range of AEDs used to  
352 treat IE in dogs differs from those used in humans, a variety of side effects have been reported that are  
353 considered to have a major contribution to the QoL of dogs with IE, including polyphagia, polydipsia,  
354 weight gain, polyuria, increased sleeping, ataxia, restlessness, pruritus, vomiting and diarrhoea  
355 (Wessmann and others 2014). The side effects of AEDs can predispose affected dogs to obesity, due to  
356 the combined effects of enhanced appetite (polyphagia) and reduced activity (sedation). Obesity may  
357 impede a dog's ability to behave normally and predispose them to obesity-related diseases (German  
358 2006). Obesity has also been found to have a significant negative impact upon QoL of dogs with other  
359 neurological disorders (Rutherford and others 2012)/ Behavioural side effects of AEDs may also occur,  
360 with increases in abnormal reactivity (anxiety with unpredicted movements or with sudden or loud  
361 noises), attachment disorder (signs of separation anxiety), demented behaviour (reduced ability to  
362 recognize family members or familiar people, aimless pacing or wandering), and apathetic behaviour  
363 (reduced interest in activities, agitation if not allowed to sleep) observed in dogs with IE receiving

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

367

368 In many cases, side effects are present at their greatest intensity in the first 2-4 weeks of treatment, and  
369 subside after this period once serum levels reach a steady state (Boothe and others 2012; Podell 1998;  
370 Schwartz-Porsche and others 1985). In some dogs, side effects are permanent (Dewey 2006), with  
371 chronic effects observed particularly in dogs receiving polytherapy (more than one AED) rather than  
372 monotherapy. Dogs receiving three AEDs have been found to have a lower QoL than those on less than  
373 3 AEDs (Wessmann and others Submitted). Accordingly, for dogs with a low seizure frequency, the  
374 impact of AED side effects on QoL may be greater than the seizures themselves, and thus careful  
375 consideration must be given over the necessity of medication.

376

### 377 *Complications*

378 In addition to these known effects that can be explained by the known pharmacological properties of  
379 the drug (Zaccara and others 2007), reactions that are not dose related, are independent of the known  
380 mechanism of action of the drug can occur which may pose a threat to life, and require discontinuation  
381 of treatment (Zaccara and others 2007). Phenobarbital (PB) also has been associated with idiosyncratic  
382 adverse drug reactions, including haematological abnormalities (PBIHA, ‘phenobarbital induced  
383 haematological abnormalities’) such as neutropenia, anaemia and thrombocytopenia (Behne and  
384 Engelhardt 2010; Jacobs and others 1998; Khoutorsky and Bruchim 2008; Thrift and others 2010;  
385 Vargo and others 2007; Von Klopmann and others 2006; Weiss 2005; Weiss and Smith 2002). The  
386 prevalence of these abnormalities is variable, with estimates of 4.2%-22% (Bersan and others 2014;  
387 Haböck and Pakozdy 2012). Although up to a fifth of dogs may be affected, the effects of PBIHA on  
388 the animal may be minimal; for example, in a case series of 37 PB treated dogs, 8 dogs showed PBIHA  
389 (22%), but only 2 of these (5%) were clinically significant (Haböck and Pakozdy 2012). As such,  
390 PBIHA may only be welfare relevant in the most severely affected cases, where PB should be  
391 discontinued and another AED added (Bersan and others 2014).

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

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

408

### 409 **Ethical considerations**

410

411 The ethics of epilepsy treatment is complex, with a fine balance of the potential benefits of AEDs versus  
412 potential harms. This balance varies between dogs, and over an individual's disease course. Factors that  
413 may influence this balance may include the initial seizure frequency, response to AEDs, and the number  
414 of AEDs required to provide adequate seizure control. In addition to the side effects described above,  
415 there may be iatrogenic consequences of treating epilepsy, that is, unintentional adverse effects that  
416 may occur as a by-product of diagnosis and treatment, even when used appropriately (Yeates 2012). As  
417 IE is a diagnosis of exclusion, a variety of diagnostic tests may be carried out including blood tests  
418 requiring venipuncture that may be uncomfortable and distressing to the individual, as well as invasive  
419 diagnostics requiring general anaesthesia (cerebrospinal fluid analysis and MRI of the brain) that carry  
420 a small risk of death (Brodbelt 2009). Hospitalisation to carry out these tests may be aversive to the  
421 dog, and has been associated with an increase heart rate (Väisänen and others 2005) and cortisol levels  
422 (Van Vonderen and others 1998). As dogs with epilepsy may show increases in fear/anxiety,  
423 hospitalisation may be particularly stressful, and restraint and punishment of these dogs should be  
424 avoided as they may increase fear-related behaviours (Herron and others 2009; Rosado and others  
425 2009). Once AED treatment has been initiated, regular monitoring of serum drug concentrations (PB  
426 and KBr), and blood tests (haematology/serum biochemistry) are required, with periodic checks every  
427 3-6 months, dependent upon AED and the dog's response to it. These visits may be aversive to the dog,  
428 with veterinary practice visits increasing heart rate and blood pressure (Kallet and others 1997), cortisol  
429 (Van Vonderen and others 1998), and fear-related behaviours (Döring and others 2009). As epilepsy is  
430 a chronic condition, efforts should be made to ensure these visits are positive, as dogs with only positive  
431 previous experiences in veterinary surgeries were significantly less 'fearful' than dogs that had a  
432 previous negative experience (Döring and others 2009).

433

### 434 **Quantity of life**

435

436 Canine epilepsy has the potential to substantially reduce quantity of life. The median longevity of  
437 102,609 owned dogs attending first opinion veterinary practices was 12.0 years (IQR 8.9–14.2) (O’Neill  
438 and others 2013). In contrast, the median age at death of dogs with epilepsy was 7.0 years in two separate  
439 studies (Berendt and others 2007; Proschowsky and others 2003). In single breed studies, the life  
440 expectancy for Irish Wolfhounds is shortened by almost 2 years in epileptic dogs compared with  
441 seizure-free relatives (Casal and others 2006); however, the lifespan of Belgian Shepherds with epilepsy  
442 was not significantly shortened, despite being the predominant cause of death (Gulløv and others 2012).  
443 Within a mixed population of dogs with epilepsy, those that died or were euthanased because of epilepsy  
444 had a shorter lifespan than those euthanased due to other causes (4 years vs. 12 years) (Berendt and  
445 others 2007). After diagnosis, the median number of years that a dog lived with epilepsy was 2.3 years  
446 (Berendt and others 2007). That study was in both pure and mixed bred dogs, and in a single breed  
447 population of Border Collies, similar results were observed, with a median survival time after first  
448 seizure of 2.07 years (Hülsmeier and others 2010). The majority of deaths of dogs with epilepsy are  
449 epilepsy related, with more than 60% of Irish Wolfhounds (Casal and others 2006) and 70% of Belgian  
450 Shepherds with epilepsy dying of epilepsy-related reasons (Gulløv and others 2012).

451

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

459

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

468

## 469 **Conclusions**

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

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

482



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

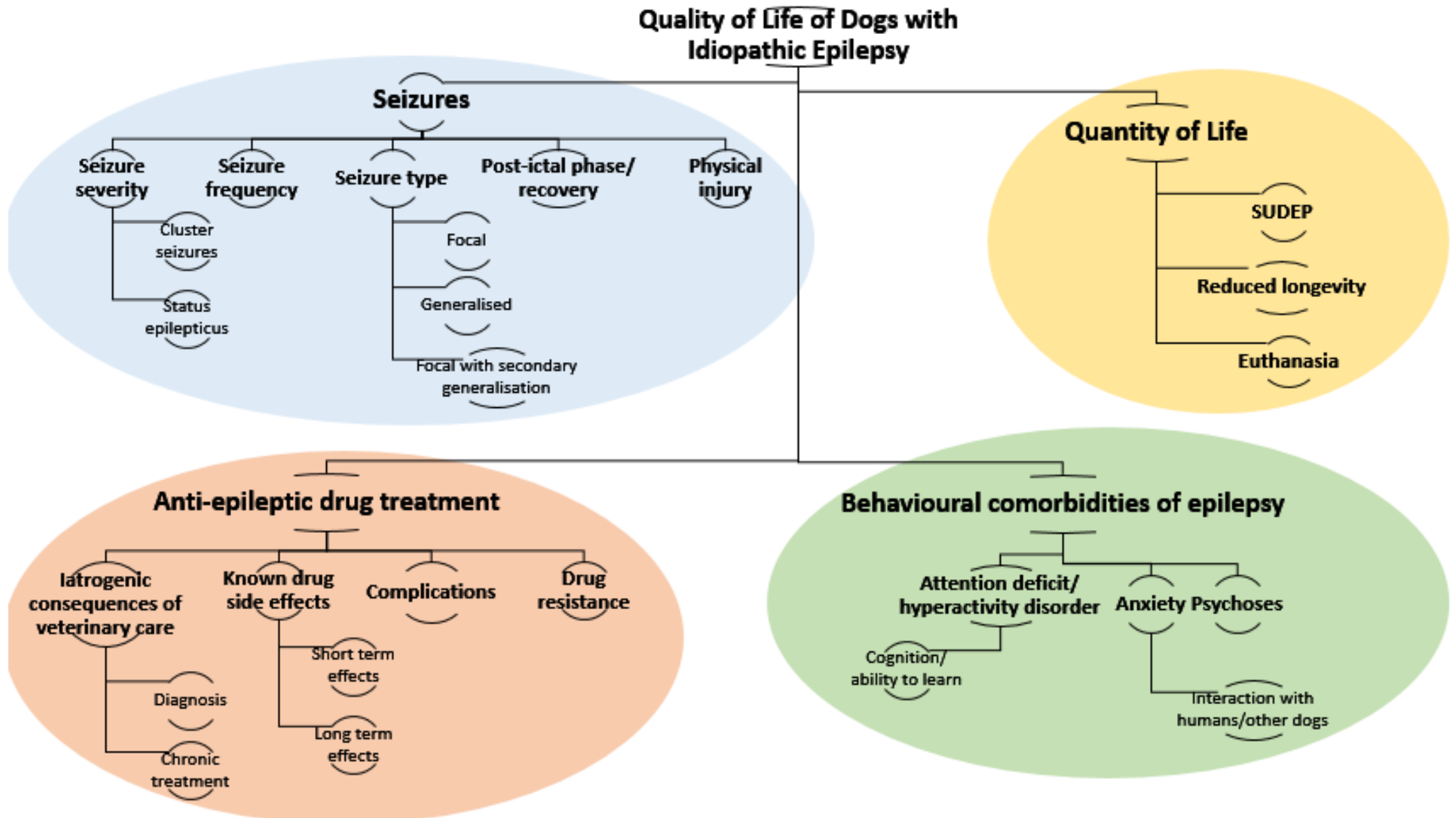


Table 1. Scales and items that compromise the Quality of Life in Epilepsy (QOLIE-89) inventory, an instrument to measure health-related quality of life (HRQOL) in people with epilepsy

<b>Scale</b>	<b>Item</b>	<b>General description</b>
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)

<b>Five Freedoms Framework</b>	<b>Potential impact of epilepsy upon freedom</b>	<b>Potential impact of anti-epileptic drugs upon freedom</b>
<b>Freedom from hunger and thirst</b>	Postictal hunger	Polyphagia, polydipsia due to antiepileptic drug treatment such as phenobarbital and/or potassium bromide treatment
<b>Freedom from discomfort</b>	Venipuncture for blood tests required for diagnosis of IE	Venipuncture for blood serum monitoring
<b>Freedom from pain, injury and disease</b>	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
<b>Freedom to behave normally</b>	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
<b>Freedom from fear and distress</b>	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