Review

A review of treatment options for behavioural manifestations of clinical anxiety as a comorbidity in dogs with idiopathic epilepsy.

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Abstract

Psychiatric comorbidities affect a large percentage of people with epilepsy and have a detrimental impact on their quality of life. Recently, behavioural comorbidities, with similar characteristics to human psychiatric diseases, have been identified in dogs with idiopathic epilepsy. In particular, behaviours motivated by the fear-anxiety emotional system have been found to be associated with the occurrence of idiopathic epilepsy in both dogs receiving anti-epileptic drugs, and drug-naïve dogs. There has been little research into the relationship between epilepsy and behavioural signs, and even less into potential treatment protocols. The following article will review available literature from human medicine to describe the current state of knowledge about the bi-directional relationship between anxiety and epilepsy, draw parallels from reported anxiogenic and anxiolytic properties of anti-epileptic drugs and attempt to provide pharmaceutical and behavioural guidance for veterinary patients with epilepsy and comorbid anxiety.

Keywords: Idiopathic epilepsy; Psychiatric comorbidity; Canine behaviour; Anxiety; Dog

Introduction

The existence of comorbid psychiatric disorders with epilepsy is long-established in human medicine and prevalence is much higher for epilepsy than other chronic medical conditions or healthy controls (Davies et al., 2003). The most common psychiatric comorbidities for epilepsy patients include depression, cognitive dysfunction and anxiety disorder with reported prevalence rates of 36.5% (Ettinger et al., 2015), 26.4% (Berg et al., 2008) and 22.8% (Tellez-Zenteno et al., 2007), respectively. Of course, prevalence alone does not make psychiatric comorbidities important, and the effect on a patient's quality of life (QoL) should also be taken into account (Brandt and Mula, 2016).

In the veterinary world, idiopathic epilepsy (IE) is a common neurological condition (Heske et al., 2014; Kearsley-Fleet et al., 2013). Some breeds show high disease prevalence or increased odds of having IE such as Belgian Shepherds, Border Terriers, Labradors and German Shepherd Dogs (Berendt et al., 2015; Hülsmeyer et al., 2015; Kearsley-Fleet et al., 2013). Despite epilepsy being a common brain disease in dogs, few studies to date have investigated the presence of neurobehavioural comorbidities in canine epilepsy. Shihab et al. (2011) and Jokinen et al. (2015) have reported behavioural changes in dogs following onset of IE and similarities to the comorbidities experienced by people. The recent consensus statements published by the International Veterinary Epilepsy Task Force (IVETF) agree that neurobehavioural changes should be monitored in future treatment trials (Potschka et al., 2015). As voiced by Packer and Volk (2015), QoL for epileptic dogs is of paramount importance, especially to owners (Chang et al., 2006; Packer et al., 2016), and psychiatric comorbidities will contribute to this. This article will address anxiety disorder comorbid with epilepsy (ADCE), will focus on the evidence reported in people and draw parallels to veterinary

medicine to raise awareness of this behavioural comorbidity in dogs and how it may be improved to promote canine QoL.

Anxiety disorder comorbid to epilepsy in people

Anxiety can be a normal, transient mental (emotional) state in specific situations, but abnormal anxiety, which is not justified by the context or results in behavioural responses which are out of proportion in intensity or duration can occur[2]. Anxiety disorder can be related to concurrent physical health issues and this would lead to a separate diagnosis from other anxiety disorders (American Psychiatric Association, 2015). In people with epilepsy, comorbid anxiety disorders can manifest in a multitude of ways (Beyenburg et al., 2005) and occur twice as often in people with epilepsy than those without (Tellez-Zenteno et al., 2007). Comorbid anxiety disorders can have a negative impact on health-related QoL, which has been found to be more significant than both seizure chronicity and severity (Johnson et al., 2004). Considering their high prevalence, these anxiety disorders are chronically under-diagnosed and under-treated in people (Kimiskidis and Valeta, 2012; Thomé-Souza et al., 2007). Under-diagnosis of anxiety disorders in veterinary patients has been extensively described (Overall et al., 2016). Misinterpretation of normal and pathological anxiety (Tami and Gallagher, 2009) and lack of recognition of mild clinical signs by owners (Mariti et al., 2012) are likely to contribute to the under reporting of comorbid anxiety disorders in veterinary species.

What links anxiety disorders and epilepsy?

It is thought that shared anatomy and physiology through the amygdala, hippocampus and neuronal pathways such as the serotonin, glutamate and gamma-aminobutyric acid pathways explain why epilepsy and anxiety disorders are linked, and support a bi-directional

[2] American Psychiatric Association, 2017. What are anxiety disorders? https://www.psychiatry.org/patients-families/anxiety-disorders/what-are-anxiety-disorders (accessed 29 July 2017).

relationship (Loss et al., 2012; Brandt and Mula, 2016; Kwon and Park, 2014; Mula, 2013). Evidence of a bi-directional relationship has been shown in genetic rat models of epilepsy; not only were those rats more anxious than controls, but anxiety began before the onset of epilepsy, which disregards psychosomatic, psychosocial and neurodegenerative causes for anxiety following onset of epilepsy (Jones et al., 2008). The existence of a bi-directional relationship is corroborated by two human studies where a significantly increased incidence rate ratio of anxiety disorders was found two years before and three years after initial epilepsy diagnosis compared to controls (Hesdorffer et al., 2012) and increased odds of seizure development was found pre- and post-anxiety diagnosis (Adelöw et al., 2012).

Anxiety disorders as a comorbidity in dogs

Anxiety disorders are common in veterinary species, regularly leading to behavioural responses which are reported as being problematic (Dreschel, 2010). Unfortunately, as Roshier and McBride (2013) explains, there is poor and incomplete recognition of animal behaviour within the veterinary profession, and, whilst research documenting specific psychological disorders in dogs is evident (Cannas et al., 2010; Palestrini et al., 2010), little in known in relation to epileptic patients. Shihab et al. (2011) found significantly increased anxiety in dogs following IE onset, assessed using the Canine Behavioural Assessment and Research Questionnaire. Fear and anxiety levels were increased in both drug-naïve and those receiving various antiepileptic drugs (AEDs), suggesting that anxiety could either be an adverse effect of AEDs alone, or a combination of both adverse effect and comorbidity. De Risio et al., (2015) reported behavioural changes such as anxiety in Italian Spinone's, following onset of IE but prior to commencing AED therapy. The effect of anxiety disorders on the health-related QoL of dogs should not be underestimated; chronic anxiety disorders can have a significant

impact, causing chronic fatigue, contributing to a range of physical health concerns and other behaviours (Bowen and Heath, 2005).

Anxiogenic/Anxiolytic effects of AEDs

Anxiogenic and anxiolytic effects of AEDs are well described in human medicine. Unfortunately, studies are small with high variability in method and population and, conflicting results are common due to lack of blinded and randomized studies. Veterinary research currently only addresses owner-reported increases in anxiety as an adverse effect, making the true anxiolytic effect of AEDs in dogs challenging to conclude. Owner-reported adverse effects have limitations including likelihood of subjectivity and poor owner perception of anxiety.

In human medicine, phenobarbital and potassium bromide have fallen out of favour, and so little evidence of psychiatric merit or disadvantage exists. Phenobarbital has a complex mechanism of action (Mula et al., 2007) and, despite historical use as an anxiolytic (Yasiry and Shorvon, 2012), its use has been largely superseded by newer generations of medication and it's lack of anxiolytic properties has become apparent. Primidone, which is rapidly metabolized to phenobarbital (Podell et al., 2016), is thought to increase the likelihood of anxiety disorders in epileptic patients; Lopez-Gomez and Espinola (2008) found that use of primidone predicted anxiety disorders in a cross-sectional study of 196 patients with epilepsy, though it was impossible to separate this from other predictive factors and analyse the effect of AEDs in this study. Levetiracetam could be considered anxiolytic due its mild GABAergic action (Landmark, 2008; Muralidharan and Bhagwagar, 2006) and evidence from rat models (Gower et al., 2003). Hagemann et al. (2013) found that add-on and monotherapy levetiracetam decreased seizure frequency and improved QoL, anxiety and depression scores

in 65 of 140 patients. However, a systematic review by Cramer et al. (2003) found that epilepsy patients treated with levetiracetam, were more likely to show affective anxiety symptoms than those taking a placebo, but rates were lower than rates reported for other AEDs used in people where sufficient data exists such as lamotrigine, vigabatrin and zonisamide.

Pregabalin has been investigated more than other AEDs for anxiolytic potential and is licensed in treatment for generalised anxiety disorder in people (Brandt et al., 2013; Mula et al., 2007). Although not licensed as a treatment for ADCE (Brandt and Mula, 2016), Mula (2013) has suggested that it should be considered the first-line AED in such patients. Brandt et al. (2013) found that pregabalin reduced seizure frequency and significantly reduced anxiety scores in people with ADCE. Gabapentin is also considered an effective anxiolytic as it enhances GABAergic neurotransmission (Kwon and Park, 2014; Landmark, 2008; Weintraub et al., 2007) and has shown no significant anxiogenesis between control or treated adults as an add-on AED (Harden et al., 1999). Zonisamide is largely anxiolytic and has been shown to significantly decrease anxiety in historically non-responsive adults with epilepsy (Kinrys et al., 2007) and in newly-diagnosed children with epilepsy (Eun et al., 2011). However, a 3% increase in anxiety was seen in treated patients compared to controls in a double-blinded add-on trial (Cramer et al., 2003).

Topiramate has a complex mechanism of action (Howard et al., 2011; Perucca and Mula, 2013). In the literature, Mula and Trimble (2003) reported that 2.55% of epileptic patients treated with topiramate developed anxiety disorders, though overall adverse effect rate was higher (35.90%). Similarly, Marson et al. (2007) reported a 3.97% incidence of anxiety as an adverse effect in 378 patients receiving topiramate, amongst an overall adverse effect incidence of >50%. Felbamate is thought to be an anxiogenic (Ketter et al., 1996; Kimiskidis

158 and Valeta, 2012; Kwon and Park, 2014) due to its antiglutamatergic action (Beyenburg et al.,
159 2005; Vazquez and Devinsky, 2003). A small, randomized, placebo controlled study by
160 Theodore et al. (1995) found that six of 13 patients receiving felbamate monotherapy dropped
161 out due to intolerable adverse effects including anxiety disorder.
162
163 In veterinary medicine, a systematic review and meta-analysis (Charalambous et al.,
164 2016) found no reports of increased anxiety in dogs receiving phenobarbital, potassium
165 bromide, levetiracetam, zonisamide and felbamate, though the evidence was considered weak
166 for the latter. The authors reported that anxiety was an adverse effect of primidone, reported
167 in just under 10% of studies (Charalambous et al., 2016). There was not enough evidence into
168 the efficacy of pregabalin, gabapentin or topiramate as AEDs to assess safety profile or adverse
169 effects, additionally there is insufficient evidence to suggest that pregabalin works as an
170 effective AED in veterinary patients (Bhatti et al., 2015). A consensus statement by The
171 American College of Veterinary Internal Medicine (ACVIM) (Podell et al., 2016) listed hyper-
172 excitability and restlessness as predictable and dose-dependent adverse effects of phenobarbital
173 treatment; both behaviours could be interpreted by owners as a clinical sign of anxiety or have
174 other causes (Bowen and Heath, 2005). Podell et al. (2016) concurred with Charalambous et
175 al. (2016) in reporting no anxiety-related adverse effects in dogs taking potassium bromide
176 alone or in addition to phenobarbital. Unfortunately, both the systematic review and consensus
177 statement referenced here are subject to ascertainment bias. Many of the adverse effects
178 reported have not been purposefully screened for, it is unknown whom they were identified by
179 and what diagnostic criteria or tool was used to come upon the report of “anxiety”.
180 Additionally, carefully agreed and accurate terminology is desperately needed for canine
181 anxiety diagnosis, especially in instances of comorbidity (Overall, 2005). This is particularly

important in comorbid disorders, where occurrence of clinical signs can be separate from signs of the comorbid disorder, or altered by it (Overall et al., 2001).

Imepitoin is licensed solely for dogs, first being developed for humans due to its good anticonvulsant and anti-anxiety properties in rodent models (Rundfeldt and Löscher, 2014). The ACVIM consensus statement reported no anxiety as an adverse effect of imepitoin (Podell et al., 2016), however, Charalambous et al. (2016) states that around 10% of studies reported dose-dependent and reversible anxiety when receiving imepitoin. Rundfeldt et al. (2015) found central nervous system effects were among the most common in dogs treated with low (1mg/kg) and high-dose (30mg/kg) imepitoin, shown in 52% and 72% of dogs, respectively. Rundfeldt et al. (2015) reported significantly increased adverse effects and adverse reactions in the high-dose group. Central nervous system adverse effects were not individually specified but included ataxia, restlessness, hyperactivity and disorientation. Packer et al. (2017) found no change in fear and anxiety-related behavioural scores in 85 dogs before or during treatment for IE with imepitoin, but this could be due to the retrospective nature of the study design or be caused by differences in effect of the drug upon the epileptic brain and the 'normal' brain, particularly for drug-resistant dogs. The use of imepitoin in canine behavioural medicine for the management of sound related fears has been reported (McPeake and Mills, 2017). Anecdotally, there is one report of imepitoin used to treat anxiety in a cat (Dube, 2015).

In veterinary medicine polypharmacy is common in attempts at seizure control, let alone in the considerations of other problems such as anxiety. Research into the likelihood of polypharmacy-induced anxiogenesis in people is mixed; Ettinger et al. (1998) and IJff et al. (2015) found no significant difference in anxiety or increased adverse effects in polypharmacy patients compared to monotherapy human patients. However, others (Adewuya and Ola, 2005;

Oguz et al., 2002; Williams et al., 2003) found that polypharmacy was a significant risk factor associated with increased anxiety disorder in children and adolescent patients. Whilst the link between increased anxiety disorders and polypharmacy remains questionable we must also consider the possibility that a patient with a more drug-resistant phenotype might have other abnormalities in the brain which predispose them to more anxiety than drug-responsive phenotypes. Alternatively, multiple medications might not be the direct cause of increased levels of anxiety, but that having a more intractable epilepsy phenotype necessitating polypharmacy, might make a patient more likely to have detrimental levels of anxiety (Ekinci et al., 2009).

It is important to remember that, for dogs, only phenobarbital and imepitoin are licensed for first-line treatment in the European Union; all other drugs are either only licensed as add-on adjunctive therapies or unlicensed so only approved for use following failure of approved drugs, those include; levetiracetam, zonisamide, felbemate, topiramate, gabapentin and pregabalin (Bhatti et al., 2015).

Pharmacological treatment of anxiety in epileptic patients

In 2011, the International League Against Epilepsy (ILAE) produced consensus statements to set out unequivocal guidelines on the treatment of neuropsychiatric conditions associated with epilepsy in people (Kerr et al., 2011). The ILAE consider selective serotonin reuptake inhibitors (SSRIs) to be the first-line drug for the treatment of anxiety disorders, and indeed depression, in people with epilepsy due to their low adverse effect profile and their lack of effect on seizure threshold. Beyenburg et al. (2005) found SSRIs to carry a 0.1% risk of seizures so they are considered ‘low risk’. A Cochrane Library systematic review (Maguire et al., 2015) concluded that the evidence for use of any antidepressant in the presence of epilepsy

was low but that the few studies available indicated that SSRIs do not significantly increase seizure frequency. Thomé-Souza et al. (2007) followed 36 children and adolescents with epilepsy and depression for at least three months prior to and until one year after starting fluoxetine or sertraline treatment. Two children had increased seizure frequency, one of which was resolved by adjusting the AED and the other withdrew from the study. Both SSRIs were found to be effective for the comorbid depression, with few adverse effects. A similar study (Kanner et al., 2000) found that in 100 adult patients with epilepsy and depression prescribed sertraline, only six had an increase in seizure frequency, which was controlled by AED dosage adjustments in five patients. Fifty-four percent of participants' depression responded to the SSRI, which the authors explained is in line with the general population without epilepsy. Most research into efficacy of SSRIs and effect on seizure frequency in people with epilepsy are in relation to depression, rather than anxiety. In a population of people with epilepsy and comorbid depression and/or anxiety disorder, Ribot et al. (2017) has shown has reported a clinical response to SSRIs (reduction in depression and/or anxiety) in more than 70% of their patient cohort and SSRIs did not seem to affect their seizure frequency, actually reducing it by >50% in 48% of patients.

Interestingly, two literature reviews (Cardamone et al., 2013; Igelström and Heyward, 2012) found that the majority of research into the effect of SSRIs on seizure frequency on animal models of epilepsy found them to be either anticonvulsant or to exert no effect at all on seizure frequency. In rat and mouse models of epilepsy, fluoxetine and its active metabolite norfluoxetine have been shown to reduce seizure frequency or reduce seizure threshold when compared to positive and negative controls, in stressed and non-stressed conditions (Hernandez et al., 2002; Kecskeméti et al., 2005; Peričić et al., 2005; Richman and Heinrichs, 2007). Similar research into SSRI usage to treat dogs with ADCE is lacking, however, it can be

assumed that they are safe and only anxiolytic efficacy must be proven in future. SSRIs have been used in healthy dogs with anxiety problems in combination with behaviour modification plans with good effect (Simpson et al., 2007; Ibáñez and Anzola, 2009; Karagiannis et al., 2015; Pineda et al., 2014), which can also be said of clomipramine (King et al., 2000; Crowell-Davis et al., 2003).

The ILAE also deemed serotonin and norepinephrine reuptake inhibitors, benzodiazepines, azapirones, antihistamines and pregabalin safe for treatment of people with ADCE (Kwon and Park, 2014). Despite anecdotal, off-license use of fluoxetine in veterinary epilepsy patients with anxious behaviour, it should be noted that the ILAE consensus statement advises against fluoxetine and fluvoxamine due to possible cytochrome inhibition, which affects the pharmacokinetics of drug metabolism, particularly of phenobarbital, phenytoin and St. John's Wort (Bhatti et al., 2015; Hemeryck and Belpaire, 2002; Kerr et al., 2011; Zanger and Schwab, 2013), leading them to recommend sertraline as a safer substitute. There are a number of references in behavioural medicine text books on sertraline's use in dogs with anxiety (Bowen and Heath, 2005; Horwitz and Mills, 2010; Overall, 2013).

One veterinary study has looked at the owner-perceived effect of the AED imepitoin on anxiety in dogs with IE but reported no difference between pre- and post-treatment levels (Packer et al., 2017). Regardless of the negative results, this study contributes an important starting point towards the development of potential treatments for dogs with ADCE. Dogs are considered a naturally-occurring model of human epilepsy and so pharmacokinetics and neuronal pathways could, believably, be quite similar (Berendt et al., 2004; Chandler, 2006; Licht et al., 2002), allowing application of human research and medication recommendations within the confines of prescribing laws. Assuming, based on ILAE guidelines as mentioned

above, that SSRIs should be the first choice in dogs with ADCE to treat the anxiety disorder alongside their chosen AEDs, then fluoxetine should be considered first. Frustratingly, given the evidence described here, it is currently contraindicated in animals with a history of seizures (BSAVA, 2014), though this is not consistent worldwide and some merely advise caution (Plumb, 2008). Additional options for the safe treatment of dogs with ADCE; selegiline, a monoamine oxidase inhibitor, and clomipramine hydrochloride, a tricyclic antidepressant (TCA) are both suboptimal choices, as will be explained.

In human medicine, TCAs have been shown to have a significantly higher risk of seizures than SSRIs; 1% for clomipramine compared to 0.1% for SSRIs (Ekinci et al., 2009; Kanner, 2016), but evidence of this in animals receiving therapeutic doses is unestablished (Petersen et al., 1985). In veterinary medicine in the UK, clomipramine is licensed for use in dogs with separation-related behaviours with proven efficacy (King et al., 2000; Landsberg, 2001; Overall and Dunham, 2002; Seksel and Lindeman, 2001). Despite this, no research exists that investigates the effect of clomipramine on dogs with ADCE, though prescribing instructions note that care is warranted in epileptic dogs as plasma levels of some AEDs such as phenytoin and carbamazepine may be increased (BSAVA, 2014; Landsberg, 2001). Selegiline is licensed to treat emotional behavioural disorders in dogs in Europe (BSAVA, 2014) because it has been suggested to reduce anxiety in some cases, although there is limited evidence for efficacy. However, there are caveats about using this medication in households with a history of inter-dog tension, due to the potential effect of increased confidence on the relationship between them (Bowen and Heath, 2005). Some authors have suggested caution in households where there is a history of aggression, which could be of concern in epileptic dogs that display aggressive behaviour during the post-ictal stage. Shihab et al. (2011) has shown that drug naïve dogs with IE have increased aggression compared to before the onset of disease,

so risk-taking with drugs that could potentially elevate this behaviour should be avoided. Many benzodiazepines can be used off-license in dogs with anxiety disorders and are generally not contraindicated for use in dogs with seizures or epilepsy and, of course, some of these drugs are used to halt seizure activity in an emergency situation (BSAVA, 2014). However, long-term treatment with these drugs is contraindicated due to their interference with memory and learning; additionally, there are suggestions in the veterinary literature that benzodiazepines can cause disinhibition, where a dog could become more likely to respond aggressively to a situation (BSAVA, 2014). However, this is not consistent with some reports in the human psychiatric literature for example a retrospective review of a heterogeneous population of 323 psychiatric inpatients (Rothschild et al., 2000) suggested that disinhibition associated with benzodiazepine use may not be an clinically relevant problem. Extrapolation of information from human literature should always be considered with caution but this does highlight the need for more research into the potential behavioural side effects of medications in non-human animals.

Given that the necessary drugs are currently described as contraindicated for epilepsy, prescription of any drug would be 'off data-sheet'. An SSRI should be trialled initially. In epileptic patients, human medicine recommends a dose 6-8 times smaller than the usual starting dose that is titrated up to effect (Kwon and Park, 2014), but there are no such recommendations for dogs. There is more evidence for efficacy of fluoxetine for treatment of anxiety disorder in dogs (Ibáñez and Anzola, 2009; Landsberg et al., 2008) and therefore, despite the contraindications this should be the first drug of choice. Based on the guidelines described above, fluoxetine can be started at 0.125-0.167mg/kg/day in dogs with ADCE, based on the dosing recommendation of 1-2mg/kg/day in BSAVA (2014). Efficacy of SSRIs may not become apparent for 3-6 weeks following commencement of treatment (Brandt and Mula,

2016); in human medicine doses are reviewed every 3-4 weeks and changed as necessary[3]. Between psychoactive drugs of different class (e.g. SSRI to TCA), gradual dose reduction and a drug-free period of at least a week, sometimes longer, is recommended to avoid withdrawal or rebound phenomena (Cerovecki et al., 2013). If the dog is affected by separation anxiety, in particular, then a clinician might consider starting with clomipramine in the same manner, whilst being cautious of the possibility for increasing seizure activity and monitoring pharmacointeractions. Local drug prescribing laws and regulations will need to be considered.

As reported in human medicine papers described above, it may be that alterations to AED doses are required should seizure activity increase with any of these medications. It may be that having IE causes the brain to respond differently to a drug when compared to a dog without a global brain disorder and, therefore, whilst a drug has anxiolytic properties these may not apply to a dog with ADCE.

Alternative treatment of anxiety in epileptic patients

Ketogenic diets are recommended for people with drug-resistant epilepsy and they have been shown to reduce seizure frequency (Neal et al., 2008). Ketogenic diets come in many forms, classically in a 4:1 or 3:1 ratio of fat to minimal protein and carbohydrate (Neal et al., 2008). A modified version uses mainly medium-chain triglycerides as a fat source as they yield more ketones and are absorbed and metabolised more efficiently (Lambrechts et al., 2017; Neal et al., 2009) whilst allowing safer levels of protein and carbohydrate to be eaten (Neal et al., 2009). The aim of a ketogenic diet is to induce a metabolic response similar to that seen after

[3] NICE, 2017. British National Formulary: Fluoxetine https://www.evidence.nhs.uk/formulary/bnf/current/4-central-nervous-system/43-antidepressant-drugs/433-selective-serotonin-re-uptake-inhibitors/fluoxetine (accessed 15 February 2017)

354 starvation, which causes the brain to use ketone bodies, ß-hydroxybutyrate and acetoacetate,
355 as its primary energy source due to an inadequate supply of glucose (Neal et al., 2009).
356 However, the full neurological benefit and mechanism remains unknown; studies in people
357 have reported reduction in ADHD-like behaviour (Pulsifer et al., 2001) and the offspring of
358 rats fed a ketogenic diet whilst pregnant have been found to be less susceptible to anxiety and
359 depression postnatally, compared to controls (Sussman et al., 2015). A Cochrane Review
360 (Levy et al., 2012) concluded that a ketogenic diet could improve seizure control but was
361 generally intolerable, though evidence levels were low and largely in children. Veterinary
362 trials with ketogenic or medium-chain triglyceride diets have largely focused on their potential
363 to reduce seizure frequency, and have had mixed results (Law et al., 2015; Pan et al., 2010;
364 Patterson et al., 2005). A randomized, double-blinded, placebo-controlled, crossover trial
365 (Packer et al., 2016) found reduced scores for stranger-directed fear in dogs receiving a diet
366 shown to be ketogenic despite low levels of medium-chain triglycerides, suggesting a positive
367 effect on anxiety levels. A strict, pre-packaged ketogenic diet is easier to enforce in a dog than
368 in a child or adult without impacting on QoL and so further research into the anxiolytic, and
369 anticonvulsant, effects of ketogenic diets in dogs with ADCE is warranted.
370
371 Additionally, alternative therapies have been used to reduce seizure frequency in people
372 such as cognitive behavioural therapy and bright light therapy (Brandt and Mula, 2016),
373 however, evidence into their use as an anxiolytic is limited. Cognitive behavioural therapy was
374 shown to significantly lower anxiety scores in a small pilot study (Macrodimitris et al., 2011)
375 and bright light therapy showed significant difference between treatment and control groups,
376 however, the placebo effect could not be accounted for (Baxendale et al., 2013). Herbal therapy
377 such as betony and valerian have been used by people with epilepsy for their anxiolytic
378 qualities, however, evidence into their efficacy is poor with no evidence specifically in patients

with epilepsy (Pearl et al., 2011). Owners should take care with complementary therapies as there are risks that they interact with AEDs and can have toxic adverse effects.

There is weak evidence of anxiolytic effect of supplements marketed for dogs. Kato et al. (2012) found a significantly smaller rise in urine cortisol to creatinine ratio following nail clipping in dogs who were fed a diet supplemented with alpha-casozepine and L-tryptophan compared to the same dogs when fed a control diet, whilst Bosch et al. (2009) found no change in anxiety-related behaviour in dogs fed a tryptophan supplement compared to controls. Palestrini et al, (2010) demonstrated a significant decrease in cortisol levels in anxious dogs that received alpha-casozepine as a dietary supplement, though behavioural changes were not so clear. Cannas et al. (2013) found a significant decrease in anxiety scores in dogs fed a diet containing Valeriana officinalis, Melissa officinalis and tryptophan compared to a control group. Beata et al. (2007) found no statistical difference in anxiety scores and successful treatment of dogs receiving alpha-casozepine compared to positive controls receiving selegiline hydrochloride. Dog appeasing pheromone has shown mixed efficacy in controlling anxiety (Grigg and Piehler, 2015; Landsberg et al., 2015) and a systematic review found insufficient evidence for this product (Frank et al., 2010). None of these therapies have been tested for their anxiolytic effect in dogs with ADCE so direct comparisons cannot be made.

Pharmacokinetic interactions

Prior to commencement of antidepressants, potential pharmacokinetic drug interactions should be noted. Phenobarbital can increase serum concentrations of antidepressants whilst fluoxetine, fluvoxamine and paroxetine can increase serum concentrations of AEDs. In people gabapentin, levetiracetam, pregabalin, topiramate and zonisamide can be used safely in conjunction with most antidepressants, whilst citalopram, escitalopram, sertraline, duloxetine,

venlafaxine and mirtazapine are considered to have limited interaction with AEDs. It is worth noting to owners who pursue herbal remedies that St. John's Wort can interfere with AED pharmacokinetics causing hepatotoxicity. For all drug combinations, regular serum concentration monitoring should take place (Kondziella and Asztely, 2009). Pharmacokinetic interactions in veterinary behavioural medicine are discussed in detail in Overall (2013).

Behavioural treatment of anxiety in epileptic dogs

Treatment of anxiety disorders in dogs *without* epilepsy via behavioural modifications can be efficacious with time and repetition, however, the potency of these techniques in an epileptic dog with additional neuropathology is unknown. In order to alter a negative emotional response, such as fear or anxiety, to a given stimulus, a veterinary behaviourist would use a combination of desensitisation and counterconditioning techniques, but this approach will be limited in effectiveness if the animal has a high residual level of emotional arousal, which would require preliminary reduction as a first step. Desensitisation involves associating the problematic stimulus with a neutral emotional state and involves presentation of the stimulus in ways which alters its size or salience, for example by increasing the distance at which it is encountered. Over time, the potential effect of the stimulus can be increased until the animal exhibits no behavioural signs of an emotional response when confronted with the previously anxiety-inducing stimulus. Counterconditioning involves associating a positive emotional state, through the provision of a positive emotional cue such as food and play, with the previously anxiety-inducing stimulus, to avoid the animal redeveloping negative associations with the stimulus (Bowen and Heath, 2005). Instrumental conditioning may also have a role to play in behavioural modification for these patients through reinforcing an appropriate behavioural response in situations where there is unavoidable exposure to an anxiety-inducing stimulus. An example would be the teaching of the use of an appropriate safe

refuge to dogs who are anxious or fearful in the presence of loud noises. The aim is to teach the dog to use a behavioural response which will minimise its exposure to the stimulus and enable it to take some control over its environment. This is preferable to encouraging a dog to find refuge with their owner during fearful or anxious times as this can result in a dependence on the owner who may not always be present when the stimulus is encountered. Lack of access to a learnt coping strategy runs the risk of increasing anxiety but also inducing the emotional response of frustration. When dealing with an anxious or fearful dog punishment should never be used as it will usually increase negative emotional motivations (Overall, 1997), which is not only counterproductive in terms of establishing positive emotional responses, but also raises concerns related to welfare and QoL.

Conclusion

Anxiety disorders in people with epilepsy is garnering more attention and research, but the extent to which it affects dogs is under-investigated and there has been limited veterinary-specific testing of potential treatments. Therefore, with the absence of veterinary specific data, evidence-based medicine from people with epilepsy must be cautiously and carefully adapted and applied. In ideal circumstances, for veterinary patients with ADCE, an AED with a low risk of anxiety should be selected based on human research and reported adverse effects in dogs, alongside adequately controlling seizure frequency and severity. Additionally, a behavioural modification plan should be implemented with or without anxiolytic medication as described above. The animal's emotional state should be assessed and closely monitored in newly-diagnosed dogs with epilepsy or throughout initiation of a new AED therapy or anxiolytic medication so that acute and chronic changes can be accurately accounted for and treatment can be tailored effectively. AED serum levels should be closely monitored when incorporating additional medications.

Of course, anxiety disorders are not the only psychological comorbidity to be considered; a change in AED or additional medication could improve clinical signs of anxiety but cause hyperactivity or decrease attention capability, for example. Additionally, control of a comorbidity will not necessarily improve seizure control and improving seizure control may not reduce behavioural comorbidities, so a vet and an owner should work together to find a balance for each patient to carefully assess specific features of the disease and how that impacts a patient and their family day to day, with the aim of optimising QoL for them all. Clearly further veterinary research is warranted on the effect and treatment of dogs with epilepsy and psychological and behavioural comorbidities and it is vital that general practice and neurology specialists clinicians work with veterinary behaviour specialists to improve and validate diagnostics and treatment of these patients. QoL of an epileptic patient is paramount and we would do our companions a great disservice by considering epilepsy as a condition solely defined by seizures.

Conflict of interest statement

Unless stated below, none of the authors have personal or financial relationships with other people or organizations that might inappropriately influence or bias the content of the paper. There are no patents, products in development, or marketed products to declare.

Rachel Casey: Employed by Dogs Trust.

Holger Volk: Served as paid consultant for Boehringer Ingelheim and CEVA animal health. Served as contract researcher for: Nestle 2012–2014 and 2017-2019, dietary modification of epilepsy in dogs; Desitin Pharma, 2012, the role of levetiracetam in a referral hospital; industrial Funding, 2014–2015, investigating the effects of imepitoin behavioural, physiologic and owner-reported indicators of anxiety in dogs treated for idiopathic epilepsy. Received

competitive research grants for: RCVS pump primer grant, 2010– 2013, pharmacometabonomic profiling of epileptic dogs; Waltham Foundation, 2011–2014, determination of plasma omega-3 fatty acid status in dogs with primary epilepsy and relationship to antiepileptic drug metabolism; CASE BBSRC PhD studentship, 2012–2016 metabolic profiling of epilepsy in dogs; American Kennel Club, American Health Foundation, 2016-2018, Investigating the Effect of a Ketogenic Medium Chain Triglycerides Supplement on the treatment of Canine Idiopathic Epilepsy and its behavioural comorbidities; BBSRC, 2017-2020, Investigating the relationship between epilepsy, drug-resistance and affective disorders in the domestic dog.

Clare Rusbridge: Employed by the University of Surrey and Fitzpatrick Referrals Ltd, Surrey, GU7 2QQ. She has served as a paid consultant for Boehringer Ingelheim . The University of Surrey and Fitzpatrick Referrals did not play a role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript and only provided financial support in the form of authors' salaries.

Rowena Packer: Received industrial funding as a co-applicant from Boehringer Ingelheim (2014-15; Investigating the effects of imepitoin on behavioural, physiologic and owner-reported indicators of anxiety in dogs treated for idiopathic epilepsy) and Nestle (2017-19; Dietary modification of epilepsy in dogs). Received competitive research grants from the American Kennel Club (2016-18; Investigating the effect of a ketogenic medium chain triglycerides supplement on the treatment of canine idiopathic epilepsy and its behavioural comorbidities); BBSRC (2017-20; Investigating the relationship between epilepsy, drug-resistance and affective disorders in the domestic dog; BB/P001874/1) and (2017-2020; Comorbidity and characteristics of canine neurodevelopmental disorders and their impact on animal welfare; BB/P010881/1).

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975 **Table 1: Summary table of evidence for anxiogenic and anxiolytic**
976 **effects of AED in human and veterinary medicine.**
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Anti-epileptic drug (AED)	Evidence for anxiolytic action from human medicine	Evidence for anxiogenic action from human medicine	Evidence for from veterinary medicine
Phenobarbital		Use of primidone predicted anxiety after logistic regression analysis in a cross-sectional study of 196 patients with epilepsy. (Lopez-Gomez et al, 2008)	No evidence of increased anxiety as an adverse effect based on a systematic review of 43 monotherapy papers. (Charambolous et al, 2016)
Potassium Bromide			No evidence of increased anxiety as an adverse effect based on a systematic review of 8 monotherapy papers and 16 adjunctive therapy papers. (Charambolous et al, 2016)
Levetiracetam	Levetiracetam could be both an efficacious AED and anxiolytic. (Hagemann et al, 2013) A systematic review found that patients treated with levetiracetam had lower incidence of behavioural problems. (Cramer et al, 2003)		No evidence of increased anxiety as an adverse effect based on a systematic review of 2 monotherapy papers and 4 adjunctive therapy papers. (Moore et al, 2010; Fredso et al, 2015)
Pregabalin	Reduced seizure frequency and significantly reduced anxiety scores in epileptic patients diagnosed with a comorbid anxiety disorder. (Brandt et al, 2013)		There was not enough evidence to assess safety profile or adverse effects. (Charambolous et al, 2016)
Gabapentin	Considered a mood enhancer and showed		There was not enough evidence to assess

	no significant anxiogenesis between control or treated adults as an add-on AED. (Harden et al, 1999)		safety profile or adverse effects. (Charambolous et al, 2016)
Zonisamide	Significantly decreased anxiety in historic non-responders and in newly-diagnosed children. (Kinrys et al, 2007) (Eun et al, 2011)	A 3% increase in anxiety was seen in treated patients compared to controls in a double-blinded add-on trial. (Cramer et al, 2003)	No evidence of increased anxiety as an adverse effect based on a systematic review of 5 monotherapy papers. Evidence was considered weak. (Charambolous et al, 2016)
Topiramate		12.9% of epileptic patients with add-on topiramate developed anxiety. (Mula and Trimble, 2003) Less than 5% reported incidence of anxiety in 429 epileptic patients during short- and long-term drug therapy. (Bootsma et al, 2009)	There was not enough evidence to assess safety profile or adverse effects. (Charambolous et al, 2016)
Felbamate		A small, randomized, placebo controlled study found that six of 13 patients receiving felbamate monotherapy dropped out due to intolerable adverse effects including anxiety. (Theodore et al, 1995)	No evidence of increased anxiety as a adverse effect based on a systematic review of 3 monotherapy papers. Evidence was considered weak. (Charambolous et al, 2016)
Imepitoin			No change in fear and anxiety-related behavioural scores in 85 dogs before or during treatment for IE with imepitoin. (Packer at al, 2017) ACVIM consensus statement reported no

			anxiety as an adverse effect of imepitoin. (Podell et al, 2016) Anxiety reported as a less common, dose-dependent and reversible adverse effect in a systematic review of 6 monotherapy and 2 adjunctive therapy papers. (Charambolous et al, 2016)
Polypharmacy	No significant difference in anxiety levels or increased adverse effect levels in polypharmacy patients compared to monotherapy human patients. (Ettinger et al, 1998) (Ijff et al (2015)	Polypharmacy was a significant risk factor associated with increased anxiety following regression analysis in 35, 102 and 101 children and adolescent patients. (Oguz, 2002) (Adewuya & Ola, 2005) (Williams et al, 2003)	No evidence available.

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