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INVESTIGATING OWNER USE OF DIETARY SUPPLEMENTS IN DOGS WITH IDIOPATHIC EPILEPSY

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Abstract

Epilepsy is the most common chronic neurological disorder in dogs. Some diets have been shown to have a positive impact upon the seizure activity in dogs with idiopathic epilepsy (IE), while other diets and dietary supplements (DS), although marketed as providing health benefits, lack conclusive scientific evidence on their actual beneficial effects.

A web-based owner questionnaire was designed to assess how and why owners of dogs with IE use different dietary regimes and DS. The study cohort, with 297 valid responses, consisted mainly of pure-breed (82.5%) male neutered (52.9%) dogs. Over two-thirds of owners (67.7%) changed their dog's diet after their dog received a diagnosis of IE. Nearly half of the owners (45.8%) reported giving DS, the most common being coconut oil or derived medium-chain triglyceride oil (71.3%). Some owner justifications of DS use included improvement of seizure frequency (88.2%), seizure severity (61.8%) and protection from potential drug side effects (62.5%).

Many owners give DS to their dog with IE. The pharmacokinetic properties of anti-epileptic drugs, such as efficacy, absorption and clearance can be influenced by other medications, diets and possibly by DS. We propose that use of DS should be considered and monitored by veterinary surgeons in epilepsy management.

Highlights

- Over $\frac{2}{3}$ of owners changed their dog's diet after the diagnosis of IE.
- Nearly $\frac{1}{2}$ of owners report giving DS on a daily basis supporting epilepsy management.
- The most common DS types belonged to fatty acid group (94 %).
- The top three used DS were coconut-, fish- or derived oils, and milk thistle.
- Reduction of seizure frequency, drug side effects and severity were mainly aimed in DS use.

Keywords

Veterinary Neurology, Neurodietetics, Epilepsy, Diet, Dietary Supplement, Seizure

List of abbreviations

| ABBREVIATIONS | |
|---------------|--|
| DS | Dietary supplement/s |
| AED | Anti-epileptic drug |
| ADHD | attention-deficit/hyperactivity disorder |
| CS | Cluster Seizure |
| LCT | Long chain triacylglyceride |
| MCT | Medium chain triacylglyceride |
| Ω-3 FAs | omega-3 fatty acids |
| QoL | Quality of Life |
| SE | Status Epilepticus |
| VFI | Voluntary food intake |

Introduction

Epilepsy is defined as the enduring predisposition of having epileptic seizures (Berendt et al., 2015), and is the most common chronic neurological disorder in dogs, affecting an estimated 0.6% of dogs in the general population (Kearsley-Fleet et al., 2013). The chronic, often lifelong administration of seizure-suppressing drugs, such as phenobarbital, potassium bromide and imepitoin, currently represents the most important form of treatment in veterinary medicine (De Risio et al., 2015; Royaux et al., 2017). However, anti-epileptic drug (AED) usage can be accompanied by undesirable side effects including polyphagia, sedation, restlessness or ataxia which might outweigh the seizure suppressing benefits of these medications (Charalambous et al., 2014; Charalambous et al., 2016) and negatively affect quality of life (QoL) (Wessmann et al., 2016). When conventional AEDs fail to achieve satisfactory seizure control, finding an appropriate and effective epilepsy management for the individual can be a difficult and lengthy process (Munana, 2013; Podell, 1998; Podell and Fenner, 1993). New treatment strategies are needed in epilepsy management (Martle et al., 2014; Munana, 2013; Munana et al., 2012).

Diet is increasingly recognized as having an impact upon the seizure activity and behavior of dogs with epilepsy (Bosch et al., 2007; Law et al., 2015; Packer et al., 2016). Ketogenic diets (KD) have been shown to be efficient in reducing seizure frequency and severity in human patients and rodent models of epilepsy (Achanta and Rae, 2017; Augustin et al., 2018; Lusardi

et al., 2015; Mantis et al., 2014; Martle et al., 2014; Patterson, 2014; Wijnen et al., 2017). The mechanism of antiepileptic action is not yet fully understood, but might be led by a rise in brain ketones improving brain function. KD may have anti-inflammatory properties (Dupuis et al., 2015) and prevent neuronal hyperexcitability via pH, direct inhibition of ion channels, influencing mitochondrial functions and alteration in amino acid metabolism linked to inhibitory neurotransmitter production [27, 28].

In addition to complete dietary interventions such as the KD, dietary supplements (DS) of different vitamins (Snoeiijen-Schouwenaars et al., 2015), minerals (Kumar et al., 2015; Yuen and Sander, 2012), fatty acids (Bromfield et al., 2008; Chang et al., 2013; DeGiorgio et al., 2015; DeGiorgio and Taha, 2016; Taha et al., 2010; Yuen et al., 2012; Yuen et al., 2005) or other nutrients (Ciarlone et al., 2016) have been extensively explored in rodent models of epilepsy (Betti et al., 2011; Flores-Mancilla et al., 2014; Giroto et al., 2013; Liu et al., 2012; Smeland et al., 2012) and human patients (Jackson et al., 2015; Lee and Chung, 2010; Neal et al., 2012; Zupec-Kania and Zupanc, 2008). While some studies found that dietary supplementation with individual nutrients can improve seizure control (DeGiorgio and Taha, 2016; Kumar et al., 2015; Scorza et al., 2009b), reduce seizure frequency (Ciarlone et al., 2016; Yuen et al., 2005) and improve other health aspects of epileptic patients, others have failed to confirm similar findings (Matthews et al., 2012; Sarmiento Vasconcelos et al., 2016; Yuen et al., 2012).

In veterinary medicine, there remains a lack of data regarding dietary intervention for epilepsy management. In comparison to human medicine, few studies exist on the use of nutritional management in dogs with IE (Matthews et al., 2012; Scorza et al., 2013; Scorza et al., 2009b). In 2004, a trial of eight dogs with drug-resistant epilepsy and signs of gastrointestinal hypersensitivity treated with an exclusion diet was reported (Lujan A, 2004). In this preliminary study, seven out of eight dogs had a reduction in seizure frequency. In a randomised, double-blinded, placebo-controlled study, dogs with IE fed with a medium-chain-triglyceride (MCT) enriched diet over three months showed significantly lower seizure frequency in comparison to placebo diet (Law et al., 2015). Improvements in seizure outcome was accompanied by positive modification in attention-deficit/hyperactivity disorder (ADHD) related behaviours and potential anxiolytic effects (Packer et al., 2016). The effects of other DS in canine epilepsy have been mixed. A positive impact of omega-3 fatty acids (Ω -3 FAs) supplementation was reported in one dog with drug-resistant epilepsy (Scorza et al., 2013;

Scorza et al., 2009b). In contrast, Matthews et al. (Matthews et al., 2012) reported no reduction in seizure frequency and severity in fifteen dogs with IE when supplemented with an oil containing long essential fatty acids (eicosapentaenoic acid, docosahexaenoic acid, Vitamin E) for 12 weeks.

Many online epilepsy support groups recommend dietary interventions in epilepsy management, often based on anecdotal evidence. Currently, the type of DS recommended from owner to owner, the source of their recommendations and exactly which DS owners use for their dogs with epilepsy is unknown. As with any ‘therapeutic’ intervention, there is the potential that certain dietary interventions could benefit or have no effect, but also potentially harm the patient either directly or through diet-drug interactions.

This study aims to increase our understanding on the current use of diets and DS in canine epilepsy management. The objectives of this study are:

- (i) To describe owner use of DS and nutritional management in canine IE
- (ii) To describe reasons for and against DS use by owners of dogs with IE
- (iii) To identify information sources utilised by owners to choose DS
- (iv) To describe owner-perceived side effects of DS use

As DS are becoming increasingly available to owners, this study will equip veterinary surgeons with important insights to be considered when managing a patient with IE.

Materials and Methods

From April to June 2017, an online questionnaire study was hosted on SurveyMonkey™ (SurveyMonkey Europe, Shelbourne Road, Dublin, Ireland). Owners of dogs with IE were recruited via social media. Consent was gained via a statement at the start of the questionnaire, and the study was approved by the Royal Veterinary College’s Ethics and Welfare Committee (approval number URN 2016 1558).

Epilepsy data

To be included in the analysis, the dog must have met the International Veterinary Epilepsy Task Force (IVETF) tier I confidence level for the diagnosis of idiopathic epilepsy (De Risio

et al., 2015). Dogs with a history of seizures that did not meet these criteria (e.g. those with epilepsy with an identifiable cause, insufficient diagnostic testing, where seizure onset was <6 months old or >6 years old with no MRI to rule out structural causes) were excluded from the study. Only completed questionnaires were considered in the analysis. Based on supplementation habits, owners were allocated to one of three groups: (1) owner recently used, (2) previously used or (3) never used dietary interventions for epilepsy management. Details on their dog's signalment, seizure phenotype (total number of seizures, number of seizures over the last three months, history of cluster seizures and/or status epilepticus), AED medication, diet (type, frequency, routine, purchase, and treats) and owner demographics were gathered.

Dietary supplement data

According to the United States Food and Drug Administration (FDA) under the US Dietary Supplement Health and Education Act of 1994 ((FDA), 1994) and the European Union's (EU) Food Supplements Directive of 2002 (R 2002/46/EG) (UNION, 2002), the term DS is defined as a product taken by mouth that contains a dietary ingredient intended to supplement the diet. The FDA and EU regulations require supplements to be demonstrated as safe, both in dosages and purity. However, these definitions apply to human consumers and not companion animals (Vandeweerd et al., 2013). Because the term DS has no overall regulatory or legal definition in veterinary medicine, for the purposes of this study, a DS was defined as “*an edible product added to a dog's main diet on a regular or irregular basis which is intended to provide additional support to health*”.

Owners were asked to report details of the DS they currently or previously used in their dogs epilepsy management, including what types of DS (> 40 options, others, free input) they administered to their dog (if any) and reasons to start or to stop supplementation. In addition, owners reported their personal experience of DS use (self-supplementation), way of choosing DS for their dog, the way they decided upon their DS-administration regime and their individual perception of possible DS effects. Details of all questions are available in the full survey (Supplementary file 1).

Statistical analysis

Data were handled using IBM SPSS (v23.0), Microsoft Excel (v2017) and GraphPad Prism 7.

Chi-squared tests were used to investigate the association between owner self-supplementation and use of DS in their dog. Data were tested for normality of distribution using the Kolmogorov-Smirnov test; variables that were normally distributed are stated as mean \pm SD, and non-normally distributed stated as median (m, min-max). The continuous data were not normally distributed, therefore non-parametric statistic tests were used (Mann-Whitney-U-Test). All tests were two-sided and $p < 0.05$ was considered to be significant.

Results

Overall, 547 responses were collected, of which 297 were complete and met the inclusion criteria. The majority of respondents were female (81.5 %) and aged between 46 to 60 years (38.4 %), with 20 years' experience of dog ownership (20.20 ± 13.9 years). The majority of respondents were from the UK (37.4 %), followed by USA (36.7%), Canada (10.4%), Germany (6.7%) and Australia (2.4%). Nearly every second owner (47.0%, $n=140$) included DSs for general health (33%, $n=99$) or a specific condition (14.1%, $n=42$) into their own diet. Owners supplementing their own diets with DS were significantly more likely to give their own dog DSs as well ($X^2=38.620$, $p=0.001$).

The study population consisted mainly of male neutered dogs (52.9 %) with a mean age of 66.7 ± 31.5 months and body weight of 25.1 ± 15.3 kg. With 73 different breeds represented, most study dogs were pure-breed (82.5 %), with the most common pure-breed being the Border Collie ($n=40$, 13.5 %).

Epilepsy phenotype

Most owners reported that their dog had generalized seizures (71.0%). The majority of dogs currently received AEDs (87.8%, $n=261$) with the most frequently reported drug being phenobarbital (79.3%, $n=207$), as a monotherapy (23.4%, $n=61$) or in combination with other AEDs (55.1%, $n=146$). Comparing the daily number of AEDs administered in association to the use of DS, dogs who currently or who used to get DS (2, 0-6) were on significantly more AEDs per day than dogs not receiving DS (1, 0-6; $p=0.012$).

Dogs were reported to have had a mean of 6.18 ± 9.7 seizures within the last three months, and a mean of 27.22 ± 22.57 during their life to date. Dogs that currently receive DS or used to receive DS (25.5, 3-10 seizures) had not suffered from significantly more seizures in their life than the dogs not receiving DS (20, 9-30 seizures, $p=0.064$).

Cluster seizures were reported in more than three-quarters of all dogs (78.1%, $N=232$), and almost a quarter (24.6 %, $N=73$) were reported to have experienced a seizure that lasted longer than 5 minutes without regaining consciousness (status epilepticus). Whilst the occurrence of CS was not significantly associated ($X^2= 2.119$, $p=0.714$) with the administration of DS, dogs that experienced SE in past were more likely to receive DS (28%, $X^2=15.209$, $p=0.004$).

Main dietary regime

In total, two thirds of owners (67.7%) reported to have changed their dog's diet since diagnosis with IE (Fig. 1). The majority of dogs (60.6%) were fed dry food as a complete diet or dry food in combination with wet food (25.6%), followed by home-cooked (17.8%) or raw food (21.9 %) diets. The majority of dogs were fed twice daily (68.0%). Pet shops (39.1 %) or online stores (37.4 %) were the most common places of purchase for diet and DS. Less than one-third of owners based their dog's main dietary regimen on the advice of a veterinary surgeon (27.6 %), with 13.8% basing their feeding regime on information published online, and 37.5% citing 'other' as a source of information.

Dietary supplementation

In the study cohort nearly half of the owners (45.8 %) reported that they currently gave their dog DS to manage their dog's epilepsy. As shown in Figure 2, the most common DS type belonged to fatty acid group (94 %). Micro- and macronutrients containing DS were routinely given by 66.0% of owners. Over half of dogs received additional vitamins (57.0%) or amino acid products (44.0%) alongside their normal food. In most cases, DS were given on a daily basis (51.2%, $n=80$).

The top three most commonly used DS were coconut or coconut-derived oils ($N = 112$, 77.3%), fish or fish-derived oils ($N = 105$, 66.9%) and milk thistle ($N = 67$, 42.7%). Other frequently

used DS were cannabis oil (N = 66, 42%), Vitamin B12 products (N=39, 24.8%), homeopathic remedies (20.4 %), glucosamine and/ or chondroitin (19.1%), taurine (17.2%) and dried herbs (15.9%) (Figure 2).

While less than one fifth of owners consulted their vet on the use of DS (17.5%), the most common source of advice for DS use was online owner support groups (38.2%) or online information (20.6 %). The main reasons given by owners to use DS for their epileptic dog were; (i) Reduction of seizure frequency (88.2%), (ii) Protection of the dog's body from potential side effects of AED medication (62.5%) and (iii) Reduction of seizure severity (61.8 %) (Fig. 3). Other objectives for the use of a DS were to improve the postictal recovery phase (42.6%), for the reduction of AED side-effects (41.2%) or epilepsy co-morbidities, such as cognition or behavioral issues (30.1%). One third of all owners (34%, n=101) would recommend using DS as management for their dog's epilepsy to other owners.

Cessation of dietary supplementation

A minority of owners in the study population (N = 21) had stopped giving their dog DS, as they did not believe it had any recognisable, beneficial effect (33.3%) or were afraid of potential damaging side effects (9.5%). In 9.5% of owners, chronic administration of DS was stopped because the dog refused to take it.

Non-use of dietary supplementation

Half of study respondents (47.1%, n=140) did not currently, and had not previously given their dogs DS. More than half of this group were not aware of DS (57.8%). Other reasons for not using DS in epilepsy management included feeling uncomfortable giving DS without veterinary supervision (32.1%), needing scientific evidence on beneficial effects in epilepsy management for them to be used (11.4%) or were afraid of potentials harms associated with DS (11.4%). However, 92.5 % of owners (N = 149) who stopped or had never previously used DS would reconsider DS administration when more scientific evidence would support such products.

Common side-effects of used DS

Overall, side effects associated to DS administration were not frequently reported by owners (N=157, of those who currently or previously used DS). However, the most common adverse events seen with DS consumption in dogs were sedation (18.5%, N =29), followed by more frequent water intake (14.6%, N = 24) and weight gain (14.6%, N=22).

Discussion

Dietary modification and supplementation is common in dogs with epilepsy; two thirds of owners adjusted their dog's diet after diagnosis of IE and nearly half gave DS as additional management. As pharmacokinetic properties of AEDs are known to be influenced by other medications (Munana et al., 2015) or diets (Gindiciosi et al., 2014; Munana et al., 2015; Patsalos, 2000; Rundfeldt et al., 2014; Shaw et al., 1996; Thurman et al., 1990), different DS may also affect their efficacy, absorption and excretion (Kverneland et al., 2015; Larsen et al., 2014). As such, awareness of safe DS-AED combinations and feeding practices is of importance to owners and veterinary surgeons alike. For example, high dietary chloride content is associated with a decrease in therapeutic serum bromide concentrations and increased seizure frequency in epileptic dogs (Shaw et al., 1996). Likewise, a pharmacokinetic study showed that dietary protein or fat restriction significantly increased the clearance and elimination rate of phenobarbital (Maguire et al., 2000). As such, dogs on chronic AEDs should be kept on a relatively constant diet regime.

Although data on the efficacy, safety, or beneficial effects of different DSs on canine epilepsy are lacking (Bontempo, 2005; Law et al., 2015; Manteca, 2011; Matthews et al., 2012; Pan et al., 2010; Scorza et al., 2009a), and where evidence is available, it is mostly reported in humans (Gaby, 2007; Gilby et al., 2009; Grey and Bolland, 2014; Pearl et al., 2011; Widenhorn-Muller et al., 2014; Yuen et al., 2012; Yuen and Sander, 2012; Yuen et al., 2005), DS are commonly used by owners to manage their dogs epilepsy. The current study showed that various oils are often used as DS for dogs with IE. In one third of epileptic dogs treated with potassium bromide or phenobarbital long-term, there may be an increased risk of pancreatitis due to induced hypertriglyceridemia (Bossens et al., 2016; Kluger et al., 2008; Thomas, 2010). Accordingly, for dogs receiving additional oil DS on a daily basis (James et al., 2009), it may be

recommendable to monitor serum triglyceride concentration and canine pancreas-specific lipase (Albarracin et al., 2015) more periodically than usual to avoid complications. The influence of dietary long-chain fatty acids on the absorption and excretion of commonly used AEDs should also be considered; a previous clinical trial of dietary effects on the pharmacokinetics of phenobarbital found that fat may be able to increase absorption rate and decrease drug clearance (Maguire et al., 2000).

The most common DS in this study, consumed by more than 75% of epileptic dogs, was coconut oil or the derived MCT oil. MCT oils typically contain large amounts of MCTs and glycerolesters with saturated 8- to 12-carbon fatty acids, with an absence of long-chain triglycerides (LCTs) (St-Onge and Jones, 2002). The main constituents, octanoic (C8; caprylic) and decanoic (C10; capric) triglycerides (TAGs), along with their downstream metabolites, are thought to have antiepileptic effects (Chang et al., 2013). A recent study revealed that decanoic acid acting as a non-competitive AMPA receptor antagonist results in direct inhibition of excitatory neurotransmission, and thus exerts an anticonvulsant effect (Chang et al., 2015). Beta-hydroxybutyrate (BHB) has been shown to reduce seizure-like neuronal activity and is thought to assert its effectiveness via K_{ATP} channel activity and inhibition of GABA_B signalling in a *Drosophila in vitro* model (Li et al., 2017). Furthermore, oral MCT supplementation leads to significant elevation in ketone BHB concentrations and improved seizure control in dogs (Law et al., 2016). Whether ketogenic MCTs as purified oil or within coconut oil can be both an effective anticonvulsant in dogs with IE requires further investigation.

The second most mentioned DS, fish oils, commonly contains higher amounts of Ω -3 FAs (Bauer, 2011, 2016) contributing to CNS development and reducing risk of neurological disorders such as epilepsy (Bourre, 2004). These fatty acids can modulate ion channels, and have been described to induce mechanisms of action in reducing excitability within the CNS (DeGiorgio and Taha, 2016). While in humans, Ω -3 FAs have been shown to reduce seizure frequency in chronic epilepsy (Yuen et al., 2005), there little evidence in dogs with IE. In a single case report, addition of Ω -3 FAs had a positive impact on seizure occurrence and subjective QoL in a dog with drug-resistant IE (Scorza et al., 2009b). This efficacy was, however, not confirmed in a placebo controlled twelve-week long study using a Ω -3 FAs DS for dogs with IE (Matthews et al., 2012). Further evidence is needed to explore the potential of Ω -3 FAs in the management of IE in dogs.

Dried herbs, including milk thistle, valerian, skullcap or Chinese herb mixtures, were reported to be given by dog owners for epilepsy management. In particular, milk thistle products are frequently used in epileptic dogs to try to prevent AED hepatotoxicity. All aforementioned supplements have been recommended for use in epilepsy in humans, or the rationale for their antiepileptic action are critically discussed in a study of US adults (Wells et al., 2010). Paradoxically, some dried herbs are reported to have more inadvertent seizure provoking than anticonvulsant effects (Pearl et al., 2011). Milk thistle (*Silybum marianum*) is a commercially available hepatoprotective product available in diverse forms (dried herbs, extracts, oil, tablets) (Pradhan and Girish, 2006). Antioxidant (Pradhan and Girish, 2006), cytoprotective and anti-inflammatory properties mean that milk thistle is used in the treatment of liver diseases in humans (Trappoliere et al., 2009) and in dogs (Vandeweerd et al., 2013; Webster and Cooper, 2009). Substantial *in vitro* and *in vivo* evidence suggest that *silymarin* can protect the liver from toxin, drug and ischemic-induced injuries (Marjani et al., 2016; Muriel and Mourelle, 1990; Pradhan and Girish, 2006; Vogel et al., 1984). Most findings were made in humans with a variety of liver conditions, and these beneficial properties must be reassessed in dogs. Most recently, based on *in-vitro* experiments, flavonoid compounds were proposed as reversing agents for multidrug resistance against several AEDs, and in humans have been demonstrated to be able to increase intracellular concentrations (Ferreira et al., 2018). Therefore, chronic oral supplementation of milk thistle might protect the liver from damage, but paradoxically may increase the plasma concentration of certain AEDs and therefore potentially aggravate the hepatotoxic effect of some of the AEDs.

Other herbal products, aqueous extracts of *Valerian* or *Baldrian* showed anticonvulsant effects in animal models, likely to be mediated through activation of the adenosine system (Giraldo et al., 2010; Rezvani et al., 2010; Torres-Hernandez et al., 2015; Verma and Thuluvath, 2007). To date, there is insufficient data on the safe and efficacious application of these herbs for canine epilepsy management.

Recently, the medicinal use of cannabidiol (CBD) in people has become widespread especially for neurological disorders (Solimini et al., 2017). Although at present there is limited scientific evidence on its efficacy and safety (Iffland and Grotenhermen, 2017), independent use has become popular in people (Fairman, 2016; Whiting et al., 2015). CBD oil was reported to effectively reduce seizure frequency and duration in humans and some animal models (Devinsky et al., 2016; Kaplan et al., 2017); however, information on toxicological parameters

from long-term administration are lacking (Iffland and Grotenhermen, 2017). The underlying physiological and molecular mechanisms mediating beneficial therapeutic effects have not yet been explored. In human medicine, CBD oil was recently shown to increase the serum level of commonly used AEDs with increasing CBD dose (Gaston et al., 2017). Cannabis, however can be toxic for dogs (Meola et al., 2012). There are now ongoing studies on the effects of CBD in dogs with epilepsy that will shed light in this area on efficacy and safety (Colorado State University).

Vitamin B was part of their daily regime of 25% of dogs receiving DS. Vitamin B1 or thiamine is known to be an essential factor in a number of different biochemical pathways in the brain. A deficiency can result in progressive encephalopathy, neuropathies and seizure occurrence (Garosi et al., 2003; Markovich et al., 2013; Zera and Zastre, 2017). A link between neurotransmitter production and thiamine availability has been discussed (Cheney et al., 1969); however, in comparison to cats, dogs are less susceptible to thiamine deficiency. Dietary restriction (Baird and Ravindranath, 2015) or some diet components might be capable of decreasing adequate thiamine absorption (Singh et al., 2005). Excessive prolonged epileptic episodes are linked to oxidative brain damage often related to mitochondrial dysfunction through an increase of free oxygen radicals in neuronal cells (Cardenas-Rodriguez et al., 2013; Loscher, 2002; Markowitz et al., 2010). Therefore, molecules such as thiamine that have been shown to have positive and preventive effects on drug induced oxidative stress (Turan et al., 2014a) are of great interest in epilepsy treatment.. There is no reliable evidence to support the routine use of any other vitamins in human patients with epilepsy to date (Ranganathan and Ramaratnam, 2005). Further long-term studies are required to elucidate the potential benefits of vitamin supplementation, and whether they may prevent or reverse the effects of deficiencies that result from epileptic seizures or the use of AEDs (Gaby, 2007).

In one third of owners, management of cognitive and behavioural co-morbidities of epilepsy was a reason for DS use. Although we are just beginning to understand the behavioural and cognitive comorbidities of epilepsy in the dog, many of the neurobehavioral comorbidities observed in human epilepsy patients are being discovered in dogs with epilepsy, including anxiety (Shihab et al., 2011), ADHD-like behaviour (Jokinen et al., 2015; Packer et al., 2016) and cognitive impairments (Packer et al., 2016; Packer et al., 2018a; Packer et al., 2018b; Winter et al., 2018). An increasing number of studies report significant impacts of diets on canine behaviour (Munana, 2013; Orlando, 2018; Shihab et al., 2011). As dietary ingredients

are precursors of many neurotransmitters involved in regulation of behaviour and can alter cerebrospinal fluid composition (Delion et al., 1994; DeNapoli et al., 2000; Galan et al., 2014), changes in the diet composition could conceivably influence behaviour (Bosch et al., 2007). The growing interest on risk factors for prevention and attenuation of cognitive decline in older dogs has led to an unprecedented interest in the relationship between diet and cognitive function (Di Cerbo et al., 2017b; Overall, 2011; Snigdha et al., 2016). Nutritional interventions to delay cognitive ageing are becoming increasingly important. A recent study reported that 6 months of supplementation with a nutrient blend consisting of antioxidants, B vitamins, fish oil and l-arginine, can have cognition-improving effects on aged dogs between 9 and 11.5 years old (Pan et al., 2018). In addition, studies have found that brain function of aged dogs was significantly improved by a specific diet formula with 5.5% MCT content. Therefrom, it was hypothesized that this occurs from MCT consumption providing the brain with an alternative energy source through an increasing ketone body level (Pan et al., 2010).

This study has a number of limitations; primarily that owners in this population may not be representative of all epileptic dog owners: owners of dogs with more severe epilepsy phenotypes may be more likely to use online support groups due to higher levels of psychological stress and need for peer-peer support (D'Aniello et al., 2017; Packer et al., 2017; Wessmann et al., 2014), and the study population was heavily biased towards female owners. As reported here, vets were rarely the source of information owners used to discuss diet or the use of DS as management tools for their dog's epilepsy. These data on the relatively high prevalence of DS use in canine epilepsy aim to inform and empower vets to engage with clients on this topic, and encourage active discussion on their clients' epilepsy management beyond traditional drug treatment. Potential interactions of DS with AEDs are yet to be explored, and thus we must consider that DS may pose dangers to epileptic patients. With a paucity of data on the short- and long-term effects of DS on dogs with epilepsy, caution should be exercised when discussing or recommending such products. A greater understanding of the owners of chronically ill patients, including the role of parenting styles in the owner-dog relationship (Herwijnen et al., 2018), peer-peer support and the internet as information sources (Belshaw et al., 2016) should be explored further to better understand owner decision-making in their dog's treatment. Interestingly, owners who supplemented their own diet had a higher tendency to give DS to their dogs. This emphasizes a link between an owner's perception of their own nutrition and their pet's diet.

Conclusions

There remains limited knowledge about the benefits of DS in canine epilepsy management; however, an increasing number of studies are being published in this area and many owners of dogs with IE already use DS to help manage canine epilepsy without evidence to support their use. As such, and veterinary surgeons should be aware of this activity and actively engage with their clients to discuss the management of these patients beyond the drugs they prescribe. Diet composition, content and some of the DS mentioned could influence pharmacokinetic properties of AEDs and potentially modulate their efficacy and safety profile (Berendt et al., 2015; Floerchinger et al., 2015; Scorza et al., 2009b). Canine nutrition needs to be considered when taking a clinical history for clinical trials (Di Cerbo et al., 2017a) and we recommend that all vets collect information on diet and DS use as part of a dietary history in epilepsy cases. The general use of DS should be considered and monitored by veterinary surgeons in long-term epilepsy management and the chronic intake of different DS types should be re-evaluated and adjusted in the process of therapeutic intervention for better seizure control. Future experimental, epidemiological and clinical studies are needed to evaluate the potential benefits and harms of the various DS reported here in epilepsy management. Understanding the complex interplay between medication and diet will improve future management of epileptic patients in veterinary medicine.

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Table 1: The most common DS side effects reported by owners

| Side-effect | Not present | Present | Very mild | Mild | Moderate | Severe | Very Severe |
|--------------------------------------|--------------------|----------------|------------------|-------------|-----------------|---------------|--------------------|
| Sleeping more than before | 81.5% | 18.5% | 9.6% | 4.5% | 3.2% | 0 | 1.3% |
| Drinking more | 84.7% | 15.3% | 6.4% | 6.4% | 1.9% | 0.6% | 0 |
| Gaining weight | 85.4% | 14.6% | 5.7% | 3.8% | 3.8% | 1.3% | 0 |
| Urinating more | 87.9% | 12.1% | 3.8% | 4.5% | 3.2% | 0.6% | 0 |
| Wobbly/ not coordinated when walking | 93.6% | 6.4% | 3.2% | 1.9% | 0 | 0.6% | 0.6% |
| Restlessness/ Pacing | 93.6% | 6.4% | 4.5% | 0.6% | 0.6% | 0 | 0.6% |
| Itchiness or skin rash | 91.7% | 8.3% | 3.2% | 1.3% | 3.8% | 0 | 0 |
| Diarrhea | 91.7% | 8.3% | 5.1% | 2.5% | 0 | 0 | 0.6% |
| Coughing | 86% | 14.0% | 2.5% | 5.7% | 4.5% | 0.6% | 0.6% |

Figure captures

Figure 1: Alteration of Diet and Use of Dietary Supplement for Epilepsy Management –

The bar charts illustrate the number of owners in percent (%) altered their dogs diet or administer DS with the aim of achieving better epilepsy management. Over two-third of owners have altered their dogs diet, while every second started to supplement. Over 60% of owners giving their dog DS currently use DS in their own dietary plan.

Figure 2: Types of DS in use for Epilepsy Management –

Almost every second owner give DS to manage their dog`s epilepsy from the nutritive side. The distribution scaled in percent of owners (%) about used DS types highlight the main use of oil DS. Every two out of three epileptic dogs under dietary supplementation receives coconut, fish or from these derived oils as add-on. Beside oils, micro- and macronutrient or vitamin containing DS appeared to be the second often administered products.

Figure 3: Owner`s reasons to use or not to use DS as additional support for their dog`s

epilepsy management – Reasons to give or not to give DS can come from different source. The bar charts show up in per cent of all owners (%) why decided to put their dog on DS or withheld nutritive add-ons from their dog`s food.

Figure 4: Owner`s reasons to stop using DS as additional management for their dog`s

epilepsy – A small portion of the study population stopped to administer DS in the past. The reasons why they quitted nutritive supplementation are summarized as bar chart in percent of owners.

Supplementary Files

Supplementary Files 1: Owner questionnaire to investigate the use of dietary supplements in dogs with idiopathic epilepsy

Figure 1: Alteration of Diet and Use of Dietary Supplement for Epilepsy Management – The bar charts illustrate the number of owners in percent (%) altered their dogs diet or administer DS with the aim of achieving better epilepsy management. Over two-third of owners have altered their dogs diet, while every second started to supplement. Over 60% of owners giving their dog DS currently use DS in their own dietary plan.

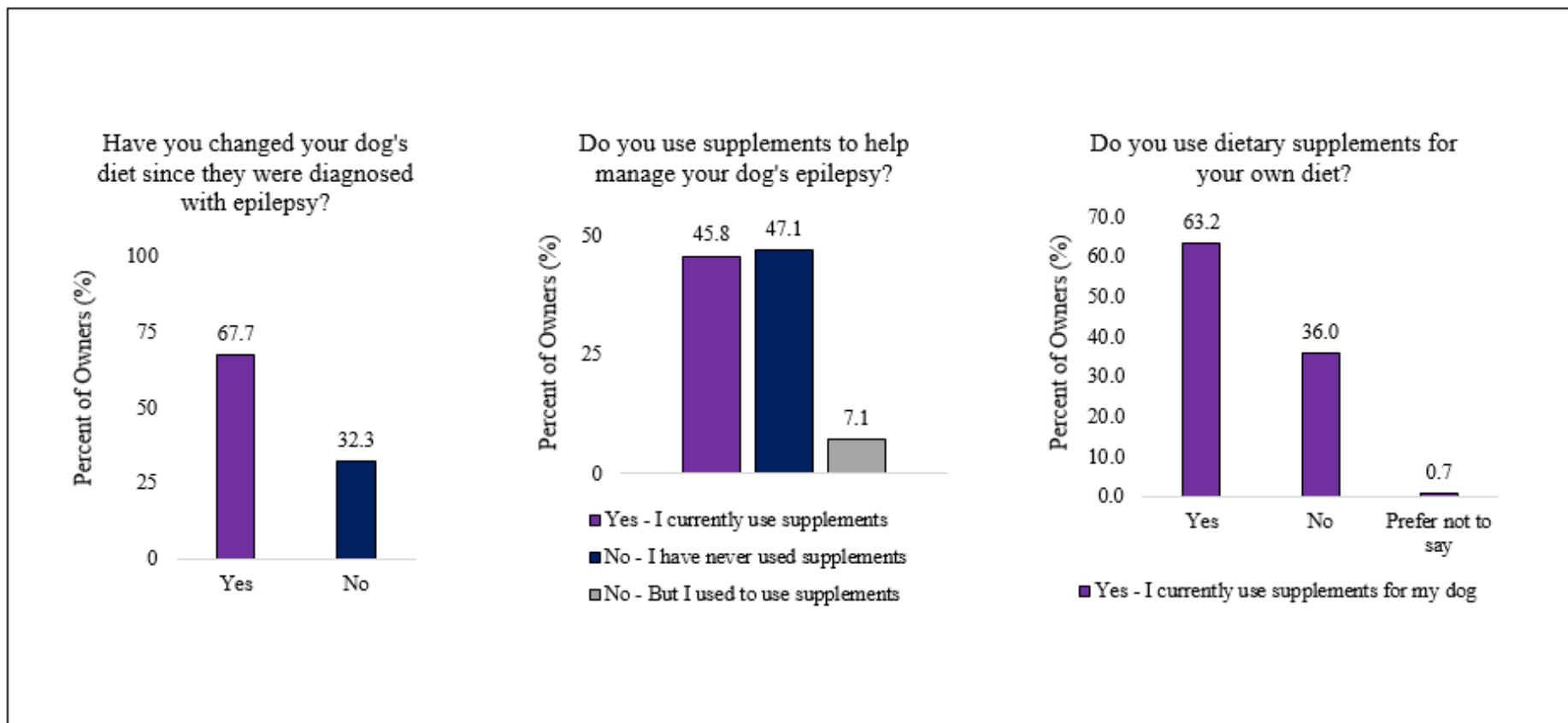


Figure 2: Types of DS in use for Epilepsy Management – Almost every second owner give DS to manage their dog`s epilepsy from the nutritive side. The distribution scaled in percent of owners (%) about used DS types highlight the main use of oil DS. Every two out of three epileptic dogs under dietary supplementation receives coconut, fish or from these derived oils as add-on. Beside oils, micro- and macronutrient or vitamin containing DS appeared to be the second often administered products.

Types of Dietary Supplements in Use for Epilepsy Management in Dogs

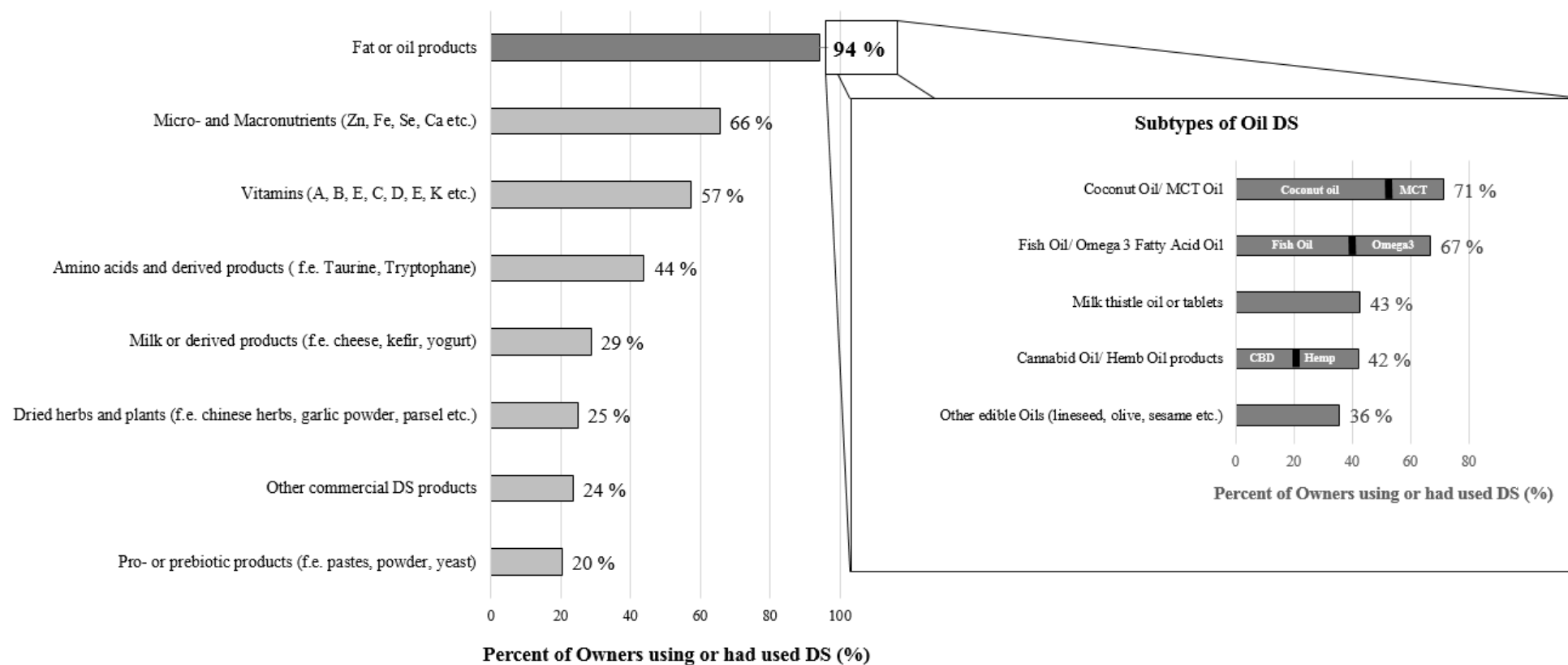


Figure 3: Owner's reasons to use or not to use DS as additional support for their dog's epilepsy management – Reasons to give or not to give DS can come from different source. The bar charts show up in per cent of all owners (%) why decided to put their dog on DS or withheld nutritive add-ons from their dog's food.

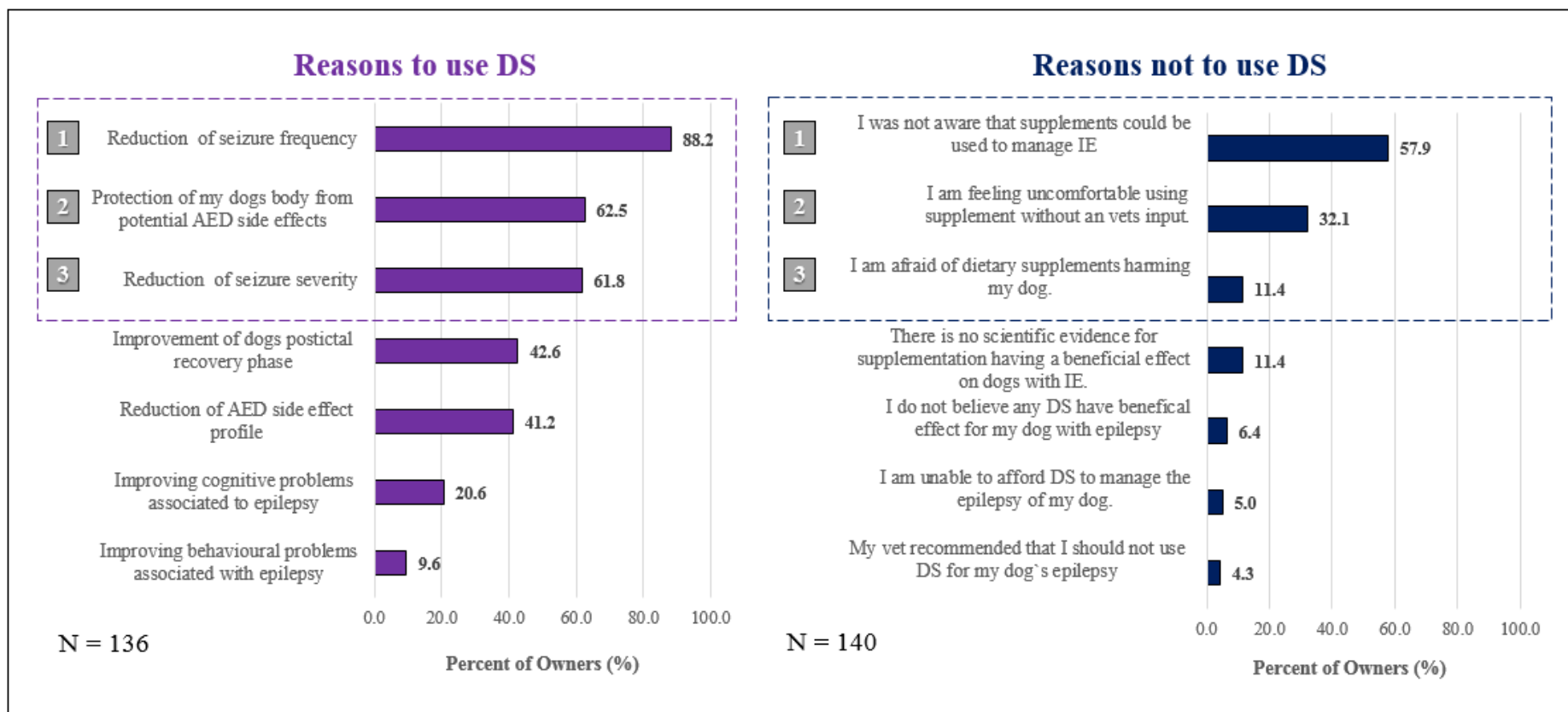


Figure 4: Owner's reasons to stop using DS as additional management for their dog's epilepsy – A small portion of the study population stopped to administer DS in the past. The reasons why they quitte nutritive supplementation are summarized as bar chart in percent of owners.

