INVESTIGATING OWNER USE OF DIETARY SUPPLEMENTS IN DOGS WITH IDIOPATHIC EPILEPSY

Affiliations and addresses of the authors:

Benjamin Andreas Berk[12], Rowena Mary Anne Packer[1], Tsz Hong Law[1], Holger Andreas Volk. [1]

[1] Royal Veterinary College, Department of Clinical Science and Services (CSS), Hatfield, United Kingdom

[2] Tierarztpraxis Strassenheim, Ortsstraße, Mannheim, Germany

E-mail address, telephone and fax numbers of the corresponding author:

Dr Benjamin Andreas Berk MSc MRCVS

The Royal Veterinary College

Department of Clinical Science and Services

Hawkshead Lane

North Mymms

Hatfield, Hertfordshire

AL9 7TA

United Kingdom

Number: +44 (0)1707 666333

Email: bberk@rvc.ac.uk

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 $^2/_3$ of owners changed their dog's diet after the diagnosis of IE.
- Nearly $^1/_2$ 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

List of abbreviations

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 supressing 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 (Snoeijen-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; Girotto 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; Sarmento 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 and 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

5

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 ± 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 glyceroesters 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 in 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 being 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.

Acknowledgements

References

1.	(FDA), U.F.a.D.A., 1994. DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994, PUBLIC LAW 103-417, 103RD CONGRESS.

2.	Achanta, L.B., Rae, C.D., 2017. beta-Hydroxybutyrate in the Brain: One Molecule, Multiple Mechanisms. Neurochemical research 42, 35-49.

3.	Albarracin, V., Teles, M., Melendez-Lazo, A., Rodon, J., Pastor, J., 2015. Canine Pancreas-Specific Lipase and C-reactive Protein in Dogs Treated With Anticonvulsants (Phenobarbital and Potassium Bromide). Topics in companion animal medicine 30, 57-61.

4.	Augustin, K., Khabbush, A., Williams, S., Eaton, S., Orford, M., Cross, J.H., Heales, S.J.R., Walker, M.C., Williams, R.S.B., 2018. Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders. The Lancet. Neurology 17, 84-93.

5.	Baird, J.S., Ravindranath, T.M., 2015. Vitamin B deficiencies in a critically ill autistic child with a restricted diet. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition 30, 100-103.

6.	Bauer, J.E., 2011. Therapeutic use of fish oils in companion animals. Journal of the American Veterinary Medical Association 239, 1441-1451.

7.	Bauer, J.E., 2016. The essential nature of dietary omega-3 fatty acids in dogs. Journal of the American Veterinary Medical Association 249, 1267-1272.

8.	Belshaw, Z., Asher, L., Dean, R.S., 2016. The attitudes of owners and veterinary professionals in the United Kingdom to the risk of adverse events associated with using non-steroidal anti-inflammatory drugs (NSAIDs) to treat dogs with osteoarthritis. Preventive Veterinary Medicine 131, 121-126.

9.	Berendt, M., Farquhar, R.G., Mandigers, P.J., Pakozdy, A., Bhatti, S.F., De Risio, L., Fischer, A., Long, S., Matiasek, K., Munana, K., Patterson, E.E., Penderis, J., Platt, S., Podell, M., Potschka, H., Pumarola, M.B., Rusbridge, C., Stein, V.M., Tipold, A., Volk, H.A., 2015. International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals. BMC veterinary research 11, 182.

10.   Betti, M., Minelli, A., Ambrogini, P., Ciuffoli, S., Viola, V., Galli, F., Canonico, B., Lattanzi, D., Colombo, E., Sestili, P., Cuppini, R., 2011. Dietary supplementation with alpha-tocopherol reduces neuroinflammation and neuronal degeneration in the rat brain after kainic acid-induced status epilepticus. Free radical research 45, 1136-1142.

11.   Bontempo, V., 2005. Nutrition and health of dogs and cats: evolution of petfood. Veterinary research communications 29 Suppl 2, 45-50.

12.   Bosch, G., Beerda, B., Hendriks, W.H., van der Poel, A.F., Verstegen, M.W., 2007. Impact of nutrition on canine behaviour: current status and possible mechanisms. Nutrition research reviews 20, 180-194.

13.   Bossens, K., Daminet, S., Duchateau, L., Rick, M., Van Ham, L., Bhatti, S., 2016. The effect of imepitoin, a recently developed antiepileptic drug, on thyroid parameters and fat metabolism in healthy Beagle dogs. Veterinary journal (London, England : 1997) 213, 48-52.

14.   Bourre, J.M., 2004. Roles of unsaturated fatty acids (especially omega-3 fatty acids) in the brain at various ages and during ageing. The journal of nutrition, health & aging 8, 163-174.

15.   Bromfield, E., Dworetzky, B., Hurwitz, S., Eluri, Z., Lane, L., Replansky, S., Mostofsky, D., 2008. A randomized trial of polyunsaturated fatty acids for refractory epilepsy. Epilepsy & behavior : E&B 12, 187-190.

16.   Cardenas-Rodriguez, N., Huerta-Gertrudis, B., Rivera-Espinosa, L., Montesinos-Correa, H., Bandala, C., Carmona-Aparicio, L., Coballase-Urrutia, E., 2013. Role of oxidative stress in refractory epilepsy: evidence in patients and experimental models. International journal of molecular sciences 14, 1455-1476.

17.   Chang, P., Augustin, K., Boddum, K., Williams, S., Sun, M., Terschak, J.A., Hardege, J.D., Chen, P.E., Walker, M.C., Williams, R.S., 2015. Seizure control by decanoic acid through direct AMPA receptor inhibition. Brain : a journal of neurology 139, 431-443.

18.   Chang, P., Terbach, N., Plant, N., Chen, P.E., Walker, M.C., Williams, R.S., 2013. Seizure control by ketogenic diet-associated medium chain fatty acids. Neuropharmacology 69, 105-114.

19.   Charalambous, M., Brodbelt, D., Volk, H.A., 2014. Treatment in canine epilepsy--a systematic review. BMC veterinary research 10, 257.

20.   Charalambous, M., Shivapour, S.K., Brodbelt, D.C., Volk, H.A., 2016. Antiepileptic drugs' tolerability and safety--a systematic review and meta-analysis of adverse effects in dogs. BMC veterinary research 12, 79.

21.   Cheney, D.L., Gubler, C.J., Jaussi, A.W., 1969. Production of acetylcholine in rat brain following thiamine deprivation and treatment with thiamine antagonists. Journal of neurochemistry 16, 1283-1291.

22.   Ciarlone, S.L., Grieco, J.C., D'Agostino, D.P., Weeber, E.J., 2016. Ketone ester supplementation attenuates seizure activity, and improves behavior and hippocampal synaptic plasticity in an Angelman syndrome mouse model. Neurobiology of disease 96, 38-46.

23.   Clanton, R.M., Wu, G., Akabani, G., Aramayo, R., 2016. Control of seizures by ketogenic diet-induced modulation of metabolic pathways. Amino Acids.

24.   Colorado State University, A., Efficacy of cannabidiol for the treatment of canine epilepsy.

25.   D'Aniello, B., Semin, G.R., Alterisio, A., Aria, M., Scandurra, A., 2017. Interspecies transmission of emotional information via chemosignals: from humans to dogs (Canis lupus familiaris). Animal cognition.

26.   De Risio, L., Bhatti, S., Munana, K., Penderis, J., Stein, V., Tipold, A., Berendt, M., Farqhuar, R., Fischer, A., Long, S., Mandigers, P.J., Matiasek, K., Packer, R.M., Pakozdy, A., Patterson, N., Platt, S., Podell, M., Potschka, H., Batlle, M.P., Rusbridge, C., Volk, H.A., 2015. International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs. BMC veterinary research 11, 148.

27.   DeGiorgio, C.M., Miller, P.R., Harper, R., Gornbein, J., Schrader, L., Soss, J., Meymandi, S., 2015. Fish oil (n-3 fatty acids) in drug resistant epilepsy: a randomised placebo-controlled crossover study. Journal of neurology, neurosurgery, and psychiatry 86, 65-70.

28.   DeGiorgio, C.M., Taha, A.Y., 2016. Omega-3 fatty acids (-3 fatty acids) in epilepsy: animal models and human clinical trials. Expert review of neurotherapeutics 16, 1141-1145.

29.   Delion, S., Chalon, S., Herault, J., Guilloteau, D., Besnard, J.C., Durand, G., 1994. Chronic dietary alpha-linolenic acid deficiency alters dopaminergic and serotoninergic neurotransmission in rats. J Nutr 124.

30.   DeNapoli, J.S., Dodman, N.H., Shuster, L., Rand, W.M., Gross, K.L., 2000. Effect of dietary protein content and tryptophan supplementation on dominance aggression, territorial aggression, and hyperactivity in dogs. Journal of the American Veterinary Medical Association 217, 504-508.

31.   Devinsky, O., Marsh, E., Friedman, D., Thiele, E., Laux, L., Sullivan, J., Miller, I., Flamini, R., Wilfong, A., Filloux, F., Wong, M., Tilton, N., Bruno, P., Bluvstein, J., Hedlund, J., Kamens, R., Maclean, J., Nangia, S., Singhal, N.S., Wilson, C.A., Patel, A., Cilio, M.R., 2016. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. The Lancet Neurology 15, 270-278.

32.   Di Cerbo, A., Morales-Medina, J.C., Palmieri, B., Pezzuto, F., Cocco, R., Flores, G., Iannitti, T., 2017a. Functional foods in pet nutrition: Focus on dogs and cats. Research in veterinary science 112, 161-166.

33.   Di Cerbo, A., Sechi, S., Canello, S., Guidetti, G., Fiore, F., Cocco, R., 2017b. Behavioral Disturbances: An Innovative Approach to Monitor the Modulatory Effects of a Nutraceutical Diet. Journal of visualized experiments : JoVE.

34.   Dupuis, N., Curatolo, N., Benoist, J.F., Auvin, S., 2015. Ketogenic diet exhibits anti-inflammatory properties. Epilepsia 56, e95-98.

35.   Fairman, B.J., 2016. Trends in registered medical marijuana participation across 13 US states and District of Columbia. Drug and Alcohol Dependence 159, 72-79.

36.   Ferreira, A., Rodrigues, M., Fortuna, A., Falcao, A., Alves, G., 2018. Flavonoid compounds as reversing agents of the P-glycoprotein-mediated multidrug resistance: An in vitro evaluation with focus on antiepileptic drugs. Food research international (Ottawa, Ont.) 103, 110-120.

37.   Floerchinger, A.M., Jackson, M.I., Jewell, D.E., MacLeay, J.M., Paetau-Robinson, I., Hahn, K.A., 2015. Effect of feeding a weight loss food beyond a caloric restriction

period on body composition and resistance to weight gain in dogs. Journal of the American Veterinary Medical Association 247, 375-384.

38. Flores-Mancilla, L.E., Hernandez-Gonzalez, M., Guevara, M.A., Benavides-Haro, D.E., Martinez-Arteaga, P., 2014. Long-term fish oil supplementation attenuates seizure activity in the amygdala induced by 3-mercaptopropionic acid in adult male rats. Epilepsy & behavior : E&B 33, 126-134.

39. Gaby, A.R., 2007. Natural approaches to epilepsy. Alternative medicine review : a journal of clinical therapeutic 12, 9-24.

40. Galan, A., Carletti, B.E., Morgaz, J., Granados, M.M., Mesa, I., Navarrete, R., Lombardo, R., Martinez, C.M., Martin-Suarez, E.M., 2014. Comparative study of select biochemical markers in cerebrospinal fluid of healthy dogs before and after treatment with nutraceuticals. Veterinary clinical pathology 43, 72-77.

41. Garosi, L.S., Dennis, R., Platt, S.R., Corletto, F., de Lahunta, A., Jakobs, C., 2003. Thiamine Deficiency in a Dog: Clinical, Clinicopathologic, and Magnetic Resonance Imaging Findings. Journal of Veterinary Internal Medicine 17, 719-723.

42. Gaston, T.E., Bebin, E.M., Cutter, G.R., Liu, Y., Szaflarski, J.P., the, U.A.B.C.B.D.P., 2017. Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia, n/a-n/a.

43. Gilbert, D.L., Pyzik, P.L., Freeman, J.M., 2000. The ketogenic diet: seizure control correlates better with serum beta-hydroxybutyrate than with urine ketones. Journal of child neurology 15, 787-790.

44. Gilby, K.L., Jans, J., McIntyre, D.C., 2009. Chronic omega-3 supplementation in seizure-prone versus seizure-resistant rat strains: a cautionary tale. Neuroscience 163, 750-758.

45. Gindiciosi, B., Palus, V., Eminaga, S., Villiers, E., Bruto Cherubini, G., 2014. Serum bromide concentrations following loading dose in epileptic dogs. The Journal of small animal practice 55, 108-111.

46. Giraldo, S.E., Rincon, J., Puebla, P., Marder, M., Wasowski, C., Vergel, N., Guerrero, M.F., 2010. [Isovaleramide, an anticonvulsant molecule isolated from Valeriana pavonii]. Biomedica : revista del Instituto Nacional de Salud 30, 245-250.

47.   Girotto, F., Scott, L., Avchalumov, Y., Harris, J., Iannattone, S., Drummond-Main, C., Tobias, R., Bello-Espinosa, L., Rho, J.M., Davidsen, J., Teskey, G.C., Colicos, M.A., 2013. High dose folic acid supplementation of rats alters synaptic transmission and seizure susceptibility in offspring. Scientific reports 3, 1465.

48.   Grey, A., Bolland, M., 2014. Clinical trial evidence and use of fish oil supplements. JAMA internal medicine 174, 460-462.

49.   Hackett, E.S., Twedt, D.C., Gustafson, D.L., 2013. Milk thistle and its derivative compounds: a review of opportunities for treatment of liver disease. J Vet Intern Med 27, 10-16.

50.   Heo, G., Kim, S.H., Chang, M.J., 2017. Effect of ketogenic diet and other dietary therapies on anti-epileptic drug concentrations in patients with epilepsy. Journal of clinical pharmacy and therapeutics.

51.   Herwijnen, I.R.V., van der Borg, J.A.M., Naguib, M., Beerda, B., 2018. The existence of parenting styles in the owner-dog relationship. PLoS One 13, e0193471.

52.   Iffland, K., Grotenhermen, F., 2017. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. Cannabis and cannabinoid research 2, 139-154.

53.   Jackson, C.F., Makin, S.M., Marson, A.G., Kerr, M., 2015. Non-pharmacological interventions for people with epilepsy and intellectual disabilities. The Cochrane database of systematic reviews, Cd005502.

54.   James, F.E., Mansfield, C.S., Steiner, J.M., Williams, D.A., Robertson, I.D., 2009. Pancreatic response in healthy dogs fed diets of various fat compositions. American journal of veterinary research 70, 614-618.

55.   Jokinen, T.S., Tiira, K., Metsähonkala, L., Seppälä, E.H., Hielm-Björkman, A., Lohi, H., Laitinen-Vapaavuori, O., 2015. Behavioral Abnormalities in Lagotto Romagnolo Dogs with a History of Benign Familial Juvenile Epilepsy: A Long-Term Follow-Up Study. Journal of Veterinary Internal Medicine 29, 1081-1087.

56.   Kaplan, J.S., Stella, N., Catterall, W.A., Westenbroek, R.E., 2017. Cannabidiol attenuates seizures and social deficits in a mouse model of Dravet syndrome. Proceedings of the National Academy of Sciences of the United States of America.

57. Kearsley-Fleet, L., O'Neill, D.G., Volk, H.A., Church, D.B., Brodbelt, D.C., 2013. Prevalence and risk factors for canine epilepsy of unknown origin in the UK. The Veterinary record 172.

58. Kluger, E.K., Malik, R., Ilkin, W.J., Snow, D., Sullivan, D.R., Govendir, M., 2008. Serum triglyceride concentration in dogs with epilepsy treated with phenobarbital or with phenobarbital and bromide. Journal of the American Veterinary Medical Association 233, 1270-1277.

59. Kumar, H., Katyal, J., Gupta, Y.K., 2015. Low dose zinc supplementation beneficially affects seizure development in experimental seizure models in rats. Biological trace element research 163, 208-216.

60. Kverneland, M., Tauboll, E., Selmer, K.K., Iversen, P.O., Nakken, K.O., 2015. Modified Atkins diet may reduce serum concentrations of antiepileptic drugs. Acta neurologica Scandinavica 131, 187-190.

61. Larsen, J.A., Owens, T.J., Fascetti, A.J., 2014. Nutritional management of idiopathic epilepsy in dogs. Journal of the American Veterinary Medical Association 245, 504-508.

62. Law, T.H., Davies, E.S., Pan, Y., Zanghi, B., Want, E., Volk, H.A., 2015. A randomised trial of a medium-chain TAG diet as treatment for dogs with idiopathic epilepsy. The British journal of nutrition 114, 1438-1447.

63. Law, T.H., Davies, E.S., Pan, Y., Zanghi, B., Want, E., Volk, H.A., 2016. A randomised trial of a medium-chain TAG diet as treatment for dogs with idiopathic epilepsy - CORRIGENDUM. The British journal of nutrition 115, 1696.

64. Lee, S.W., Chung, S.S., 2010. A review of the effects of vitamins and other dietary supplements on seizure activity. Epilepsy & behavior : E&B 18, 139-150.

65. Li, J., O'Leary, E.I., Tanner, G.R., 2017. The ketogenic diet metabolite beta-hydroxybutyrate (beta-HB) reduces incidence of seizure-like activity (SLA) in a Katp- and GABAb-dependent manner in a whole-animal Drosophila melanogaster model. Epilepsy research 133, 6-9.

66. Liu, S.H., Chang, C.D., Chen, P.H., Su, J.R., Chen, C.C., Chaung, H.C., 2012. Docosahexaenoic acid and phosphatidylserine supplementations improve antioxidant

activities and cognitive functions of the developing brain on pentylenetetrazol-induced seizure model. Brain research 1451, 19-26.

67.   Loscher, W., 2002. Animal models of epilepsy for the development of antiepileptogenic and disease-modifying drugs. A comparison of the pharmacology of kindling and post-status epilepticus models of temporal lobe epilepsy. Epilepsy research 50, 105-123.

68.   Lujan A, S.S., Anderson TK 2004. The role of diet in refractory canine epilepsy - a retrospective case series [abstract], BSAVA Congress 2004: Scientific Proceedings. British Small Animal Veterinary Association, Quedgeley, UK, p. p. 53.

69.   Lusardi, T.A., Akula, K.K., Coffman, S.Q., Ruskin, D.N., Masino, S.A., Boison, D., 2015. Ketogenic diet prevents epileptogenesis and disease progression in adult mice and rats. Neuropharmacology 99, 500-509.

70.   Maguire, P.J., Fettman, M.J., Smith, M.O., Greco, D.S., Turner, A.S., Walton, J.A., Ogilvie, G.K., 2000. Effects of diet on pharmacokinetics of phenobarbital in healthy dogs. Journal of the American Veterinary Medical Association 217, 847-852.

71.   Manteca, X., 2011. Nutrition and behavior in senior dogs. Topics in companion animal medicine 26, 33-36.

72.   Mantis, J.G., Meidenbauer, J.J., Zimick, N.C., Centeno, N.A., Seyfried, T.N., 2014. Glucose reduces the anticonvulsant effects of the ketogenic diet in EL mice. Epilepsy research 108, 1137-1144.

73.   Marjani, M., Baghaei, P., Kazempour Dizaji, M., Gorji Bayani, P., Fahimi, F., Tabarsi, P., Velayati, A.A., 2016. Evaluation of Hepatoprotective Effect of Silymarin Among Under Treatment Tuberculosis Patients: A Randomized Clinical Trial. Iranian Journal of Pharmaceutical Research : IJPR 15, 247-252.

74.   Markovich, J.E., Heinze, C.R., Freeman, L.M., 2013. Thiamine deficiency in dogs and cats. Journal of the American Veterinary Medical Association 243, 649-656.

75.   Markowitz, G.J., Kadam, S.D., Boothe, D.M., Irving, N.D., Comi, A.M., 2010. The pharmacokinetics of commonly used antiepileptic drugs in immature CD1 mice. Neuroreport 21, 452-456.

76.   Martle, V., Van Ham, L., Raedt, R., Vonck, K., Boon, P., Bhatti, S., 2014. Non-pharmacological treatment options for refractory epilepsy: an overview of human

treatment modalities and their potential utility in dogs. Veterinary journal (London, England : 1997) 199, 332-339.

77.   Matthews, H., Granger, N., Wood, J., Skelly, B., 2012. Effects of essential fatty acid supplementation in dogs with idiopathic epilepsy: a clinical trial. Veterinary journal (London, England : 1997) 191, 396-398.

78.   Meola, S.D., Tearney, C.C., Haas, S.A., Hackett, T.B., Mazzaferro, E.M., 2012. Evaluation of trends in marijuana toxicosis in dogs living in a state with legalized medical marijuana: 125 dogs (2005-2010). Journal of veterinary emergency and critical care (San Antonio, Tex. : 2001) 22, 690-696.

79.   Mesdaghinia, A., Alinejad, M., Abed, A., Heydari, A., Banafshe, H.R., 2017. Anticonvulsant effects of thiamine on pentylenetetrazole-induced seizure in mice. Nutritional neuroscience, 1-9.

80.   Munana, K.R., 2013. Management of refractory epilepsy. Topics in companion animal medicine 28, 67-71.

81.   Munana, K.R., Nettifee-Osborne, J.A., Papich, M.G., 2015. Effect of chronic administration of phenobarbital, or bromide, on pharmacokinetics of levetiracetam in dogs with epilepsy. J Vet Intern Med 29, 614-619.

82.   Munana, K.R., Thomas, W.B., Inzana, K.D., Nettifee-Osborne, J.A., McLucas, K.J., Olby, N.J., Mariani, C.J., Early, P.J., 2012. Evaluation of levetiracetam as adjunctive treatment for refractory canine epilepsy: a randomized, placebo-controlled, crossover trial. J Vet Intern Med 26, 341-348.

83.   Muriel, P., Mourelle, M., 1990. Prevention by silymarin of membrane alterations in acute CCl4 liver damage. Journal of applied toxicology : JAT 10, 275-279.

84.   Neal, E.G., Zupec-Kania, B., Pfeifer, H.H., 2012. Carnitine, nutritional supplementation and discontinuation of ketogenic diet therapies. Epilepsy research 100, 267-271.

85.   Orlando, J.M., 2018. Behavioral Nutraceuticals and Diets. The Veterinary clinics of North America. Small animal practice.

86.   Overall, K.L., 2011. That dog is smarter than you know: advances in understanding canine learning, memory, and cognition. Topics in companion animal medicine 26, 2-9.

87.   Packer, R.M., Law, T.H., Davies, E., Zanghi, B., Pan, Y., Volk, H.A., 2016. Effects of a ketogenic diet on ADHD-like behavior in dogs with idiopathic epilepsy. Epilepsy & behavior : E&B 55, 62-68.

88.   Packer, R.M., Shihab, N.K., Torres, B.B., Volk, H.A., 2015a. Responses to successive anti-epileptic drugs in canine idiopathic epilepsy. The Veterinary record 176, 203.

89.   Packer, R.M.A., McGreevy, P.D., Pergande, A., Volk, H.A., 2018a. Negative effects of epilepsy and antiepileptic drugs on the trainability of dogs with naturally occurring idiopathic epilepsy. Applied Animal Behaviour Science 200, 106-113.

90.   Packer, R.M.A., McGreevy, P.D., Salvin, H.E., Valenzuela, M.J., Chaplin, C.M., Volk, H.A., 2018b. Cognitive dysfunction in naturally occurring canine idiopathic epilepsy. PLoS One 13, e0192182.

91.   Packer, R.M.A., Nye, G., Porter, S.E., Volk, H.A., 2015b. Assessment into the usage of levetiracetam in a canine epilepsy clinic. BMC veterinary research 11.

92.   Packer, R.M.A., Volk, H.A., Fowkes, R.C., 2017. Physiological reactivity to spontaneously occurring seizure activity in dogs with epilepsy and their carers. Physiol Behav 177, 27-33.

93.   Pan, Y., Kennedy, A.D., Jonsson, T.J., Milgram, N.W., 2018. Cognitive enhancement in old dogs from dietary supplementation with a nutrient blend containing arginine, antioxidants, B vitamins and fish oil. The British journal of nutrition 119, 349-358.

94.   Pan, Y., Larson, B., Araujo, J.A., Lau, W., de Rivera, C., Santana, R., Gore, A., Milgram, N.W., 2010. Dietary supplementation with medium-chain TAG has long-lasting cognition-enhancing effects in aged dogs. The British journal of nutrition 103, 1746-1754.

95.   Patsalos, P.N., 2000. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. Pharmacology & therapeutics 85, 77-85.

96.   Patterson, E.E., 2014. Canine epilepsy: an underutilized model. ILAR journal 55, 182-186.

97.   Paulová, J., Dvořák, M., Kolouch, F., Váňová, L., Janečková, L., 1990. Evaluation of the hepatoprotective and therapeutic effects of silymarin in liver damage experimentally produced with carbon tetrachloride in dogs. Veterinární Medicína 35, 629-635.

98.   Pearl, P.L., Drillings, I.M., Conry, J.A., 2011. Herbs in epilepsy: evidence for efficacy, toxicity, and interactions. Seminars in pediatric neurology 18, 203-208.

99.   Podell, M., 1998. Antiepileptic drug therapy. Clin Tech Small Anim Pract 13, 185-192.

100.   Podell, M., Fenner, W.R., 1993. Bromide therapy in refractory canine idiopathic epilepsy. J Vet Intern Med 7, 318-327.

101.   Pradhan, S.C., Girish, C., 2006. Hepatoprotective herbal drug, silymarin from experimental pharmacology to clinical medicine. The Indian journal of medical research 124, 491-504.

102.   Puchowicz, M.A., Smith, C.L., Bomont, C., Koshy, J., David, F., Brunengraber, H., 2000. Dog model of therapeutic ketosis induced by oral administration of R,S-1,3-butanediol diacetoacetate. J Nutr Biochem 11, 281-287.

103.   Ranganathan, L.N., Ramaratnam, S., 2005. Vitamins for epilepsy. The Cochrane database of systematic reviews, Cd004304.

104.   Rezvani, M.E., Roohbakhsh, A., Allahtavakoli, M., Shamsizadeh, A., 2010. Anticonvulsant effect of aqueous extract of Valeriana officinalis in amygdala-kindled rats: possible involvement of adenosine. Journal of ethnopharmacology 127, 313-318.

105.   Rindi, G., Laforenza, U., 2000. Thiamine Intestinal Transport and Related Issues: Recent Aspects. Proceedings of the Society for Experimental Biology and Medicine 224, 246-255.

106.   Royaux, E., Van Ham, L., Broeckx, B.J., Van Soens, I., Gielen, I., Deforce, D., Bhatti, S.F., 2017. Phenobarbital or potassium bromide as an add-on antiepileptic drug for the management of canine idiopathic epilepsy refractory to imepitoin. Veterinary journal (London, England : 1997) 220, 51-54.

107.   Rundfeldt, C., Gasparic, A., Wlaz, P., 2014. Imepitoin as novel treatment option for canine idiopathic epilepsy: pharmacokinetics, distribution, and metabolism in dogs. Journal of veterinary pharmacology and therapeutics 37, 421-434.

108.   Samara, E., Bialer, M., 1988. Pharmacokinetics of the dimethylheptyl homolog of cannabidiol in dogs. Drug metabolism and disposition: the biological fate of chemicals 16, 875-879.

109. Samara, E., Bialer, M., Mechoulam, R., 1988. Pharmacokinetics of cannabidiol in dogs. Drug metabolism and disposition: the biological fate of chemicals 16, 469-472.

110. Sarmento Vasconcelos, V., Macedo, C.R., de Souza Pedrosa, A., Pereira Gomes Morais, E., Porfirio, G.J., Torloni, M.R., 2016. Polyunsaturated fatty acid supplementation for drug-resistant epilepsy. The Cochrane database of systematic reviews, Cd011014.

111. Schwartz-Porsche, D., Loscher, W., Frey, H.H., 1985. Therapeutic efficacy of phenobarbital and primidone in canine epilepsy: a comparison. Journal of veterinary pharmacology and therapeutics 8, 113-119.

112. Scorza, C.A., Calderazzo, L., Cavalheiro, E.A., Scorza, F.A., Cysneiros, R.M., 2013. Sudden unexpected death in dogs with epilepsy: risks versus benefits of omega-3 fatty acid supplementation for man's best friend. Epilepsy & behavior : E&B 27, 508-509.

113. Scorza, F.A., Cavalheiro, E.A., Arida, R.M., Terra, V.C., Scorza, C.A., Ribeiro, M.O., Cysneiros, R.M., 2009a. Positive impact of omega-3 fatty acid supplementation in a dog with drug-resistant epilepsy: A case study. Epilepsy & Behavior 15, 527-528.

114. Scorza, F.A., Cavalheiro, E.A., Arida, R.M., Terra, V.C., Scorza, C.A., Ribeiro, M.O., Cysneiros, R.M., 2009b. Positive impact of omega-3 fatty acid supplementation in a dog with drug-resistant epilepsy: a case study. Epilepsy & behavior : E&B 15, 527-528.

115. Shaw, N., Trepanier, L.A., Center, S.A., Garland, S., 1996. High dietary chloride content associated with loss of therapeutic serum bromide concentrations in an epileptic dog. Journal of the American Veterinary Medical Association 208, 234-236.

116. Shihab, N., Bowen, J., Volk, H.A., 2011. Behavioral changes in dogs associated with the development of idiopathic epilepsy. Epilepsy & behavior : E&B 21, 160-167.

117. Sills, M.A., Forsythe, W.I., Haidukewych, D., MacDonald, A., Robinson, M., 1986. The medium chain triglyceride diet and intractable epilepsy. Archives of disease in childhood 61, 1168-1172.

118. Singh, M., Thompson, M., Sullivan, N., Child, G., 2005. Thiamine deficiency in dogs due to the feeding of sulphite preserved meat. Australian veterinary journal 83, 412-417.

119. Smeland, O.B., Meisingset, T.W., Sonnewald, U., 2012. Dietary supplementation with acetyl-l-carnitine in seizure treatment of pentylenetetrazole kindled mice. Neurochem Int 61, 444-454.

120. Snigdha, S., de Rivera, C., Milgram, N.W., Cotman, C.W., 2016. Effect of mitochondrial cofactors and antioxidants supplementation on cognition in the aged canine. Neurobiology of aging 37, 171-178.

121. Snoeijen-Schouwenaars, F.M., van Deursen, K.C., Tan, I.Y., Verschuure, P., Majoie, M.H., 2015. Vitamin D supplementation in children with epilepsy and intellectual disability. Pediatric neurology 52, 160-164.

122. Solimini, R., Rotolo, M.C., Pichini, S., Pacifici, R., 2017. Neurological Disorders in Medical Use of Cannabis: An Update. CNS & neurological disorders drug targets 16, 527-533.

123. St-Onge, M.P., Jones, P.J., 2002. Physiological effects of medium-chain triglycerides: potential agents in the prevention of obesity. J Nutr 132, 329-332.

124. Taha, A.Y., Burnham, W.M., Auvin, S., 2010. Polyunsaturated fatty acids and epilepsy. Epilepsia 51, 1348-1358.

125. Thomas, W.B., 2010. Idiopathic epilepsy in dogs and cats. The Veterinary clinics of North America. Small animal practice 40, 161-179.

126. Thurman, G.D., McFadyen, M.L., Miller, R., 1990. The pharmacokinetics of phenobarbitone in fasting and non-fasting dogs. Journal of the South African Veterinary Association 61, 86-89.

127. Torres-Hernandez, B.A., Del Valle-Mojica, L.M., Ortiz, J.G., 2015. Valerenic acid and Valeriana officinalis extracts delay onset of Pentylenetetrazole (PTZ)-Induced seizures in adult Danio rerio (Zebrafish). BMC complementary and alternative medicine 15, 228.

128. Trappoliere, M., Caligiuri, A., Schmid, M., Bertolani, C., Failli, P., Vizzutti, F., Novo, E., di Manzano, C., Marra, F., Loguercio, C., Pinzani, M., 2009. Silybin, a component of sylimarin, exerts anti-inflammatory and anti-fibrogenic effects on human hepatic stellate cells. Journal of hepatology 50, 1102-1111.

129. Trepanier, L.A., Van Schoick, A., Schwark, W.S., Carrillo, J., 1998. Therapeutic serum drug concentrations in epileptic dogs treated with potassium bromide alone or

in combination with other anticonvulsants: 122 cases (1992-1996). Journal of the American Veterinary Medical Association 213, 1449-1453.

130.   Turan, M.I., Cayir, A., Cetin, N., Suleyman, H., Siltelioglu Turan, I., Tan, H., 2014a. An investigation of the effect of thiamine pyrophosphate on cisplatin-induced oxidative stress and DNA damage in rat brain tissue compared with thiamine: thiamine and thiamine pyrophosphate effects on cisplatin neurotoxicity. Human & experimental toxicology 33, 14-21.

131.   Turan, M.I., Tan, H., Cetin, N., Suleyman, H., Cayir, A., 2014b. Effects of thiamine and thiamine pyrophosphate on epileptic episode model established with caffeine in rats. Epilepsy research 108, 405-410.

132.   Twedt, D.C., 2001. A review of traditional and not so traditional therapies for liver disease. Proceedings, 19th Annual American College of Veterinary Internal Medicine Forum, American College of Veterinary Internal Medicine, pp. 610-612.

133.   UNION, T.E.P.A.T.C.O.T.E., 2002. Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements (Text with EEA relevance), Official Journal L 183 , 12/07/2002 P. 0051 - 0057.

134.   Vandeweerd, J.M., Cambier, C., Gustin, P., 2013. Nutraceuticals for canine liver disease: assessing the evidence. The Veterinary clinics of North America. Small animal practice 43, 1171-1179.

135.   Verma, S., Thuluvath, P.J., 2007. Complementary and alternative medicine in hepatology: review of the evidence of efficacy. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 5, 408-416.

136.   Vogel, G., Tuchweber, B., Trost, W., Mengs, U., 1984. Protection by silibinin against Amanita phalloides intoxication in beagles. Toxicology and applied pharmacology 73, 355-362.

137.   Webster, C.R., Cooper, J., 2009. Therapeutic use of cytoprotective agents in canine and feline hepatobiliary disease. The Veterinary clinics of North America. Small animal practice 39, 631-652.

138. Wells, R.E., Phillips, R.S., Schachter, S.C., McCarthy, E.P., 2010. Complementary and alternative medicine use among US adults with common neurological conditions. Journal of neurology 257, 1822-1831.

139. Wessmann, A., Volk, H.A., Packer, R.M., Ortega, M., Anderson, T.J., 2016. Quality-of-life aspects in idiopathic epilepsy in dogs. The Veterinary record 179, 229.

140. Wessmann, A., Volk, H.A., Parkin, T., Ortega, M., Anderson, T.J., 2014. Evaluation of quality of life in dogs with idiopathic epilepsy. J Vet Intern Med 28, 510-514.

141. Whiting, P.F., Wolff, R.F., Deshpande, S., et al., 2015. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 313, 2456-2473.

142. Widenhorn-Muller, K., Schwanda, S., Scholz, E., Spitzer, M., Bode, H., 2014. Effect of supplementation with long-chain omega-3 polyunsaturated fatty acids on behavior and cognition in children with attention deficit/hyperactivity disorder (ADHD): a randomized placebo-controlled intervention trial. Prostaglandins Leukot Essent Fatty Acids 91.

143. Wijnen, B.F., de Kinderen, R.J., Lambrechts, D.A., Postulart, D., Aldenkamp, A.P., Majoie, M.H., Evers, S.M., 2017. Long-term clinical outcomes and economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy. Epilepsy research 132, 91-99.

144. Winter, J., Packer, R.M.A., Volk, H.A., 2018. Preliminary assessment of cognitive impairments in canine idiopathic epilepsy. Veterinary Record.

145. Yuen, A.W., Flugel, D., Poepel, A., Bell, G.S., Peacock, J.L., Sander, J.W., 2012. Non-randomized open trial of eicosapentaenoic acid (EPA), an omega-3 fatty acid, in ten people with chronic epilepsy. Epilepsy & behavior : E&B 23, 370-372.

146. Yuen, A.W., Sander, J.W., 2012. Can magnesium supplementation reduce seizures in people with epilepsy? A hypothesis. Epilepsy research 100, 152-156.

147. Yuen, A.W., Sander, J.W., Fluegel, D., Patsalos, P.N., Bell, G.S., Johnson, T., Koepp, M.J., 2005. Omega-3 fatty acid supplementation in patients with chronic epilepsy: a randomized trial. Epilepsy & behavior : E&B 7, 253-258.

148. Zera, K., Zastre, J., 2017. Thiamine deficiency activates hypoxia inducible factor-1alpha to facilitate pro-apoptotic responses in mouse primary astrocytes. PLoS One 12, e0186707.

149.   Zupec-Kania, B., Zupanc, M.L., 2008. Long-term management of the ketogenic diet: seizure monitoring, nutrition, and supplementation. Epilepsia 49 Suppl 8, 23-26.

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.
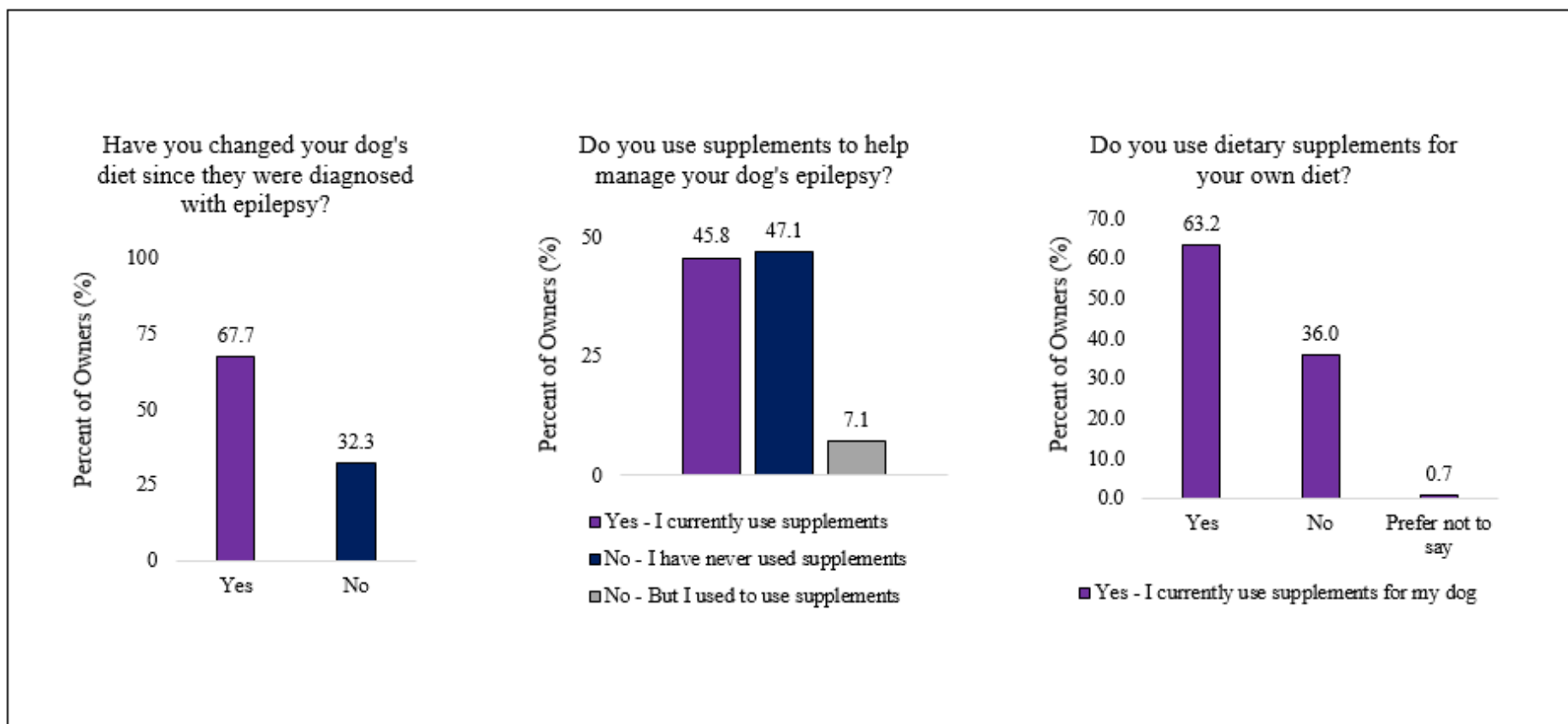
Figure 2: Types of DS in use for Epilepsy Management – Almost every second owner give DS to manage their dog`s epilepsy from the nutritive side. The distribution scaled in percent of owners (%) about used DS types highlight the main use of oil DS. Every two out of three epileptic dogs under dietary supplementation 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.

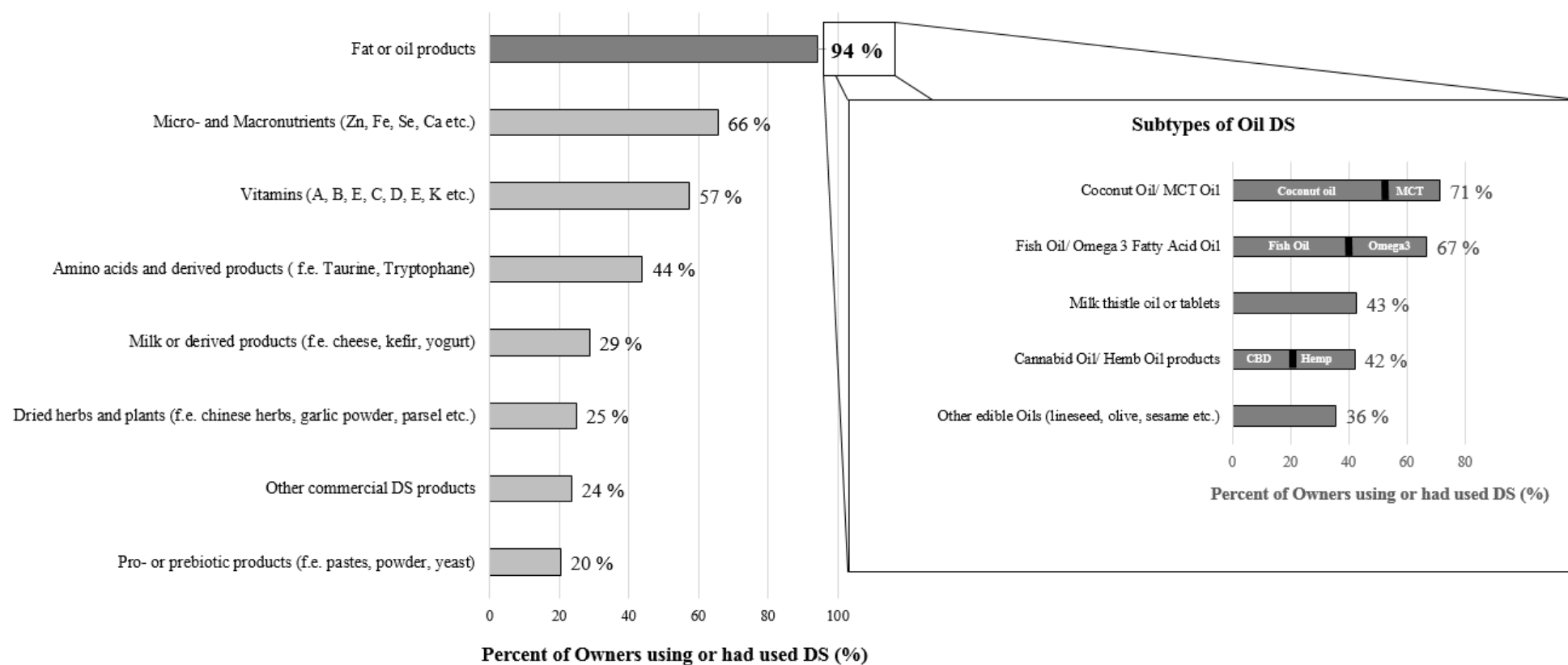Types of Dietary Supplements in Use for Epilepsy Management in Dogs

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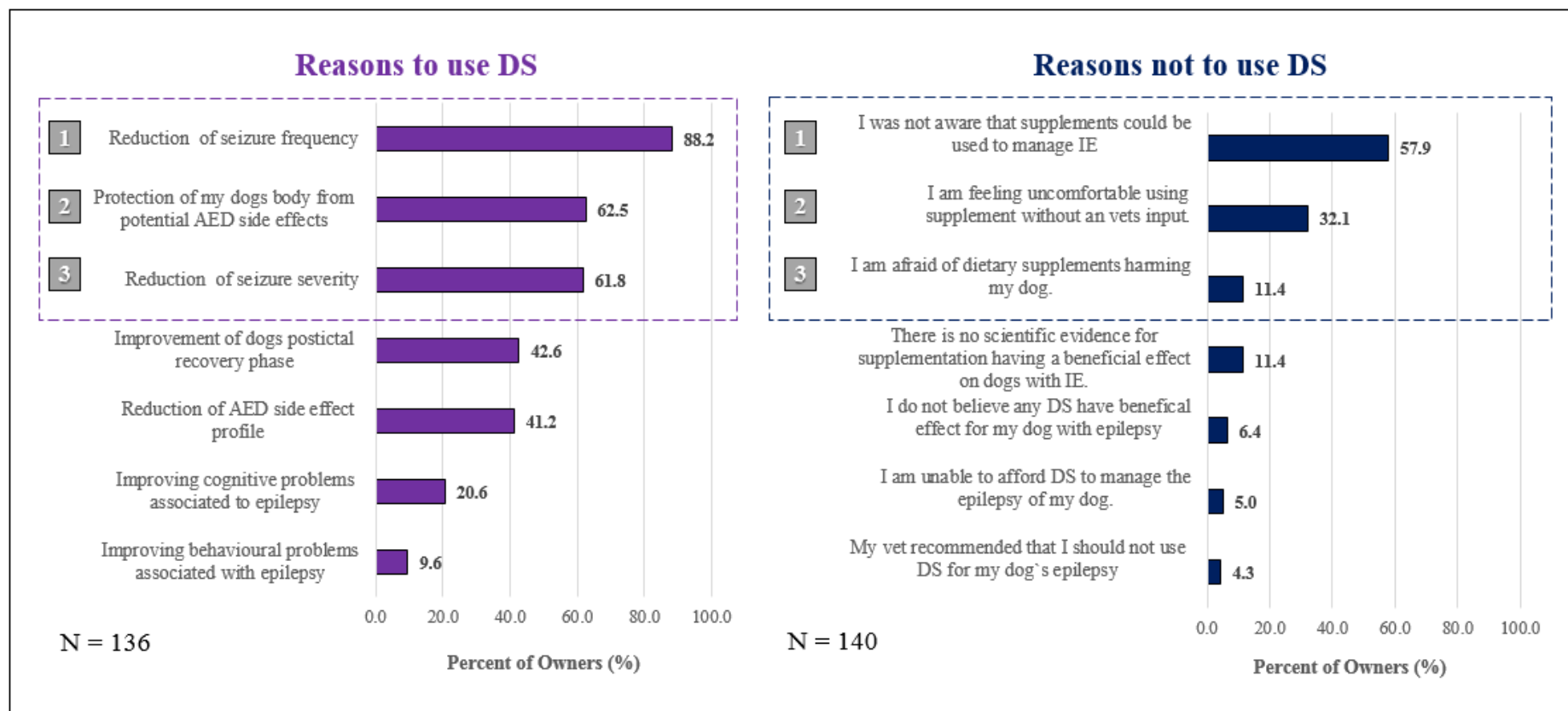
Figure 4: Owner`s reasons to stop using DS as additional management for their dog`s epilepsy – A small portion of the study population stopped to administer DS in the past. The reasons why they quitted nutritive supplementation are summarized as bar chart in percent of owners.

Reasons to stop use of DS

Reason	Percent
I do not believe it had any benefical effect.	33.3
My dog refused to be given DS.	9.5
I was unable to afford DS to manage the epilepsy of my dog any longer.	9.5
I was afraid of it harming my dog/	9.5
The DS had a negative impact on my dog`s health.	4.8
I felt uncomfortable using DS without an input by my vet.	4.8
There is no scientific evidence for supplementation having a beneficial effect on dogs with IE.	4.8

N = 21

Percent of Owners (%)