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ORIGINAL RESEARCH

Efficacy of medium chain triglyceride oil dietary supplementation in reducing seizure frequency in dogs with idiopathic epilepsy without cluster seizures: a non-blinded, prospective clinical trial

Jenifer Molina,[1] Clementine Jean-Philippe,[2] Lisa Conboy,[2] Sonia Añor ,[3] Cristian de la Fuente,[3] Marcin Adam Wrzosek,[4] Andrea Spycher,[5] Eva Luchsinger,[6] Bettina Wenger-Riggenbach,[7] Patricia Montoliu,[8] Gualtiero Gandini,[9] Marika Menchetti,[9] João Carlos Ribeiro,[10,11] Artur Varejão,[12,13] Antonio Ferreira,[14] Brian Zanghi ,[15] Holger Andreas Volk[16,17]

Abstract

Background Despite appropriate antiseizure drug (ASD) treatment, around two-thirds of dogs with idiopathic epilepsy (IE) have seizures long-term and 20–30per cent of affected dogs remain poorly controlled.

Methods The current study aim is to test in a field trial the efficacy and tolerability of a commercially available diet enriched with 6.5per cent medium chain triglyceride (MCT) oil in dogs (n=21) with at least a tier 1 idiopathic epilepsy diagnosis, without cluster seizures, in 10 veterinary practices across Europe. Each dog's quality of life (QoL), ataxia, sedation and frequency and severity of seizures were recorded by owners throughout the study.

Results The mean seizure frequency per month, averaged over the entire 84-day study, significantly (P=0.04) decreased 32per cent compared with the baseline monthly seizure frequency recorded during the month immediately before feeding the diet. Similarly, the seizure days rate (days/month) also declined (P<0.001) by 42per cent. QoL was reported as very good to excellent (>8.5/10) in 20 of the 21 dogs before starting the diet and this remained unchanged during the trial.

Conclusions This study demonstrates the use of a diet enriched with MCTs as an adjunct to ASD treatment may have some antiseizure properties for dogs diagnosed with IE, as demonstrated in previous studies.

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[1]Technical Communications, Nestlé Purina PetCare EMENA, Barcelona, Spain
[2]Regulatory and Scientific Affairs, Nestlé Purina, Lausanne, Switzerland
[3]Animal Medicine and Surgery, Universitat Autonoma de Barcelona, Bellaterra, Barcelona, Spain
[4]Department of Internal Diseases, Uniwersytet Przyrodniczy we Wroclawiu, Wroclaw, Poland
[5]Tierarztpraxis Bärn West GmbH, Bern, Switzerland
[6]Tierarztpraxis DUOVet AG, Säriswil, Switzerland
[7]Bessy's Kleintierklinik AG, Watt, Switzerland
[8]Neurology, Ars Veterinaria, Barcelona, Barcelona, Spain
[9]Department of Veterinary Medical Sciences, University of Bologna, Ozzano Emilia, Italy
[10]Referência Veterinária, Alcabideche, Portugal
[11]Faculdade de Medicina Veterinaria da Universidada, Lisboa, Portugal
[12]Department of Veterinary Sciences, University of Trás-os-Montes e Alto Douro, Vila Real, Portugal
[13]Centre for Animal Sciences and Veterinary Studies, University of Trás-os-Montes e Alto Douro, Vila Real, Portugal
[14]Clinics, Faculty of Veterinary Medicine, University of Lisbon, Lisbon, Portugal
[15]Global Nutrition and Communications, Nestle Purina PetCare, St. Louis, United States
[16]Veterinary Clinical Sciences, Royal Veterinary College, Hatfield, UK
[17]University of Veterinary Medicine, Hannover, Germany

E-mail for correspondence: Dr Brian Zanghi, Nestle Purina PetCare Co, Saint Louis, MO 63164, USA; brian.zanghi@rd.nestle.com

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Introduction

Epilepsy is a common, chronic neurological disease affecting between 0.5per cent and 0.75per cent of dogs in the general population with a higher prevalence in some at-risk breeds.[1–4] Epilepsy is defined as two

or more unprovoked epileptic seizures occurring at least 24 hours apart.[5 6] Idiopathic epilepsy (IE) is the most common form and can be a serious condition in dogs stemming from underlying genetic abnormalities especially in specific dog breeds, but also occurs where the underlying cause could not be identified.[1–4 7] Unfortunately, IE not only affects the pet's general health, but also quality of life (QoL).[8–16] A recent review paper highlighted that dogs with epilepsy are at risk not only for reduced QoL but also quantity of life.[8] QoL can be considered diminished in some epileptic dogs, as similarly experienced by people, with the development of comorbidities such as anxiety, hyperactivity disorders, cognitive impairments and antiseizure drug (ASD) side effects.[9–17] QoL of owners of epileptic dogs can also be reduced due to worries about their dog's health and limitations in lifestyle to accommodate their epileptic pet.[18]

The disease in many cases has an early onset (with most dogs having their first seizure between one and three years of age) and is generally lifelong, typically requiring long-term use of ASDs,[19–21] with the aim of reducing seizure frequency and severity.[22] Unfortunately, 20–40per cent of patients do not respond adequately to medical management,[22] which can impact QoL. From a medical perspective, a reduction in seizure frequency of at least 50per cent is commonly considered a successful treatment.[8] For these reasons, there is great interest in finding alternative and/or adjunct treatments for canine IE.

Dietary support has long been used in seizure management in people and a recent review[23] describes how metabolic dysregulation appears to increase the probability of sporadic seizure activity. As early as the 1920s, it was noted that epileptic children experienced a reduction in seizure frequency when they were fasted.[24] In order to mimic the metabolic changes associated with fasting, ketogenic diets have been used with some success in epileptic people. One study showed that children with epilepsy put on a traditional ketogenic diet (high fat, low carbohydrate, low protein—starting at a 2:1 ratio—fat:protein and carbohydrate—and gradually increasing to a 3:1 or 4:1 ratio over 1–2 weeks, as tolerated) had significant seizure reduction compared with children on a control diet. The 38 per cent of children had >50 per cent seizure reduction and 7 per cent children had more than 90 per cent reduction in seizures (compared with 5 per cent and 0 per cent, respectively of children fed the control diet).[25] Dietary change is highly relevant to owners of epileptic dogs with a very recent survey containing 257 valid responses, two-thirds of owners (67.7 per cent) reported changed their dog's diet after receiving an IE diagnosis. Nearly half of the owners (45.8 per cent) reported giving dietary supplements, the most common being coconut oil or derived medium chain triglyceride (MCT) oil (71.3 per cent).[26]

More recently, a diet based on inclusion of MCTs was evaluated in epileptic dogs.[27] Although the exact mechanism of action of MCTs is not fully known, proposed mechanisms include provision of an alternative energy supply to the brain (energy metabolism is insufficient in epileptic dogs), global changes in lipid metabolism and effects on cerebral neurotransmitters.[28–32] The randomised, placebo-controlled, double-blinded, crossover study revealed that most dogs fed the test diet (containing MCT oil) for 90 days showed a reduction in seizure frequency.[27] In this study, 71 per cent of dogs experienced reduced seizure frequency, with 48 per cent having a ≥50 per cent reduction in seizure frequency and 14 per cent of dogs achieving complete seizure freedom. The positive effect of an MCT-enriched diet was also highlighted in a recent study comparing an MCT oil dietary supplement to a control oil (olive oil) in 28 dogs with IE being treated with standard ASD(s).[33] Overall seizure and seizure-day frequency were significantly lower in dogs that had the MCT oil dietary supplement added to their routine diet compared to dogs that had the control oil added to their food. Similar to the study by Law and others, 2015, 71 per cent of dogs improved, and 18 per cent had more than 50 per cent reduction in seizure frequency, although only 8 per cent became seizure free.[33]

Over recent years, it has become apparent that the mechanism of action of the traditional ketogenic diets, as well as diets containing MCTs, goes beyond ketone production.[34] Medium chain fatty acids are efficient in crossing the blood-brain barrier,[35] unlike long chain fatty acids, and can be directly oxidised in the brain.[36] In rats ketogenic diets may increase mitochondrial function and brain energy reserves.[37] In addition, an MCT diet has been shown to dramatically increase mitochondrial function in dogs,[38] and also to increase metabolic synthesis of polyunsaturated fatty acids (PUFA) and their uptake in the canine brain tissue.[39] Interestingly, MCTs and their downstream metabolites are thought to have multiple affects in the brain.[25 34] Recent studies have revealed that decanoic acids (C10) can act as a non-competitive AMPA receptor antagonist resulting in direct inhibition of excitatory neurotransmission, and thus exerts an anticonvulsant effect.[40] Furthermore, C10 on its own might be able to modulate mitochondrial proliferation via peroxisome proliferator-activated receptor gamma receptor.[41]

Cluster seizures are known to be a risk factor for drug-resistant epilepsy.[42] The two aforementioned canine clinical studies[27 33] had a high proportion of dogs with cluster seizures. [42]Thus, in the current investigation it was determined that including a high proportion of dogs with cluster seizures could potential bias the results regarding the diet effect. No study had formerly looked at the effect of MCTs on a population of dogs without cluster seizures. Hence, the effect was assessed in this subpopulation of patients. The objective of this

Table 1 Nutrient composition of the diet (as fed basis)

Nutrient	Value
Moisture (%)	7.5
Crude fat (%)	15.0
Crude protein (%)	30.0
Carbohydrates (%)	38.5
Crude fibre (%)	1.5
Crude ash (%)	7.5
Chloride (%)	0.8
Vitamin E (IU/kg)	519
Arginine (%)	2.2
Selenium (mg/kg)	0.46
EPA+DHA (%)	0.4
MCT oil (%)*	6.5
Energy value (kcal/g)	3.7

*MCT oil 6.5% added to the recipe (as is).
DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MCT, medium chain triglyceride.

prospective study was therefore to test the efficacy, palatability and tolerability of a commercially available diet enriched with 6.5 per cent MCT oil in dogs diagnosed with IE with single seizures across Europe. This study will further clarify the role of nutrition in epilepsy management.

Materials and methods

A prospective open-label, single-arm food study with no placebo was carried out across Europe (France, Italy, Poland, Portugal, Spain and Switzerland) with 10 veterinary practices. Study protocol was designed and followed in strict accordance with the guidelines established by the Nestlé Purina PetCare Animal Care and Use Advisory Committee. All dogs were privately owned and were enrolled only after owner consent was obtained. The aim of the study was to investigate the efficacy and tolerability of a commercially available veterinary prescription-based diet containing 6.5 per cent of MCT oil (Purina Pro Plan NC NeuroCare, Nestlé Purina, St. Louis Missouri, USA) for the management of dogs diagnosed with IE. Proximate analyses results of the diet are listed in table 1.

Twenty-two dogs diagnosed with IE, which had no reported events of cluster seizures, were recruited and included in the trial based on multiple criteria; aged between 12 months (small and medium dogs)/18 months (large dogs) and 12 years old, with a maximum bodyweight (BW) of 50 kg and with a tier 1 IE diagnosis.[43] In addition, dogs must have experienced at least three seizures in the three months before inclusion and must have been treated with at least one antiepileptic drug for a minimum of one year before inclusion. Finally, pet owners must have been in full agreement to their dogs taking part in the study.

Dogs were not included in the study if they had another identifiable cause of their seizures (eg, brain neoplasm, brain trauma, etc), were experiencing cluster seizures (more than one seizure per day), had concomitant diseases such as liver, kidney or heart conditions or had surgery in the month before inclusion (or if surgery was planned during the study period). Pregnant or lactating females and dogs over 50 kg were also excluded from the study.

The breed, gender, age, diet and lifestyle of each dog were recorded during the inclusion appointment. A full history was taken including seizure frequency during the past 30 days to establish baseline monthly seizure rate, concomitant disease and treatments given. Dogs accepted into the trial had an initial clinical examination including body condition score (BCS) assessed using a 9-point scale,[44] BW, rectal temperature and general health status evaluation. Owner evaluations were made of the dog's QoL, ataxia, sedation and frequency and severity of seizures using a visual analogue scale as previously described[27] (see online supplementary figure 1). Dogs being treated with phenobarbital and/or potassium bromide (KBr) had blood collected during the inclusion appointment five hours after the ASD administration to monitor serum drug concentrations.

Owners who gave permission for their dog to participate in the study, were requested to change their dog onto the study diet (Purina Pro Plan NC NeuroCare) gradually over a seven-day period so that by day 7 the dogs were eating 100 per cent of the recommended amount of the study diet and nothing else other than free-access water to drink. The feeding amount was initially advised as described per the product label feeding instruction, with daily amounts determined according to metabolic energy requirements calculated according to the European Pet Food Industry Federation (FEDIAF) recommended energy equation of 110 $kcal \times BW^{0.75}$. Each clinician had the liberty to adjust daily recommended portion based on individual pet's home climate conditions, the pet's physical activity and physical health condition. Depending on the BW and animal health status in the first month visit, the amount was adjusted to ensure the BW and BCS maintenance. Daily feeding frequency (once or multiple meals daily) was at the discretion of the pet owner. Purina Pro Plan NC NeuroCare was recommended to be provided as treats or snacks.

Follow-up visits were performed at day 28, 56 and 84. At each follow up visit, a clinical examination (including BCS, BW, rectal temperature and general health status evaluation) was performed, as well as the ASD dose administered and its possible side effects were recorded. The owners also evaluated the dog's QoL, ataxia, sedation and diet consumption, as well as frequency and severity of seizures along with global evaluation of the diet's efficacy and tolerance each month as described previously.[27] Throughout the study, owners were also asked to record days when their dog experienced a seizure and number and duration of seizures experienced during that day. Similar to day 0 visit, dogs being treated with phenobarbital and/or KBr had blood collection five

Table 2 Pet-specific demographics, antiepileptic drug treatment, bodyweight, relative test food ingestion and seizure data

Case	Breed	Age (years)	Sex*	Medical treatment†	Day 0 bodyweight (kg)	Average % food consumed over trial	Number of seizure days/month			Seizure frequency/month		
							Baseline	End of trial	% change	Baseline	End of trial	% change
1	Cocker spaniel	6	F	PKBr	13.4	100	5	0.00	−100.0	5	0.00	−100.0
2	Mixed setter	5	SF	PI	7.5	60	1	0.00	−100.0	1	0.00	−100.0
3	Mixed breed	3.5	SM	P	47	100	6	0.67	−88.9	6	0.67	−88.9
4	Dachshund	6	SM	PKBr	6.1	100	3	0.67	−77.8	3	0.67	−77.8
5	Dachshund	10	M	PKBr	12.9	100	5	1.33	−73.3	5	1.67	−66.7
6	Beagle	7	M	I	15.7	100	1	0.33	−66.7	1	0.33	−66.7
7	Crossed Griffon	8	SM	I	18	100	2	0.67	−66.7	2	0.67	−66.7
8	Mixed breed	4	M	P	25.8	80	3	1.00	−66.7	3	1.00	−66.7
9	Labrador retriever	6	M	PKBr	39	100	2	1.00	−50.0	2	1.00	−50.0
10	Belgian shepherd	4.5	SF	P	30	100	3	1.67	−44.4	3	1.67	−44.4
11	Giant schnauzer	6	SM	PKBr	38.9	100	4	2.33	−41.7	4	2.33	−41.7
12	Poodle	9	M	I	6.6	83	1	0.67	−33.3	1	0.67	−33.3
13	Crossbreed	9	F	I	7.5	83	1	0.67	−33.3	1	0.67	−33.3
14	Labrador retriever	4	F	I	32.5	100	1	0.67	−33.3	1	0.67	−33.3
15	Crossbreed	8	F	PL	15.7	100	1	0.67	−33.3	1	0.67	−33.3
16	Labrador retriever	2	M	PI	34	50	2	1.67	−16.7	2	1.67	−16.7
17	English setter	3	SM	PL	23.2	93	3	3.00	0.0	3	3.00	0.0
18	Shih Tzu	6	M	PLT	12	97	3	3.00	0.0	3	3.33	11.1
19	Crossbreed	5	M	P	19.5	90	3	3.00	0.0	3	6.67	122.2
20	Crossbreed	5	M	P	34	90	2	2.33	16.7	2	2.67	33.3
21	Irish setter	7	M	PLT	38	100	1	3.67	266.7	1	4.67	366.7

*Sex and intact status.
F, female; I, imepitoin; KBr, potassium bromide; L, levetiracetam; M, male; P, phenobarbital; S, sterile; T, topiramate.

hours after the ASD administration to monitor serum drug concentrations.

At the end of the study period (12 weeks), records were taken on the pet owner's perception of the palatability and effectiveness of the food and whether or not they would recommend it for use by other epileptic dogs. The participating veterinarians were asked to also record whether or not they would recommend the dog to continue on the test diet for long term.

Statistical analysis

Data were analysed using R lme4 software package.[45] All analyses were conducted using R (V.3.2.1, accessed September 26, 2017).[46] The dog was considered the experimental unit for all analyses. To compare the BW, BCS and seizure frequency between the starting point and the day 84 (end of study), a Wilcoxon rank-sum statistical test (non-parametric paired test) was performed. Seizure frequency refers to the number of seizures per month, and seizure day rate refers to the number of days in a month with seizure occurrence. A P value <0.05 was considered to be statistically significant.

Results

Data were collected from 22 dogs (table 2) including 11 pure breeds (dachshund, Belgian shepherd, English setter, cocker spaniel, poodle, Labrador retriever, giant schnauzer, beagle, Maltese, Irish setter, Shih Tzu), and 11 mixed breed dogs table 2. A single dog (5.5 years old, female Maltese) was removed from the analysis because of lack of test food ingestion (60 per cent of ration during month two: 0 per cent of ration during month 3). Of the remaining 21 dogs, the median age was 5.7 years old (range: 2–10 years) and the gender distribution was 5 (23.8 per cent) entire females, 2 (9.5 per cent) spayed females, 10 (47.6 per cent) entire males and 5 (23.8 per cent) neutered males. No significant difference was observed for BW (P=0.269) and BCS (P=0.500) change during the trial period (table 3).

Of the 21 dogs, 14 dogs continued to only have single seizure events on a given day during the entire test period, whereas 5 dogs experienced either 1 or 2 cluster seizures, and 2 dogs had no seizures observed. Acceptance of the food was good (>70 per cent of ration) to excellent (100 per cent of ration) in 19 out of the 22 dogs in the first month and throughout the remainder of the test period.

Table 3 Effect of the diet in all dogs (n=21) and only dogs that experienced single seizure events per day (n=16) for each of the measurements (mean±se) between baseline and the end of the study

Parameter	N	Baseline	End of study	Wilcoxon rank-sum statistical test p value
BW (kg)	21	22.6 (±2.7)	22.0 (±2.6)	0.26
BCS	19	5.4 (±0.3)	5.2 (±0.3)	0.75
N° of seizure days/month	21	2.5 (±0.3)	1.4 (±0.2)	‹0.0001
Total n° of seizures/month	21	2.5 (±0.3)	1.7 (±0.4)	0.04
BW (kg)	16	22.3 (±3.3)	21.8 (±3.2)	0.27
BCS	14	5.3 (±0.4)	5.1 (±0.4)	0.50
N° of seizure days/month	16	2.4 (±0.4)	1.0 (±0.2)	‹0.0001
Total n° of seizures/month	16	2.4 (±0.4)	1.0 (±0.2)	‹0.0001

BCS, body condition score; BW, bodyweight; n°, number.

As a result of feeding the diet for 84 days, the mean seizure day rate significantly declined (P=0.002) by 42 per cent (1.4 seizure days/month; median=1.0) compared with the baseline (2.5 days/month; median=2.0) (table 3). At baseline, seizure days/month ranged from a minimum of one to a maximum of six, whereas after the diet phase it ranged from 0 to a maximum of 3.67 days/month. Of the 21 dogs, 9.5 per cent (2 of 21 dogs) became seizure free, 42.9 per cent of dogs (9 of 21 dogs) had ≥50 per cent reduction in seizure days and 33.3 per cent (7 of 21 dogs) had <50 per cent reduction. In addition, three dogs (14.2 per cent) had no change, whereas two dogs (9.5 per cent) had an increase in seizure days. Overall, 16 of 21 dogs (76.2 per cent) experienced fewer seizure days with the test diet.

For total seizure frequency, feeding the diet resulted in a 32 per cent decline (P=0.04) (1.7 seizures/month: median=1.0) compared with baseline (2.5 seizures/month; median=2.0; table 3). Generally similar to seizure day rate, the relative proportion of dogs that became seizure free was 9.5 per cent (2 dogs), 42.9 per cent had ≥50 per cent reduction (9 dogs) and 33.3 per cent (7 of 21 dogs) had <50 per cent reduction. One dog (4.8 per cent) had no change and four dogs (19.0 per cent) had an increase in seizure frequency. Overall, 16 of 21 dogs (76.2 per cent) experienced a lower seizure frequency with the test diet.

After reviewing the seizure data for each dog, five dogs had experienced at least one cluster seizure during the trial phase. Of these five dogs, there was no apparent pattern in the occurrence of the cluster seizures while on the test diet. A post hoc statistical analysis was performed that excluded the five dogs that experienced cluster seizures at some point during the treatment period (table 3) because the aim of the study was to especially study its effects on dogs with single seizures. The mean seizure day rate (1.0 seizure days/month) for the test phase significantly (P<0.001) declined by 58 per cent compared with the baseline seizure day rate (2.4 days/month) for 16 non-cluster seizure dogs. None of these 16 dogs had any worsening of seizure day rate or seizure frequency (0 per cent) and 12.5 per cent of dogs (2 of 16) were seizure-free throughout the entire 84-day feeding trial. Overall, 87.5 per cent of dogs (14 of 16) had greater than a 33 per cent reduction in seizure days and seizure frequency, with 50.0 per cent of dogs (8 of 16) experiencing greater than a 50 per cent reduction in seizures. Only two dogs (12.5 per cent) had either no change or a 17 per cent reduction in number of seizures.

Dogs were being treated with a variety of ASDs. Fourteen out of 21 dogs were being treated with phenobarbital (range 18.1–36.3 µg/mL) either alone or combined with KBr (range 280–866 mg/dL), levetiracetam or imepitoin. In addition, five dogs were being treated with imepitoin alone. Two dogs were treated with a combination of phenobarbital, levetiracetam and topiramate. Serum concentrations of phenobarbital, with or without KBr, were reported for 9 of 21 dogs. For those dogs, serum concentrations were unchanged at the end of the study compared with baseline.

QoL was reported as excellent (10/10) at the start of the study in 17 of the 21 dogs. In three dogs, the QoL was reported as very good, starting with a minimum of 8.5/10. One dog was initially reported as poor (2/10), but was reported as 10/10 throughout the entire test phase, which coincidently was a cluster seizure dog that had a 67 per cent reduction in seizure rate. The majority of dogs (17/21) maintained the same level of QoL during the study.

Regarding the ataxia level, three owners reported mild ataxia (1/10 or 3/10) at day 0, two of which improved during the study (ataxia level of 0/10 or 1/10 at day 84, respectively). One dog remained unchanged over the trial (3/10). Sedation was reported in 6 out of 21 dogs at day 0. Two dogs had a sedation level of 5/10, four had a level of ≤2/10. At the end of the study (day 84), three dogs decreased the level of sedation, and three remained in the same level.

Finally, pet owner survey results indicated that 21 of 21 owners (100 per cent) would recommend the diet for epileptic dogs. Of the veterinarians that responded to the survey, 19 (90 per cent) would recommend the diet for epileptic dogs, 1 would not and 1 did not provide an answer.

Discussion

To expand the veterinary management options for canine patients with ASD treated IE, a commercially available diet enriched with 6.5 per cent MCT oil (as fed basis) plus a blend of other nutrients was offered to pet owners as an open-label feeding trial to prospectively evaluate seizure outcomes resulting from dietary management as an adjunct to ASD treatment. This study builds on existing canine research that demonstrated the clinical efficacy of a diet enriched with MCT oil in two double-blinded, placebo-controlled, prospective diet clinical trial with a population of ASD(s)-resistant IE dogs.[27,33] In the study by Law and others, the diet contained 5.5 per cent MCT oil (as fed basis) compared with 6.5 per cent added MCT oil in this current study. Previous unpublished work from Nestlé Purina revealed that ketone production is dose-dependently increased with MCT inclusion. However practically, the inclusion level of 9 per cent MCT oil (as fed basis) to a diet has limitations because of reduced palatability observations, as demonstrated in a study of the benefits of an MCT oil-enriched food fed to dogs with canine cognitive dysfunction syndrome.[47]

Similarly, this compilation of case studies revealed that nearly 10 per cent of the study population (2 of 21) became seizure free while on the commercial diet. This is similar to previous observations in which 14

per cent of dogs (3 of 21) were seizure free when fed a diet containing 5.5 per cent MCT oil, but experienced seizures when fed the placebo food absent of MCTs.[27] Furthermore, this current data revealed a similar response rate of participants (42.8 per cent; 9 of 21 dogs) to achieve >50 per cent seizure reduction (frequency and seizure day rate) when compared with the study population reported by Law and others, in which 47.6 per cent (10 of 21 dogs) achieved >50 per cent reduction in seizure frequency and 38.0 per cent (8 of 21) achieved >50 per cent reduction in seizure day rate. A more recent study used the direct supplementation of an MCT oil performed by the pet owner by adding on top and mixed in with their dog's existing diet.[33] This MCT oil supplement trial included 28 dogs with IE and were provided supplementation equivalent to 9 per cent MCT oil as metabolic energy calculated. Most notable from this study was that only 18 per cent of the 28 dogs achieved more than 50 per cent seizure reduction or seizure freedom.[33]

The observations of dietary effect of seizure reduction reported here are statistically significant. Although, it is reasonable to consider important limitations to these results, as the number of animals involved in the study were not a large number of observations and around 30 per cent of the effect seen could possibly be due to the placebo,[47] regression to the mean, or Hawthorne effects. However, this multicentre field study does confirm two former placebo-controlled, double-blinded studies described above,[27 33] and the diet was well tolerated by most dogs, with 90 per cent of participating vets and 100 per cent of owners recommending to continue with the diet. It is also important to consider that there was an improvement in QoL and some of the side effects related to ataxia and sedation. From the five dogs that experienced the onset of cluster seizures during the study period, the authors can remark that two of them decreased the number of seizures during the study, one showed no effect and the other two increased the number of seizures compared with day 0. In addition, there was no obvious trend on when these cluster seizures were observed during the diet phase, as two dogs had clusters during month two, whereas three dogs had clusters in month three. Ultimately, this study demonstrates that there was a similar significant seizure reducing effect for IE dogs with single seizures, as well as for some dogs experiencing cluster seizures, as previously described in the other aforementioned published studies. In addition, these case studies confirm previous studies of feeding an MCT oil containing diet to dogs with IE is safe and tolerable, and with the available data, no change in ASD blood levels were recorded (data available from nine dogs) throughout the study.

This study differed in several distinguishing aspects from the former aforementioned studies and does have some additional limitations worth noting. The first notable distinguishing factor is that multiple first-opinion veterinary clinics participated in the recruitment and management of the patients that spanned over five different countries across Europe, whereas the other study[27] was performed in a single referral hospital setting and conducted entirely through the Royal Veterinary College Clinical Investigation Center referral hospital in the UK. Secondly, the level of MCT oil (6.5 per cent) differed relative to other studies referenced above. Thirdly, the recruited pet population was focused on a less severe type of IE with tier 1 diagnosis. And finally, to obtain clinically relevant data acquired by collaborating vets and their clients, the data represent a compilation of case studies, and consequently did not have a placebo-controlled arm of the experimental design. A reasonable limitation underlying this study is based on the utilisation of an unblinded diet treatment experimental design that could impart a bias on the study participants, as well as because of recent reports of placebo effects. Many studies on epilepsy were designed to evaluate for a positive response to therapy, which is defined as a ≥50 per cent reduction in seizures.[48 49] In one study which combines the results from three placebo-controlled trials, a large proportion of dogs with IE responded to placebo alone, with an approximately 30 per cent reduction in seizures following placebo administration.[48] However, the dogs in the placebo group were on conventional ASD therapy that could have affected the results and outcome. This placebo response has been attributed to the regression to the mean effect, the natural waxing and waning course of epilepsy over time, the likelihood for improved patient care during participation in the trial and investigator and participant bias.[48] The presence of the strong placebo effect found in that report suggests that results from non-blinded studies, particularly those that involve a small number of animals and short follow-up time should be interpreted with some caution.

A further limitation to this study is the incomplete collection of blood samples for ASD monitoring from all dogs at both prefeeding and postfeeding time point, leaving open the fact that the authors could not clearly demonstrate ASD concentrations in the blood remained unchanged in all dogs throughout the study period. However in a previous clinical assessment of feeding a diet containing MCT oil to epileptic dogs, ASD levels were measured.[27] The ASD treatment regimens of the dogs remained the same between the placebo and MCT diet phases. There were no significant changes in serum concentrations of phenobarbital (P=0.423) or KBr (P=0.300) between the placebo-standardised diet and MCT diet, respectively. Given that approximately 50 per cent (10 out of 21) of the dogs here showed no change in serum ASD level, and the prior findings by Law and others, the authors would expect ASD serum concentrations in the other dogs were not altered. A final limitation is that chloride content of the previous diets from the six pets receiving KBr treatment was

not specifically measured before starting the trial to specifically assess if therapeutic levels would be altered. However, for consistency across the study and consistency to previous clinical trials, all ASD regimens for all dogs were to remain unchanged throughout the study. It is also important to note that Purina Pro Plan NC NeuroCare has a chloride level of 0.20 g/100 kcal. Although the authors do not have the information of the chloride level for the pretrial diets fed to the six dogs receiving KBr in the study, by estimating that maintenance diets may likely contain chloride levels around 0.13–0.22 g/100 kcal, but could be as low as the minimum requirement of 0.03 g/100 kcal (American Association of Feed Control Officials, 2018). Thus, the test diet is at the high end of that range and consequently would have justified a potential elevation in KBr but would have confounded any observed diet effect.

The mechanism by which an MCT-enriched diet provides clinical efficacy for some patients remains unclear, but it is likely a multifactorial modality that is underlying its effectiveness, such that MCTs and/or their metabolites, in part, ameliorate some of the multiple metabolic dysfunctions that appears to be at the root of the disease.[23] The type of MCTs used in this current diet study are from the same MCT oil ingredient as previously used in IE dogs[27] and with senior dogs to evaluate cognitive performance.[47 50] Initially in 2010, a diet enriched with MCT oil was reported to improve cognitive performance in aged dogs, as demonstrated through a variety of neuropsychological tests.[50] The main mechanism of action proposed for these cognitive improvements was the generation of ketone bodies derived from the dietary source of MCTs,[50] as an alternative energy source for diminished brain energy metabolism that appears in aged dogs.[51] However, even though Law and others observed an increase in serum ketone concentrations in IE dogs fed the MCT oil-enriched diet, no relationship was observed between seizure frequency and serum ketones. This is in contrast to other evidence in children that suggests there is a direct relationship.[52] Alternatively, or in conjunction with ketones as an alternative energy source, MCTs may contribute to the maintenance of the neuronal structure via increasing concentrations of PUFA in the brain, which have also been shown to decrease as a consequence of ageing,[53] but this evidence is lacking in canine studies of IE.[54]

In a recent study by a different laboratory, specific MCTs (decanoic acid) were fed to rodents and showed positive effects in seizure control,[55 56]where pathological mechanisms or pathways involved may be similar to the ones involved in ageing. A new mechanism of action proposed in rats for explaining the antiseizure effect of MCTs is a direct effect via blocking the AMPA receptors (responsible of the excitatory neurotransmission pathway) in the brain. This function has been proposed to be accomplished by the dietary medium chain fatty acid (MCFA) decanoic acid (C10).[55] Other research as revealed that C10 and octanoic acid (C8) fatty acids fed to rats increased the seizure threshold and induced sedation, and reported to be related to primarily C8 causing an increased passage of tryptophan (Trp) into the brain.[56] This anticonvulsant effect was abolished when Trp passage into the brain was blocked, thus efficacy of a ketogenic diet may be at least partly dependent on changes in Trp metabolism. Because rats serve as a model in human medicine as well as in veterinary medicine, this mechanism of action could possibly help explain the positive effects of MCTs on seizure frequency in dogs. Further studies should be conducted in order to confirm that this mechanism of action also occurs in dogs. Interestingly, recent canine serum metabolomics data generated during the clinical study reported by Law and others has indicated that IE dogs fed MCTs demonstrate global changes in lipid metabolism, and even provide initial evidence to suggest that C17:0 moieties are involved in these metabolic pathways.[28]

Conclusion

The data reported above are consistent with the positive effects (reduction in seizure frequency and days) of MCTs in dogs diagnosed with IE, in accordance with evidence in the published literature.[27 33] The diet used in the study has been shown to be very useful as an adjunct management strategy in dogs with IE. This is important because even with ASD treatment, more than two-thirds of dogs with IE have seizures long-term and about one-third of dogs with IE continue to experience seizures that are difficult to control.[57–59] Thus, there is a great-unmet need to supply these canine patients with alternative and additional options to help support management of epilepsy, improve the QoL of the canine patients receiving ASDs, which will hopefully improve the QoL of the pet owners.

The palatability of the diet was good to excellent in the 86 per cent of the cases, which support the use of this type of MCTs in food for dogs. A survey of the vets and pet owners that participated in this study indicated that 90 per cent of these vets and 100 per cent of owners would recommend the diet for epileptic dogs. These results are encouraging. However, larger randomised controlled trials with longer follow-up periods would be valuable and needed to understand the long-term benefits of this type of diet on canine epilepsy management.

Contributors BZ, CJ-P, LC and JM designed the study with input from HAV. BZ, LC, JM and HAV handled and analysed the data. CdlF, MAW, AS, EL, BW-R, PM, GG, MM, JCR, AV and AF recruited pets and conducted study. All authors reviewed final dataset, then reviewed and participated in drafting manuscript. JM and BZ submitted manuscript.

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Competing interests BZ reports a patent US Patent No. 9789079 issued. BZ and LC are employed within the R&D Department of Nestlé Purina PetCare to conduct nutrition research for the potential use in future commercial applications

and products. JM and CJ-P are employed within the European team of Nestlé Purina PetCare communicating on the scientific studies and products, and also organising clinical trials of the products. SA, CdlF, MAW, AS, EL, BW-R, PM, GG, MM, JCR, AV and AF were paid by Nestlé Purina PetCare for clinical services related to case recruitment and conducting the trial and/or were provided the test food for the trial dogs by Nestlé Purina PetCare, and do not have any other conflicts of interest to disclose. HAV is a paid consultant for Nestlé Purina PetCare.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All available data are provided within the article.

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ORCID iDs
Sonia Añor http://orcid.org/0000-0002-1099-7698
Brian Zanghi http://orcid.org/0000-0003-3615-7918

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