**APPROACH TO INITIAL MANAGEMENT OF CANINE GENERALISED EPILEPTIC SEIZURES IN PRIMARY CARE VETERINARY PRACTICES IN THE UNITED KINGDOM**

**Abstract**

*Objectives*

To investigate how primary care clinicians in the United Kingdom approach initial management of canine generalised epileptic seizures, including factors potentially associated with prescription and choice of anti-seizure drugs (ASDs).

*Methods*

Electronic health records concerning 3,150,713 consultations (917,373 dogs) were collected from 224 veterinary practices by the Small Animal Veterinary Surveillance Network. Free-text clinical narratives were reviewed to identify those consistent with generalised epileptic seizure activity, including only those recording first presentation for seizures. Dogs older than 6 years were excluded.

*Results*

Five-hundred and seventeen cases were included. Sixty-seven dogs (13.0%) received ASDs at first presentation; this was significantly more likely in dogs presented with cluster seizures (CS) (odds ratio [OR] 13.78, 95% CI 7.26-26.14). Phenobarbital (*n*=36) and imepitoin (*n*=29) were the most frequently chosen ASDs. Presentation for a single epileptic seizure occurred in 321 dogs; 7 were prescribed ASDs. Eighty-six dogs presented with CS; 38 were prescribed ASDs, most frequently imepitoin (*n*=19) and phenobarbital (*n*=17). Of the dogs presenting with a single seizure and at least 6 months follow-up (*n*=165), 33 (20%) did not have subsequent seizures recorded.

*Clinical Significance*

Primary care clinicians rarely prescribed ASDs following a single epileptic seizure in accordance with International Veterinary Epilepsy Task Force recommendations. Less than half of dogs initially presenting with CS were prescribed ASDs. Imepitoin was frequently selected in the treatment of CS despite no authorisation for this purpose. These findings may ultimately contribute to improved cohesion in the management of canine epileptic seizures between primary care and referral institutions.

**Introduction**

Epilepsy is a disorder of the brain manifested by a propensity to suffer recurrent epileptic seizures. With a reported prevalence of 0.62-0.82%, it is one of the most frequently encountered chronic neurological complaints in dogs attending primary care veterinary practices in the UK (Kearsley-Fleet *et al*. 2013, Erlen *et al*. 2018). The perceived quality of life (QoL) of dogs with epilepsy can be profoundly impacted by factors related to the condition itself, including the frequency with which the dog experiences epileptic seizures, but also therapeutic factors such as the severity of adverse effects of anti-seizure drugs (ASDs). This, in turn, can similarly impact the QoL of the owner (Wessmann *et al*. 2016). Effective management of epilepsy therefore necessitates striking a fine balance to satisfy all parties involved, a task which can be difficult to achieve in some cases. The clinician is required to make several important therapeutic decisions, including the choice of ASD and time of initiation of treatment, as well as ongoing adjustments to therapy due to the lifelong and fluctuating nature of the condition.

A comprehensive diagnostic approach to epileptic seizures typically includes magnetic resonance imaging (MRI) of the brain and cerebrospinal fluid (CSF) analysis; these procedures frequently only being available in referral-level care. In reality, this is not always possible, particularly in cases for which the aforementioned neurological investigations are not affordable. Many dogs with epilepsy will therefore be managed entirely in a primary care setting, often with a more presumptive diagnosis of primary (idiopathic) and secondary (structural) epilepsies or reactive (metabolic or toxic) seizures (Berendt *et al*. 2015). Fortunately, a Tier I diagnosis of idiopathic epilepsy may be readily achieved without referral by fulfilling the criteria set out by the International Veterinary Epilepsy Task Force (IVETF), which includes a detailed signalment, history, physical and neurological examination, as well as routine blood tests and urinalysis (De Risio *et al*. 2015).

For dogs suffering epileptic seizures, ASDs have historically provided the cornerstone of management. Previously the choice was largely limited to the use of phenobarbital and potassium bromide which remain widely used. In recent years however, the number of ASDs available has expanded considerably. A notable addition is that of imepitoin, authorised in 2013 for use in dogs in the UK (or Europe) for first-line treatment of recurrent isolated generalised epileptic seizures as a result of idiopathic epilepsy. However the frequency with which primary care clinicians prescribe various ASDs remains unknown. The basis on which therapy is being initiated is also unclear. It is generally accepted that ASDs should be recommended if a dog has had two or more epileptic seizures within 6 months or there has been an increase in frequency or severity of seizure activity. The presence of severe post-ictal abnormalities, cluster seizures and status epilepticus are also instigators of therapy (Bhatti *et al*. 2015).

Most published trials on canine epilepsy have focussed on referral-level care populations, raising two potential biases. Firstly, dogs referred for further investigation of epileptic seizures may have more refractory disease proving more difficult to control in the primary care setting; secondly, the time and expertise available for management of chronic conditions such as epilepsy in referral practice does not reflect that in general practice. Studies that have utilised health records from primary care veterinary practices have mainly evaluated the prevalence and risk factors of epileptic seizures in both dogs and cats (Erlen *et al*. 2018, O’Neill *et al*. 2020). Less emphasis has been placed on the clinical approach to epileptic seizures by primary care clinicians. The purpose of this study was therefore to provide a better understanding of how primary care clinicians approach the initial management of epileptic seizures in dogs. We aimed to evaluate whether ASDs are being used in accordance with IVETF recommendations, and whether the primary care management mirrors that of referral institutions from which current recommendations and outcome measures have largely been derived. The hope is that this may contribute to improved cohesion in the management of canine epilepsy between primary and referral settings, potentially resulting in improved outcomes for these patients.

**Materials and Methods**

*Study design and inclusion criteria*

Electronic health records (EHRs) between 1st April 2014 and 12th January 2019 were collected from 224 veterinary practices (625 sites) in the United Kingdom that had volunteered to participate in the Small Animal Veterinary Surveillance Network (SAVSNET). All EHRs were collected via automatic submission from users of the Robovet practice management system (Vet Solutions Ltd.). For practices participating in the SAVSNET project, data is submitted to SAVSNET at the end of a consultation by the veterinary practitioner, unless the owner chooses to opt out of the process. Each EHR included species, breed, sex, neutering status, insurance status, microchip status, vaccination history, date of birth, owner’s postcode and any products dispensed at time of consultation. The EHR also contained the clinical narrative (CN), a free-text description of history, clinical examination, proposed and completed management plans, as well as other pertinent information written by the attending veterinary professional at the time of consultation. A more complete description of the SAVSNET data collection process is provided elsewhere (Sánchez-Vizcaíno *et al*. 2015).

Data was initially screened for CNs containing the word seizure, convulsion or epilepsy, including term variants and misspellings, using a supervised regular expression-based text mining approach. The regular expression was designed in an iterative manner, aiming to identify potentially appropriate CNs while also excluding likely irrelevant CNs. The final regular expression used was:

(?<!no)(?<!not)(?<!nothad)(?<!nofits/)(?<!sg)(s[ei][ei][zs]u|conv[ou]?[l](?!ute|[\s])|(?<!r)ep[ei]?[ei]l(?!a)|refract(?!(om|ive|[\s]sg))|seziure)

Within the searched time period, there were a total of 3,150,713 CNs describing 917,373 individual dogs. Initial data screening using the regular expression above identified 13,012 individual dogs originating from 153 veterinary practices (229 sites). Only dogs with an age of onset of less than 6 years old were included for manual review to try and capture dogs for which idiopathic epilepsy is the most likely diagnosis. The remaining 7,182 CNs were read independently by two of the authors. Dogs that, in the opinion of the authors, had a history of an abnormal episode(s) consistent with generalised epileptic seizure activity were identified. For inclusion in the study the description of the episodes had to include mention of tonic-clonic convulsions, with other supporting signs such as altered consciousness, presence of autonomic signs (salivation, urination or defecation) or post-ictal abnormalities. Where there was disagreement in the classification of cases the CN was reviewed again by both authors to reach a consensus conclusion. Dogs were included only if there was agreement between the authors. Dogs with episodes that were suggestive of a focal epileptic seizure(s) were not included, due to the difficulty in differentiating these from other forms of paroxysmal event based on description alone. Only dogs with a clear record of the first presentation for seizures (recorded as day 0) were included, in order to evaluate the primary care decision-making at the outset of veterinary investigation and/or management of the condition. Initial data handling is shown in Figure 1.

Pharmaceutical prescriptions were identified via the text-based product description section of each consultation, using a semi-automated rule-based text-mining method as previously described (Singleton *et al*. 2018). Pharmaceutical agents considered of direct relevance to acute or longer term management of seizure activity and/or idiopathic epilepsy were summarised in this study. This included phenobarbital, potassium bromide, levetiracetam, imepitoin and benzodiazepines (diazepam, midazolam).

*Data management*

*Animal factors*

Each record and associated CNs were read by the primary author to manually retrieve age of seizure onset, the presence or absence of intervention, the nature of intervention (ASDs or referral) and the specific ASD(s) prescribed.

Breeds were summarised to standardised breed terms before categorisation into either genotypically similar breed groups, crossbreeds, breeds not yet genetically classified (‘unclassified’), or breeds not recorded/recognisable (‘unknown’), providing a total of twelve breed groups in this study (Vonholdt *et al*. 2010). Although all groups were summarised descriptively, only a small number of dogs were found to be in the ‘sight hound’, ‘ancient/spitz’, ‘working dog’, ‘scent hound’ and ‘unknown’ groups, limiting our ability to statistically model these breed groups here. Hence, for statistical modelling these five breed groups were re-classified as ‘unclassified’.

*Owner factors*

Using pet owner’s recorded home postcode, a measure of predicted deprivation was assigned to each owner using the most recent English 2019 Indices of Multiple Deprivation (IMD). As IMD measures between countries are not directly comparable, only England was considered for this portion of analyses, with the remaining animals whose owner’s home postcode was outside of England being placed in the ‘none’ category for IMD. IMD rankings were classified into quintiles from 1 (most deprived) to 5 (least deprived).

*Statistical analysis*

The statistical programme ‘R’ (version 4.0.3) was used for all analyses. Descriptive proportions and confidence intervals were adjusted for clustering within sites (bootstrap method, n=5,000 samples).11 Univariable and multivariable mixed effects logistic regression models were fitted separately using the R package ‘lme4’.12 Likelihood ratio tests (LRT), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), were used to examine presence of clustering within veterinary practice or site, and were hence included in each constructed model as random effects according to whether each individually or both combined provided best fit. Separate analyses were undertaken to assess the association between explanatory variables and a series of binary outcomes of interest. Considering the entire dataset, the binary outcome variables included in analyses were record of a single seizure event prompting first presentation, record of cluster seizures (2 or more seizures within a 24-hour period) at first presentation, intervention at first presentation (including long-term management such as ASDs or referral, but not including acute interventions such as rectal diazepam), and ASD intervention at first presentation. Risk factors associated with the choice to prescribe imepitoin over phenobarbital for cases which had been provided with phenobarbital or imepitoin at first presentation alone were also explored.

Initial univariable screening included seven categorical variables (sex, neutered status, microchip status, insurance status, genetic breed group, IMD quintile, and record of cluster seizures) and one continuous variable (age of onset). For continuous explanatory variables, up to cubic polynomial terms were included if an LRT, AIC and BIC indicated significantly improved fit, compared to linear and lesser polynomial terms. Explanatory variables were retained for multivariable analysis if an LRT indicated P≤0.20 against a null model. A record of cluster seizures was only considered in models focused on therapy decision making.

Multivariable models underwent manual step-wise backward elimination to minimise AIC and BIC. Confounding was accounted for via assessment of effect variation upon removal of variables. Two-way interaction terms between other explanatory variables were assessed via AIC, BIC and an LRT. The Variance Inflation Factor (VIF) was used to assess multicollinearity.13 For continuous variables, projected outcome probabilities and associated 95% confidence intervals were calculated from log odds using ‘sjPlot’.14 Statistical significance was defined as P<0.05.

**Results**

There were 7,182 dogs identified by initial screening. Following manual review, a total of 517 dogs from 153 veterinary practices (229 unique sites) met the inclusion criteria. 140/517 (27.0%) were male entire and 185/517 (35.8%) were male neutered. 82/517 (15.9%) were female entire and 110/517 (21.3%) were female neutered. The most frequently represented breed groups were crossbreed (n=103, 19.9%), retriever (n=73, 14.1%), mastiff-like (n=60, 11.6%) and herding (n=60, 11.6%).The most frequently recorded individual breeds were crossbreed (n=103), Labrador Retriever (n=61), Border Collie (n=57), Staffordshire Bull Terrier (n=26) and Jack Russell Terrier (n=24). The median age at onset of the first reported seizure was 3.2 years (range 0.1-6.0 years). A full descriptive population summary is shown in Table 1.

*First presentation*

Of 517 total dogs, 321 (62.1%) were recorded as initially presenting with a history of a single seizure event. Descriptive analyses and univariable model results are summarised in Appendix. Of these dogs, 7 received intervention at day 0, specifically phenobarbital in 4 dogs and imepitoin in 3 dogs. Univariable and multivariable modelling results revealed no significant risk factors associated with a history of a single seizure at first presentation. Of the dogs that presented with a single seizure and at least 6 months follow-up period, 20% (33/165) did not have mention of a subsequent seizure in their EHRs.

Of 517 total dogs, 86 (16.6%) dogs were recorded as initially presenting with cluster seizures. Descriptive analyses and univariable model results are summarised in Appendix. On multivariable modelling, dogs that were insured were less likely (odds ratio, OR, 0.51 95% confidence interval, CI, 0.29-0.91; *P=*0.022) to initially present with a history of cluster seizures compared to those that were not insured. Crossbreed dogs were associated with 3.91 times greater odds (95% CI, 1.37-11.22; *P*=0.011), herding group dogs 3.41 times greater odds (95% CI, 1.10-10.63; *P*=0.034) and mastiff-like group dogs 5.82 times greater odds (95% CI, 1.93-17.53; *P*= 0.002) of initially presenting with cluster seizures, compared to the retriever group. There was also a significant association with age of onset, with an increased probability of presenting with cluster seizures for dogs at either end of the age range (Figure 2). Final multivariable model results are shown in Table 2. 43/86 (50.0%) dogs received intervention at day 0. Of these, 38 dogs were started on ASD therapy. The choice of ASD was imepitoin (n=19), phenobarbital (n=16), levetiracetam (n=2), or a combination of phenobarbital and levetiracetam (n=1). The remaining 7 dogs were referred for specialist care.

*Intervention*

Overall, 82/517 (15.9%) dogs received intervention (long-term ASD or referral) on day 0. Descriptive analyses and univariable model results are summarised in Appendix. On multivariable modelling, dogs that were microchipped were more likely to receive intervention at day 0 (OR 1.83, 95% CI, 1.01-3.35; *P*=0.046) compared to those that were not microchipped. Neutered dogs were also more likely to receive intervention at day 0 (OR 2.21, 95% CI, 1.21-4.04; *P*=0.01) compared to entire dogs. Dogs presenting with cluster seizures were associated with 13.78 times greater odds (95% CI, 7.26-26.14; P<0.001) of receiving intervention at day 0 compared to those not recording cluster seizures. Final multivariable model results are shown in Table 3.

67/82 dogs receiving intervention at day 0 were started on ASD therapy. Descriptive analyses and univariable model results are summarised in Appendix. The choice of ASD was phenobarbital (n=35), imepitoin (n=29), levetiracetam (n=2), or a combination of phenobarbital and levetiracetam (n=1). On multivariable modelling, dogs within the IMD2 (OR 21.98, 95% CI, 1.13-426.07; P 0.041) quintile were significantly more likely to be prescribed imepitoin rather than phenobarbital when compared to IMD1. Final multivariable model results are shown in Table 4. Fifteen dogs were referred.

209/517 (40.4%) dogs were prescribed rectal diazepam on day 0. Descriptive analyses and univariable model results are summarised in Appendix. On multivariable modelling, dogs that presented with a history of cluster seizures were significantly more likely to be prescribed rectal diazepam (OR 2.29, 95% CI, 1.37-3.83; P 0.002) than those that did not present for cluster seizures. Final multivariable model results are shown in Table 5.

**Discussion**

62.1% of dogs presented to the primary care clinician with a history of a single generalised epileptic seizure and the vast majority of these (332/338, 98.2%) were not initially started on ASDs, an approach which is in accordance with IVETF recommendations (Bhatti *et al*. 2015). A recent study similarly found that primary care clinicians frequently did not prescribe ASDs in response to a novel unprovoked seizure, however the proportion was much lower (69.2%) (Erlen *et al*. 2018). This may reflect that the study by Erlen et al evaluated cases in 2013, prior to the IVETF publications in 2015. In comparison the present study collected EHRs between 2014 and 2019. An increased awareness of IVETF recommendations may therefore have contributed to a greater proportion of primary care clinicians opting not to give ASDs following a single epileptic seizure. Although the enduring success of epilepsy management is thought to be greatest when appropriate medical management is initiated earlier in the course of disease, in people there does not appear to be a long-term prognostic benefit to starting therapy on the basis of a single unprovoked seizure (Krumholz *et al*. 2015). A significant proportion of people experiencing one unprovoked seizure will in fact not go on to develop epilepsy and the same is thought to be true of dogs (Gavvala *et al*. 2016). Indeed, of the dogs that presented with a single seizure and at least 6 months follow-up period, 20% (33/165) did not have mention of a subsequent seizure in their EHRs. Unfortunately it is not possible to determine if these dogs went on to suffer subsequent seizures beyond the available CNs, making it difficult to draw further conclusions from this finding. A large-scale prospective study following dogs that present with a single seizure would therefore be beneficial.

16.6% of dogs had a history of cluster seizures on initial presentation to the primary care clinician, for which there was an increased probability at either end of the age range. Dogs in the crossbreed, herding and mastiff-like breed groups were significantly more likely to initially present with a history of cluster seizures in comparison to the retriever group. Previous studies have shown that German Shepherds and Boxers(Monteiro *et al*. 2012), as well as Cavalier King Charles Spaniels, Staffordshire Bull Terriers and Border Collies (Packer *et* al. 2016) were more often affected by cluster seizures than Labrador Retrievers. There were supportive findings in the present study, as Boxers and Staffordshire Bull Terriers compromised more than half of the mastiff-like group (31/60), while the vast majority of the herding group were Border Collies (57/60). The predominance of these breeds may explain the prevalence of cluster seizures within their respective groups. The use of breed groups may present a limitation to this study due to the potential to mask clinically relevant findings concerning individual breeds. However, this approach seems to represent the most reasonable solution to the problem of having too many individual breeds to effectively statistically model.

Dogs presenting for cluster seizures were significantly more likely to receive intervention at the time of the first consultation when compared to dogs presenting for a single seizure. However, less than half received either initial ASD therapy or referral for specialist care. This is perhaps surprising given that the presence of cluster seizures alone is considered by the IVETF to be an indication to start medical therapy; suggesting a hesitation from some primary care clinicians to start ASDs from the outset, regardless of the initial seizure semiology. It is also possible that ASDs and/or referral were discussed and even recommended in some cases (though not clearly recorded in CNs), however the lack of uptake may have been a choice of the client. Monotherapy with imepitoin, rather than phenobarbital, was the most frequent choice of intervention for dogs initially presenting with cluster seizures. Although both imepitoin and phenobarbital have been shown to have a comparable ≥50% reduction in the frequency of single recurrent epileptic seizures(Tipold *et al*. 2015), imepitoin has not been thoroughly investigated in the primary treatment of cluster seizures and is therefore not currently recommended for this purpose.19 In fact, a recent study found that 90.3% of dogs receiving imepitoin monotherapy went on to develop cluster seizures within a 3 year follow-up period, in comparison to 36.7% of those on phenobarbital (Stabile *et al*. 2019). This is potentially significant as more frequent episodes of cluster seizures are associated with an increased incidence of euthanasia of epileptic dogs (Monteiro *et al*. 2012).

It is likely that individual patient or client factors may have contributed to the decision to prescribe imepitoin for dogs presenting for cluster seizures. Unlike with phenobarbital and potassium bromide, there is no specific requirement to measure serum concentration of imepitoin. This may be preferable in some dogs for which there is concern over the feasibility of repeated blood sampling, for example if the client cannot afford regular blood testing or if the dog is difficult to restrain. Imepitoin may also be presented to the client as a relatively benign option due to evidence of a superior safety profile in comparison to phenobarbital.18 Adverse effects of ASDs list high in the priorities of owners of epileptic dogs(Jones *et al*. 2021), therefore imepitoin may be a more attractive proposition. However recent evidence suggests that the potential adverse effects of imepitoin may warrant more discussion with clients.Stabile (2019) reported in an observational retrospective cohort study that, following initiation of ASD monotherapy, 7/31 (22.6%) dogs receiving imepitoin displayed adverse effects such as unprovoked aggression and ataxia which were deemed severe enough to switch to a different ASD. In contrast, 0/30 dogs receiving phenobarbital required withdrawal of the medication.

Although relatively few dogs were prescribed long term ASDs (67/517) at the time of the first consultation, rectal diazepam was provided in 40.4% of cases. This was significantly more likely in dogs presenting with cluster seizures, for which the use of rectal diazepam has previously been described (Podell 1995). The availability of rectal diazepam in the home setting, even if not actually used, has been shown to provide reassurance to parents of epileptic children (Kriel *et al*. 1991). This may also be true for owners of epileptic dogs. It has been suggested that intranasal midazolam may actually be more effective than rectal diazepam in the emergency management of epileptic seizures in dogs (Charalambous *et al*. 2017). Intranasal midazolam was not prescribed for any dog in the present study, however most of the EHRs were collected prior to the publication by Charalambous et al. Future evaluation of similar epileptic cohorts as described here could offer another interesting insight into how such new clinical evidence perfuses into clinical practice with time.

Dogs that were microchipped or neutered were more likely to receive intervention at the initial presentation. This may suggest that owners who take part in regular and preventative healthcare prior to the onset of their dog’s seizures could be more willing to start therapy in the earlier stages of the disease. Additionally, dogs that were insured were less likely to initially be presented for cluster seizures than dogs that were not insured, perhaps indicating a tendency for owners of insured pets to seek earlier veterinary advice. Similar trends have been identified in previous studies utilising SAVSNET. In a study evaluating pharmaceutical prescription in acute diarrhoea, dogs that were insured, neutered or vaccinated were less likely to be lost to follow-up (Singleton *et al*. 2019).Engaging clients in early preventative health programmes may therefore influence the management of subsequent health problems. This may be of particular importance for chronic or lifelong conditions such as epilepsy. Dogs within the IMD2 quintile were significantly more likely to be prescribed imepitoin rather than phenobarbital when compared to IMD1. Given that imepitoin is typically the more costly ASD, this may reflect an influence of available finances on the decision-making of clients in more deprived areas. However, this did not appear to be replicated in other less deprived IMD quintiles.

This study has several limitations, primarily due to the use of EHRs. Practices submitting EHRs to SAVSNET are recruited based on convenience, therefore are not necessarily representative of the UK population as a whole. Retrospective review of EHRs also relies on the attending veterinary practitioner to have recorded the relevant information within the CN; in the case of unrecorded or inaccurate information this may have resulted in potentially suitable cases being missed during the initial text mining and data screening. Due to the focus on appointments, any diagnostic procedures or prescriptions undertaken outside of the consultation room environment may also not be recorded. It is likely that additional cases were referred for specialist care but not recorded as such, as the inclusion of this information within the CN is entirely at the discretion of the veterinary surgeon. There was also no means of knowing the subsequent management of cases performed at referral institutions unless specifically described in the CN, although this was not the main purpose of the present study.

**Conclusion**

This study explored factors associated with the initial management of epileptic seizures in dogs presenting to primary care veterinary practices. Prescription of long term ASDs was rare for dogs presented for a single epileptic seizure, and was significantly more likely if there was a history of cluster seizures. Despite this, less than half of dogs presenting with cluster seizures were not started on long term ASDs, and for those that were the most frequently chosen ASD was imepitoin. Management of cluster seizures in primary care practice therefore appears to be an area that could be improved in line with IVETF guidelines. Future studies are required to identify differences in the therapeutic approach to dogs over 6 years of age, as well as the enduring management of epileptic seizures beyond the initial presentation.

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**Conflict of interest**

No conflicts of interest have been declared