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Should Levetiracetam or Imepitoin Be Used in Preference as Second-line Treatment in Pharmacoresistent Epileptic Cats?

A Knowledge Summary by

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KNOWLEDGE SUMMARY

PICO question

In adult cats with idiopathic epilepsy, which is poorly controlled with phenobarbital monotherapy, should levetiracetam or imepitoin be used in preference as a second line treatment in order to reduce seizure frequency?

Clinical bottom line

There is currently insufficient evidence to reliably determine whether levetiracetam or imepitoin should be used in preference as a second line treatment for the management of cats with refractory idiopathic epilepsy. There is weak evidence however to suggest clinical efficacy of levetiracetam and imepitoin in management of cats with idiopathic epilepsy. Further studies which evaluate and directly compare the efficacy of second line anticonvulsants in feline epilepsy are needed.

Clinical Scenario

A five-year-old female neutered cat is presented to you for ongoing management of presumed idiopathic epilepsy. The cat has suffered generalised seizures since she was approximately 18 months of age, and despite long-term therapy with phenobarbital anticonvulsant medication, the cat's seizure frequency has continued to increase with time. Based on recent patient serum phenobarbital concentrations, the dose of phenobarbital cannot be safely increased further. The owner has consulted internet forums and suggests you try a new 'wonder drug' named imepitoin. After consulting a colleague however, they suggest levetiracetam is a better second line treatment in this case. Of the two drugs, what is the next best option for successful pharmacological management of this cat's seizure episodes?

The evidence

Three studies of varying relevance to the PICO were reviewed including one systematic review and two uncontrolled prospective clinical trials. Although the studies provide evidence of the clinical efficacy of both levetiracetam and imepitoin, the strength of the evidence is low. Only one study specifically evaluated efficacy of levetiracetam as an adjunct to phenobarbital, and no direct comparison to date has been made between efficacy of levetiracetam or imepitoin as a second line anticonvulsant.

Summary of the evidence

Charalambous et al. (2018)	
Population:	Cats with confirmed or presumed idiopathic epilepsy, varying breeds
Sample size:	239 cats [systematic review of 40 studies]
Intervention details:	Studies were grouped based on the antiepileptic drugs evaluated and the overall quality of evidence. Details of the drugs doses, treatment period, pre and post-treatment seizure frequency, and 95% confidence interval of the successfully treated study population were provided.
Study design:	Systematic review
Outcome studied:	Objective: Individual studies were evaluated based on the quality of

	evidence (study design, size of study population, enrolment of study subjects, overall risk of bias) and outcome measures reported, including the proportion of cats with ≥ 50% reduction in seizure frequency.
Main findings: (relevant to PICO question):	• Risk of bias was high in 2/5 studies relevant to the PICO question. • Disease characterisation was variably defined in all studies relevant to the PICO question. • Small (20–50 cats) or very small (< 10 cats) populations were included in 4/5 studies relevant to the PICO question. • There was weak evidence to support efficacy of levetiracetam and imepitoin in terms of seizure reduction in cats with idiopathic epilepsy.
Limitations:	• The limitations in this review are intrinsically derived from the studies included and evaluated. • Levetiracetam and imepitoin were evaluated in only five of the 40 studies included in the review (i.e. 51 cats) and only two of these studies considered levetiracetam in combination with phenobarbital.

Bailey et al. (2008)	
Population:	Cats with presumed idiopathic epilepsy of varying breeds which continued to experience seizures despite phenobarbital therapy, suffered unacceptable side effects attributed to phenobarbital, or had unacceptably high serum phenobarbital levels.
Sample size:	12 cats
Intervention details:	• Single treatment group (no control), levetiracetam therapy initiated at a dose of 20 mg/kg every 8 hours, in addition to existing phenobarbital anticonvulsant medication. • Treatment period: ≥ 3 months.
Study design:	Prospective uncontrolled clinical trial
Outcome studied:	Objective: Seizure frequency was documented by owners with a log book both before and after initiation of levetiracetam treatment. Cats were considered to have responded to therapy when ≥ 50% reduction in seizure frequency was recorded.
Main findings: (relevant to PICO question):	• Accurate seizure logs were not maintained for two cats which were excluded from data regarding drug efficacy. • A successful response was recorded in 7/10 cats treated with levetiracetam as an adjunct to phenobarbital; in three of these successful responders the seizures were completely abolished. • Despite this there was no significant difference in the number of seizures recorded 3 months before and after the initiation of levetiracetam treatment (P = 0.109); data on this was available in only seven cats.
Limitations:	• Non-blinded, non-randomised and uncontrolled trial.

	• Small study population. • Precise doses of concurrent phenobarbital treatment and corresponding serum levels were not reported. • Outcome measure was recorded by lay personnel (i.e. owners) and therefore may not be entirely representative. • Variable inclusion criteria (i.e. 2/12 cats were included on basis they had unacceptable side effects attributed to phenobarbital or had unacceptably high serum phenobarbital levels), therefore not a completely homogenous study population. • Owners documented seizure frequency and thus were responsible for measuring outcome data; this is open to bias but realistically there are no other reliable and validated methods for recording seizures long-term in a home environment.

Engel et al. (2017)	
Population:	Epileptic cats with ≥ 2 seizures within the preceding 2 weeks of study enrolment, ≥ 9 months of age.
Sample size:	Eight cats
Intervention details:	• Single treatment group (no control), imepitoin monotherapy initiated at a dose of 30 mg/kg every 12 hours. • Treatment period: ≥ 8 weeks.
Study design:	Prospective uncontrolled clinical trial
Outcome studied:	Objective: Animals with ≥ 8 weeks of seizure freedom reported as treatment success, ≥ 50% reduction in seizure frequency reported as partial success. Seizures were recorded by owners in a patient diary.
Main findings: (relevant to PICO question):	• 4/8 cats (50%) experienced treatment success, 1/8 cats (12.5%) experienced partial success, 2/8 cats (25%) continued seizuring without success, and 1/8 cats was lost to follow-up. • There was a significant reduction in number of seizures per month following initiation of imepitoin treatment (P = 0.0313). • One of the two study cats which failed to respond received additional phenobarbital at a dose of 1 mg/kg every 12 hours and attained seizure freedom until the point of last recorded follow-up.
Limitations:	• Non-blinded, non-randomised and uncontrolled trial. • Small study population. • One cat was diagnosed with seizures secondary to feline infectious peritonitis (FIP), and therefore not idiopathic. • Owners documented seizure frequency and thus were responsible for measuring outcome data; this is open to bias but realistically there are no other reliable and validated methods for recording seizures long-term in a home environment.

Appraisal, application and reflection

Although the strength of evidence is greatest with systematic reviews or meta-analysis, only one such study was included in this knowledge summary.[1] Unfortunately however, the majority of findings from this particular study are not directly relevant to the PICO as they concern efficacy and safety of other anticonvulsants in feline epilepsy. For those aspects of the systematic review which were applicable to the PICO, the quality of evidence was low, risk of bias was frequently high, there was often incomplete outcome data, disease characterisation and study design, including drug dosages, were variable, and study group sizes were often small.

In addition, two uncontrolled prospective clinical trials were evaluated. One study specifically investigated the efficacy of adjunct treatment with levetiracetam in addition to phenobarbital in cats refractory to treatment.[2] The other study evaluated imepitoin monotherapy, although in one 'non-responder' additional therapy with phenobarbital was initiated.[3] The strength of evidence is low as both studies were non-blinded, non-randomised and uncontrolled, with very small sample sizes. This limits the conclusions we can draw.

The regulatory aspects of the prescribing cascade should be considered during selection of treatment options for management of feline epilepsy; there is currently no licensed veterinary product for feline epilepsy in the UK. Phenobarbital and imepitoin is licensed in dogs only and levetiracetam is not licenced in cats or dogs. As per the prescribing cascade, authorised veterinary medicines where available should be used first. When unlicensed veterinary medicines are used, written consent should be obtained from the animal's owner. Therefore, the legal aspects of the cascade should be considered when prescribing drugs for management of feline epilepsy.

Although drug safety and tolerability were not specifically part of the PICO, this should be considered during selection of treatment options for management of feline epilepsy. In the study by Charalambous et al. (2018), the safety profile was regarded as strong for imepitoin, while the level of evidence for the safety profile of both phenobarbital and levetiracetam was weak.

No study to date has specifically evaluated efficacy of either levetiracetam or imepitoin as a monotherapy or second line anticonvulsant with a strongly convincing clinical effect. Such a study might utilise a randomised control trial design with clear inclusion criteria and objective outcome measures. More precisely, there are no studies which directly compare efficacy of levetiracetam or imepitoin. Therefore, there is insufficient evidence to answer the current PICO.

Methodology Section

Search	
Databases searched and dates covered:	PubMed database accessed via NCBI, and CAB Abstracts accessed via OVID platform
Search strategy:	PubMed: (cat* OR feline* OR felid* OR felis) AND (epilepsy OR seizure*) AND (levetiracetam OR imepitoin) CAB abstracts: (cat* OR feline* OR felid* OR felis) AND (epilepsy OR seizure* OR epileptic) AND (levetiracetam OR imepitoin)
Dates searches performed:	25/01/2019

Exclusion / Inclusion Criteria	
Exclusion:	Single case reports, duplicate articles, review articles, book chapters or sections, articles which did not directly evaluate the effect of levetiracetam or imepitoin on seizure frequency in cats, articles where the full text was not available in English language, articles which were unavailable for review.
Inclusion:	Original peer reviewed articles including case series, observational or interventional studies, and systematic reviews which evaluate the efficacy of imepitoin or levetiracetam in cats with idiopathic epilepsy.

Search Outcome

Database	Number of results	Excluded – not relevant to the PICO	Excluded – review article	Excluded – not available in English language or unavailable for review	Excluded – book chapters or sections	Total relevant papers
PubMed	32	22	7	0	0	3
CAB Abstracts	42	25	8	2	4	3
Total relevant papers when duplicates removed						**3**

CONFLICT OF INTEREST

The author declares no conflicts of interest.

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