

ANTIEPILEPTIC DRUGS' TOLERABILITY AND SAFETY – A SYSTEMATIC REVIEW AND META-ANALYSIS OF ADVERSE EFFECTS IN DOGS

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Background

Various anti-epileptic drugs (AEDs) are used for the management of idiopathic epilepsy (IE) in dogs. Their safety profile is an important consideration for regulatory bodies, owners and prescribing clinicians. However, information on their adverse effects still remains limited with most of it derived from non-blinded non-randomized uncontrolled trials and case reports.

Aim of the study

This is the first systematic review and meta-analysis in veterinary medicine which evaluates studies that describe the safety profile of AEDs used for the management of IE in dogs, based on objective criteria.

Material & Methods

✓ Electronic searches of PubMed, Google Scholar and CAB Direct were carried out (03 January 2016) without date or language restrictions. Proceedings of ECVN/ACVIM annual congresses were searched. Peer-reviewed full-length studies describing objectively the adverse effects of AEDs in dogs with IE were included.
✓ Studies were selected based on specific inclusion criteria and a two-stage screening process. Final studies were evaluated on the grounds of their overall quality of evidence (figure1) as well as outcomes measures (table 1).

Figure 1: Criteria for evaluation of the overall quality of evidence for each study

Blinded randomized clinical trials (bRCTs) with large group sizes, clear inclusion criteria and diagnostic investigations that included clinical signs and thorough test results consistent with the diagnosis of IE, describing outcomes specific for IE and low overall risk of bias were considered to provide the highest available quality of evidence.

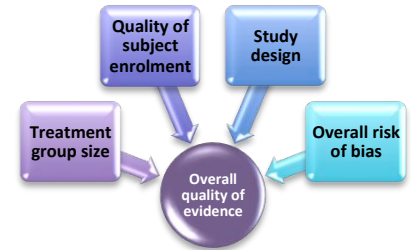


Table 1: Criteria for evaluation of AEDs' safety profile

Proportion of specific adverse effects for each AED	Prevalence and 95 % confidence interval of the affected population in each study	Comparative odds ratio of adverse effects for AEDs	Level of evidence provided for the safety profile of each AED
Calculated for each AED by dividing the number of studies that reported a specific adverse effect by the total number of the studies for this AED.	Calculated for each study by dividing the number of subjects that developed adverse effects during the specified study period by the total size of the study population.	The odds ratio (OR) was estimated in order to indicate the increased or decreased odds of observing specific adverse effect(s) in total for an AED compared to its control group (comparison AED or placebo or untreated animals). The OR for dichotomous data was calculated using the random-effects model in Review Manager 5.3. Associations were considered to be statistically significant at P < 0.05 .	' Strong ' evidence was provided for the safety profile when at least one bRCT reported or assessed the adverse effects of an AED; ' Weak ' evidence was provided for the safety profile when bRCTs were not available.

bRCT(s); blinded randomized clinical trial(s)

Results

Table 2: Level of evidence for AEDs' safety profile

Overall number of studies detected	Total number of studies evaluated after the two-stage screening process	Number of studies with the highest overall quality of evidence	Level of evidence provided for each AED safety profile	
			Strong	Weak
368	90	5	✓ Phenobarbital, Imepitoin, Potassium bromide, Levetiracetam	✓ Zonisamide, Gabapentin, Pregabalin, Sodium valproate, Felbamate, Topiramate, Primidone

Figure 2: Risk of bias

Risk of bias assessment presented as percentages across all included studies based on Cochrane and Syrcle's 'risk of bias' assessment tool. Overall high risk of bias in >90% of the studies.

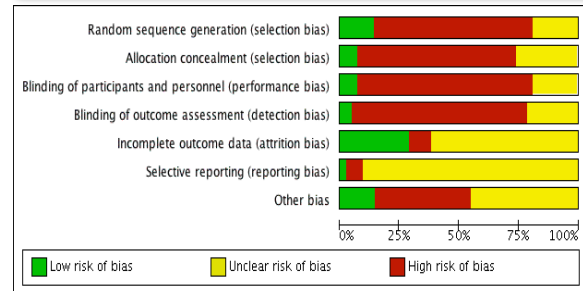
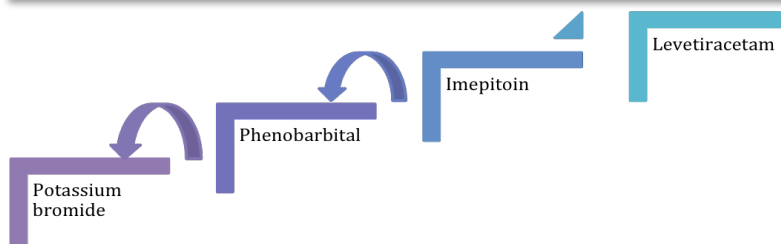


Figure 3: Staircase of AED's safety profile hierarchy

Direct comparisons suggested that imepitoin and levetiracetam might have a better safety profile than phenobarbital, whilst the latter might have a better safety profile than potassium bromide. However, **none of these comparisons showed a statistically significant difference**. Comparisons between other AEDs were not possible due to lack of relative comparison studies. Individual AED assessments indicated that levetiracetam might be one of the safest AEDs, followed by imepitoin and then phenobarbital and potassium bromide. The safety profile in other AEDs was variable.



Conclusions & Discussion

✓ Adverse effects usually appeared mild in all AEDs and subsided once doses and/or serum levels were monitored or after the AED was withdrawn.
✓ Although phenobarbital might be less safe than imepitoin and levetiracetam, there was insufficient evidence to classify it as an AED with a high risk of major adverse effects.
✓ It is important for clinicians to evaluate both AEDs' effectiveness and safety on an individual basis before the selection of the appropriate monotherapy or adjunctive AED therapy.