This talk deals with alternative treatments for idiopathic epilepsy and delineates a series of practical examples of involuntary movements so that these may be differentiated from partial seizure episodes.

**Idiopathic epilepsy**

Primary or idiopathic epilepsy (per se) is defined as that for which no underlying cause can be identified and therefore a genetic cause is presumed. Secondary or symptomatic epilepsy refers to that for which there is an underlying structural intracranial cause. Some authors refer to cryptogenic or probably symptomatic epilepsy as that for which there is no evidence of a clear aetiology despite extensive investigation, but a secondary cause is suspected. Finally, convulsive episodes may be reactionary, when due to extra-cranial causes such as toxic, endocrine or metabolic causes.

The type of seizures may in turn be subdivided into: Partial seizures, which affect the functioning of part of the brain and manifest as tics, rhythmic muscle contractions (simple), or outbreaks of altered behaviour (complex); and Generalised seizures, when the entire brain and the level of consciousness are affected. Partial seizures may progress to a generalised seizure.

Idiopathic epilepsy is therefore a disease whose diagnosis is, in most cases, presumptive following the exclusion of other causes for the seizures. It most frequently presents in animals between 1-5 years of age with a history of repeated seizures and with a complete return to neurological normality between episodes. The most commonly affected breeds are: Golden Retriever, Labrador Retriever, Beagle, Keeshond, Belgian Shepherd Tervuren, Vizsla and Shetland Sheepdog. Not all breeds present generalised seizures, such as the Hungarian Vizsla, Bull Terrier or Labrador Retriever.

Traditionally, treatment is based on the administration of anticonvulsant agents such as phenobarbital and potassium bromide. However, in 60-70% of cases, these medications do not effectively control the seizures. On other occasions, idiosyncratic side effects warrant replacing these with other less toxic anticonvulsant agents.

Over the past decade, the use of antiepileptic agents for human use (such as levetiracetam, gabapentin, zonisamide and topiramate) has facilitated more effective seizure control in animals suffering from this disease. However, due to high costs, the use of these medications should be reserved for cases in which the seizures are not properly controlled or where the side effects are severe.

**Levetiracetam**

Levetiracetam (Keppra) is a second generation antiepileptic drug commonly used as an adjunct treatment in cases of epilepsy refractory to traditional antiepileptic treatments or when these are contraindicated due to hepatic or renal disease. Its mechanism of action is not fully elucidated, although it appears to act on the synaptic vesicle protein SV2A of the presynaptic membranes. It is almost completely absorbed following oral administration, its $T_{1/2}$ is 2-4 hours; and its elimination is primarily renal. An interesting characteristic regarding the pharmacokinetics of this medication is that despite its short half-life it appears to have a cumulative effect in the brain so it may be administered every 8
hours.(2) Due to the absence of hepatic metabolism, it is useful in the treatment of hepatic encephalopathy-induced seizures or in cases of phenobarbital-induced liver damage. In a recent study, its efficacy as an adjunct therapy in the control of seizures was evaluated.(3) The author used a starting dose of 10 mg/kg q8h which may be gradually increased. On rare occasions, the only side effect observed was mild sedation. Despite its initial efficacy, some animals may experience an aggravation of seizures or even what is known as the "honeymoon effect" with its return in the long-term. It appears to be just as effective in cats as in dogs.(4) The recent introduction of the intravenous injection means that it may be used in status epilepticus. The monthly cost of the medication at the starting dose for a 10 kg dog is about €47.

**Gabapentin**

Although this medication was introduced into human medicine as a structural GABA analogue, its anticonvulsant effect is due to another mechanism. This is based on increasing the release and action of GABA and inhibiting neuronal sodium channels, although more recently it is thought to act by inhibiting voltage-sensitive calcium channels. In dogs, absorption is good following oral administration with 30-40% hepatic metabolism, although it does not induce microsomal enzymes. Its T\(\text{1/2}\) is 3-4 hours. The author uses a starting dose of 10 mg/kg q8h which may be gradually increased provided there are no side effects, the most common being sedation. Gabapentin does not appear to be as effective as seen in recent studies.(5) Nonetheless, the author reserves its use for cases in which the costs of other epileptic treatments are prohibitive. In the experience of the author, gabapentin is more useful in the treatment of neuropathic pain.

**Zonisamide**

Zonisamide (Zonegran) is an antiepileptic whose principal mechanism of action consists in inhibiting presynaptic T-type calcium channels and sodium channels.(6) Its metabolism is primarily hepatic via microsomal enzymes, though these are not induced. Its T\(\text{1/2}\) is 15 hours. As it undergoes hepatic metabolism, higher doses should be used in patients receiving phenobarbital. The author uses a dose of 5 mg/kg q12h in patients not taking phenobarbital and 10 mg/kg in those receiving this medication. Its efficacy in dogs has recently been evaluated.(7,8) Just as with levetiracetam, a "honeymoon effect" has been observed. Its main disadvantage is the high cost.

**Topiramate**

The mechanism of action of topiramate (Topamax) is complex, potentiating both the inhibitory action of GABA and blocking neuronal calcium and sodium channels and glutamate receptors. Its metabolism does not induce hepatic enzymes.(9) The recommended doses in humans are 2-25 mg/kg q12h. A gradual tapering of the dose is recommended. There are no long-term studies on its efficacy in domestic animals but the author has used it in cases refractory to the above anticonvulsants with good results. Again, its disadvantage is the high price (€60 a month for a 10 kg dog on the starting dose).

**Other anticonvulsants for human use**

Primidone and phenytoin are not used for the treatment of idiopathic epilepsy in domestic animals as they offer no advantage over phenobarbital and because they are associated with a greater probability of hepatic toxicity. In dogs, the T\(\text{1/2}\) of valproate is considerably shorter (1.7h) compared to in humans (9-16h) which makes dosing more difficult.(10) In dogs lamotrigine is metabolised to a cardiotoxic compound, so is contraindicated in this species. Vigabatrin causes blood dyscrasias, so this is also contraindicated. As the absorption of oral diazepam is low (<5%), it is of no use for the control of epilepsy in dogs. In cats, it may cause hepatic necrosis.

**Involuntary movements**

The term involuntary movement is very broad and encompasses all types of muscular movements made without the conscious participation of the individual. This description includes movements caused by the seizures mentioned above. In human medicine, knowledge of various involuntary movements has led to their classification and to the identification of genetic abnormalities responsible for many cases.
In veterinary medicine, however, its phenomenology has only been described on a few occasions and therefore knowledge of this is not as exhaustive. The greatest clinical challenge is to find a visual differentiation between an involuntary movement and a partial seizure without the use of electrodiagnostic methods (electroencephalogram). For this, a video recording of the events may help interpretation.

There has been a recent attempt to classify these neurological abnormalities in veterinary medicine. This includes two large categories depending on the origin: the muscular and nervous system.

**Involuntary movement of muscular origin**
In the first category, the only example is myotonia which consists in repetitive and persistent contractions of muscle cells that do not relax following physiological stimulation. This has been observed in the Chow-Chow and Miniature Schnauzer in the congenital form and in cases of spontaneous or iatrogenic hyperadrenocorticism in the acquired form.

**Involuntary movement of nervous origin**
Tetanus, tetany, myoclonus and dyskinesia are some of the causes of nervous system origin.

**Tetanus** is the clinical sign of sustained contraction of the extensor muscles. Two diseases are associated with this neurological abnormality: Clostridium tetani infection and hereditary polioencephalomyelopathy in the Australian Cattle Dog.

**Tetany** is the intermittent contraction of the extensor muscles. It has been observed in domestic species after strychnine poisoning and in Labrador Retriever pups with familial reflex myoclonus (a hereditary degenerative disease where a deficiency of glycine, the main neurotransmitter inhibitor in the spinal cord, is suspected).

**Myoclonus** refers to the sudden contraction and then relaxation of a group of muscles. This may be sporadic or repetitive.

Sporadic myoclonus may be benign or may be a form of partial seizure due to a structural lesion of the prosencephalon.

Repetitive myoclonus may be divided into:
- Constant which continues during sleep as observed in cases of canine distemper infection or lead poisoning
- Action-related (intention tremor) which disappears during sleep
  - congenital due to hypomyelination or demyelinisation (Springer Spaniel, Samoyed),
  - storage diseases (globoid cell leukodystrophy in WHWT, Cairn Terrier), oligodendroglial dysplasia in Bull Mastiff...
- Acquired as generalised tremor syndrome, poisoning from penitrem A, organophosphorous compounds, macadamia nuts, metaldehyde, permethrin, lead...
- Postural when the muscles responsible for maintaining body weight stable are affected. This may appear in young animals belonging to the Doberman, English or French Bulldog or Boxer breeds, affecting the head and neck muscles; or in geriatric individuals affecting the pelvic limbs. Orthostatic postural myoclonus is a variant that may affect young Great Dane dogs and which disappears during exercise or in lateral recumbency. However, it may be demonstrated by applying pressure on the plantar surface when the animal is lying down. An imbalance of the extensor reflexes is suspected in all these cases.
- Episodic non-postural or myokymia is characterised by a vermicular rippling motion of the muscles. The clearest example of this type of movement is found in hereditary ataxia in the Jack Russell Terrier. In humans, this type of activity has been described in association with neuromyotonia, an autoimmune disease of the peripheral nerves with the production of antibodies against the voltage-sensitive potassium channels. Treatment of these cases is based on the administration of antiarrhythmic drugs, procainamide or mexiletine.
- Resting: These have not been described in small animals, but the best example in humans is Parkinson's disease due to the degeneration of the substantia nigra.

**Dyskinesia** refers to a wide group of involuntary movements which are well-characterised in humans but not so in veterinary medicine. Various descriptive terms have been used with a view to classifying
these: chorea is a sudden unsustained contraction of various muscle groups; dystonia is the sustained contraction of a muscle group; athetosis is the prolonged contraction of trunk muscles causing scoliosis; and ballism involves contraction of limb muscles. Many of these types of dyskinesia have already been genetically characterised in humans although some have been associated with intracranial disease.

In veterinary medicine, these movements have been described in various breeds. In the Scottish Terrier, a combination of chorea and dystonia has been observed, normally in association with exercise or stress situations. It seems to be associated with serotonin deficiency in the spinal cord and is inherited with an autosomal recessive pattern. This type of dyskinesia has also been observed in the Cavalier King Charles Spaniel, Bichon Frise, (15) Wheaten Terrier, Norwich Terrier, Boxer (16) and possibly the Border Terrier. In the Scottish Terrier, treatment is based on the administration of phenothiazines or benzodiazepines.

**Conclusion**

It is important, therefore, to characterise the type of movement observed and to differentiate this from partial epileptic seizures. The author considers video documentation of the seizure as well as ruling out secondary intracranial causes as extremely important in the treatment of involuntary movements.

**References**