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Antiparasitic Treatment in Epileptic Dogs and Cats

Diploma Thesis

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1. Introduction

Until today very little knowledge from experimental research in epileptic dogs and cats relating to antiparasitic treatment has been gained. Furthermore, there is very limited data and rarely any published literature to find answers to the question on this topic.

In this thesis, I wanted to assess the correlation between the mode of action of antiparasitic drugs and the disease “epilepsy”. I suppose that epileptic patients react differently to antiparasitic treatments compared to non-epileptic animals due to their altered conformation of the brain. These patients have a different distribution of inhibitory and excitatory neurotransmitters. In our case, in epileptic patients, the excitatory neurotransmitters are predominant. The knowledge of this abnormal brain function in epileptic patients could be important for the right choice of antiparasitic drugs. However, most antiparasitic drugs act on the neurons in the brain and are a possible risk for side effects of antiparasitic treatment in epileptic patients.

The aim of my thesis is to find out which antiparasitic treatment can be suggested for epileptic patients. We realize that epileptic animal patients should be given antiparasitics which do not have any proconvulsive effects, so that no seizures will be provoked. This review summarizes my findings of different studies and their outcomes regarding the mechanisms of antiparasitic treatment and their adverse effects in epileptic dogs and cats.

In this review, I also wanted to assess the correlation between the effect mechanism of antiparasitic drugs and the disease “epilepsy”. The summarization of my findings of different studies and their outcomes regarding this topic are presented below.

2. Material and Methods

This thesis is based on a literature research with the assistance of different media. A lot of information is provided by various pharmacology, parasitology, and neurology textbooks. The book of pharmacology "Lehrbuch der Pharmakologie und Toxikologie für die Veterinärmedizin" by Löscher et al. (2010; Enke 8th edition) was often used, as it provides a good classification for antiparasitic agents. Moreover, "Plumb's Veterinary Drug Handbook" by Plumb (2005, Blackwell 5th edition) has often been cited, as this literature provides a lot of information about side effects of drugs. Also, "Veterinary Pharmacology & Therapeutics" by Riviere et al. (2018, Blackwell 10th edition) has been much used, because of its good description about various modes of action of the antiparasitic agents. What is more, the book "Lehrbuch der Parasitologie für die Tiermedizin" by Deplazes et al. (2012; Thieme 3rd edition) provided a good overview about all endo- and ectoparasites and their treatment for dogs and cats.

In addition to this, information was collected from different electronic scientific libraries, including "Scopus", "Pubmed" and "Google Scholar". Those search engines offer a lot of different studies and papers, which are incorporated in this thesis. The keywords of the single parasitic agent listed in this thesis, e.g. "fenbendazole" or "febantel" and additionally "neurologic" or "epilepsy" led to useful results.

Moreover, articles not available online were found in the veterinary library of Veterinärmedizinische Universität Wien. With the aid of the search engine "vetmedseeker" (https://search-uvw.obvsg.at/primo-explore/search?sortby=rank&vid=UVW&lang=de_DE), the magazines and journals on this topic were collected and analyzed.

In addition, patient information leaflets were thoroughly studied and listed with the help of the "Austria codex", which is available online and provided by the website MSD (https://www.msdconnect.at/services/austria_codex.xhtml). The Austria codex lists currently licensed pharmaceutical drugs in Austria. A lot of information about side effects and overdosage symptoms were collected by means of those instruction leaflets.

Information was also provided by the website of the "European Medicines Agency" (https://www.ema.europa.eu/en), where different pharmaceutical products are precisely described including the mode of action, adverse effects, toxicity studies, overdosage symptoms, etc.

Research on different internet websites was also carried out. Different pharmaceutical and parasitological websites helped in terms of writing this thesis. The website CliniPharm/CliniTox

(https://www.vetpharm.uzh.ch/cpthome.htm) provided a broad range of information regarding chemical composition, pharmacology, pharmacokinetics, indication, dosages, contraindications, adverse effects, toxicity, interactions with other drugs and licensed products of this agent.

The website of the European Scientific Counsel Companion Animal Parasites (ESCAAP, https://www.esccap.de/) provided information regarding the treatment, deworming strategies and examination of all kind of parasites. On this website, there is also information available on how to test and treat animals which are travelling to other countries and across borders.

The website of "Gesellschaft Schweizer Tierärztinnen und Tierärzte" https://www.gstsvs.ch/de.html provides an online archive of its magazines, where a lot of information can be found on different topics and also articles, which helped writing this thesis.

Furthermore, some websites and groups on diverse internet platforms, mostly written by pet owners, were evaluated regarding neurologic adverse reactions of antiparasitic agents. The following websites were assessed and observed critically regarding its content.

Facebook groups:

- Does Bravecto Kill Dogs (https://www.facebook.com/groups/411371212394679/)
- Does Nexgard Kill Dogs (https://www.facebook.com/groups/704330073037200/)
- Do Neurotoxic Flea & tick "remedies" and other chemicals kill pets (https://www.facebook.com/groups/945516328891378/?_rdc=1&_rdr)

Websites

- Is Bravecto safe? https://www.isbravectosafe.com/index.htm
- Petition website against Simparica https://www.change.org/p/petition-for-the-immediate-withdrawal-of-simparica-flea-tick-treatment-from-the-market

The literature research was focused on various neurologic adverse effects, neurologic overdosing symptoms, and toxicity studies with neurologic outcomes. In conclusion, it was attempted to find suitable antiparasitic treatments for epileptic dogs and cats.

3. Acknowledgements

At this point, I want to thank several people, who helped in writing and finishing this thesis. I am grateful for every single person, who supported me during this process!

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4. Overview on epilepsy

Throughout the history epilepsy has been defined by the Greeks and the Romans as “mysterious brief periodic attacks”. These attacks were one of the most invisible and dramatic symptoms. The origin of the word “epilepsy” is Greek and generally means to “seize” or “to take hold of something” (Valentin and Alarcon 2012).

The current definition of epilepsy was coined by the International League Against Epilepsy (ILAE) in 2005 which published the following widely used statement. According to ILAE epilepsy is defined as “a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures.” Usually, this definition is applied if the patient has two unprovoked seizures within 24 hours, whereas an epileptic seizure is described as “a transient occurrence of signs and/or symptom due to abnormal excessive or synchronous neuronal activity in the brain” (Fisher et al. 2014).

Epilepsy is characterized by an imbalance between excitation and inhibition in the brain, which has its cause in either genetic factors or is acquired. Genetic pathologies can occur anywhere from receptor level, e.g. abnormal amounts of GABA-receptors, to abnormal ionic-channel function, e.g. potassium channel mutations, and altered brain conformation. Acquired seizures can either be the result of a head trauma or other, e.g. age-related, alterations of the brain. In the normal development of the brain, the excitatory synaptic functions develop before the inhibitory synaptic function, which clear the way for excitatory states. These considerations explain why immature patients are more predisposed to suffering from seizures (Stafstrom and Carmant 2015).

The epileptogenesis, which describes the generation of the epilepsy, is defined as originating from a group of hyperexcitable neurons (Lorenz et al. 2011). Moreover, the epileptogenesis is influenced by inhibitory and excitatory changes. The inhibitory system and its development are important for an appropriate termination of a seizure. One important inhibitory neurotransmitter is gamma-aminobutyric acid (GABA): it has either receptors for chlorides ($GABA_A$) or potassium ($GABA_B$) and it is a hydrophilic molecule, so it does not cross the blood-brain barrier.

In addition to this, the excitatory system in epileptic patients is overdeveloped. The major excitatory neurotransmitter of the brain is glutamate and its several subtypes, such as NMDA and AMPA. A different ionic environment surrounding neurons and glia cells also influence the likelihood of developing epilepsy. In immature brains the concentration of potassium is increased in the extracellular fluid. This immaturity allows the potassium concentration to

increase, which leads to a higher excitability. Also, incomplete myelination of the nerves can lead to seizure activity. Myelination of the central nervous system starts in the last stage of gestation and increases after birth (Coates and Bergman 2005; Chuang and Reddy 2018).

Epilepsy can also be caused by genetic defects in the GABA-receptor channels, which regulate the neuronal excitability in the central nervous system.

The GABA-A receptor can be an essential target for seizure medication and plays an important role in regulating the excitability in neurons, and hence in the pathology of epilepsy. What is more, GABA-A receptors in the central nervous system cause an influx of chloride ions and thus hyperpolarization of neurons occur, which reduce neuronal excitability. This is the reason why GABA-A receptors play a key role in regulating sedation, anxiolysis, anesthesia and seizure protection in epileptic patients. Changes in the distribution or in the quantity of these GABA-A receptors can affect the drug response and play an important role in epilepsy (Chuang and Reddy 2018).

Causes for abnormal neuronal activity can be diverse: seizures can occur secondary to a structural lesion or they can indicate changes in neurotransmitters and their receptors. The most essential alteration in neurotransmitters is thought to be the GABA-neurotransmitter, as this transmitter is necessary for the development of seizures (Lorenz et al. 2011).

5. Results

In the following, the outcomes of research relating to antiparasitic treatment on epileptic dogs and cats are presented.

5.1. Overview on antiparasitic treatment

Antiparasitic drugs are chemotherapeutic substances used for treatment and prevention of endoparasitic and/or ectoparasitic infections. Before using an antiparasitic agent, it is important to make a medical diagnosis. It must be considered which agent and which application form should be chosen in terms of the localization of the parasite (Löscher et al. 2010; Riviere and Papich 2018). The aim of antiparasitic drug treatment is the eradication and the reduction of parasites, which can transmit various diseases in dogs and cats (Löscher et al. 2010).

5.2. Anti-endoparasitic agents

We have a great range of variety in terms of choosing a suitable anti-endoparasitic treatment for dogs and cats. Treatment against endoparasites in veterinary medicine are safe in use, since modern antiparasitic drugs have a high therapeutic index (Löscher et al. 2010).

Endocides can either interfere with the metabolism of parasites by depleting their energy reserves or interfere with neuromuscular transmission (Löscher et al. 2010).

Nowadays, cats and dogs have a different social position than in the past, as they now live in close contact with their family members. Due to this close relationship to people, the awareness concerning careful hygiene aspects to prevent disease transmission, i.e. zoonoses (for example *Toxocara spp*., *Echinococcus multilocularis*), has to be raised. Hand hygiene, no access to children's playgrounds and cleaning up the dogs' feces from the ground are important factors. Strategic worm diagnostics or regular anti-endoparasitic treatments are essential for human and animal health. However, not only parasites of zoonotic origin should be taken into consideration, but also species-specific parasites (Strube et al. 2019).

5.2.1. Benzimidazoles

Benzimidazoles are nowadays one of the most important and commonly used endocides in veterinary medicine. These drugs have a high tolerability and a broad spectrum of efficacy. Benzimidazoles are applied to control gastrointestinal nematodes, as well as trematodes and protozoa (Löscher et al. 2010; Riviere and Papich 2018).

The mechanism of action is the inhibition of microtubules of the parasites. Thereby, the function of the host cell is disturbed and mitochondrial reactions are secondarily decreased because of reduced glucose absorption (Löscher et al. 2010).

Overall, benzimidazoles are probably one of the least toxic anthelminthic agents available. Its high margin of safety is thought to be correlated with its low solubility in gastrointestinal fluids. Benzimidazoles are well tolerated and usually free of neurologic adverse effects at therapeutic doses. (Riviere and Papich 2018).

5.2.1.1. Fenbendazole

Fenbendazole is an orally administered agent in form of tablets or a suspension and has good efficacy against gastrointestinal nematodes and lungworms (Löscher et al. 2010).

Fenbendazole has also got a good safety index as high dosages are tolerated without any symptoms when administered orally in dogs in a dose of 500 mg/kg (van den Bossche et al. 1982) and cats in a dose of 150 mg/kg (Deplazes et al. 2012).

Moreover, no severe side effects are described. Generally, at therapeutic doses, fenbendazole does not lead to any neurological side effects (Plumb 2005).

Patient information leaflets state that only gastrointestinal side effects can occur after administration of the tablet or the suspension. Neurologic reactions are not described in adult dogs and cats when using this agent (patient information leaflet of "Panacur Tabletten für Hunde" 2016; "Panacur PetPaste zum Eingeben für Hunde und Katzen" 2020). However, puppies of bitches which had been treated with an overdose of fenbendazole, suffered from central nervous symptoms and showed reduced sensual perception (Stoye et al. 1985).

5.2.1.2. Febantel

Febantel is a “pro-benzimidazole”, which is an inactive prodrug and is converted into an active agent after biotransformation in the host organism (Löscher et al. 2010; Riviere and Papich 2018). Febantel has no anthelminthic activity itself. The effect mechanism depends on its active metabolites, which are fenbendazole and oxfendazole (Riviere and Papich 2018). This agent is orally administered in form of tablets and is highly effective against adult and larval forms of gastrointestinal nematodes and lungworms. (Löscher et al. 2010).

Symptoms of severe intoxication, i.e. 15-times higher doses than the recommended therapeutic dose (RTD), include salivation, diarrhea, vomiting and anorexia (Plumb 1991).

Patient information leaflets of febantel state that vomiting and diarrhea can occur as adverse effects (patient information leaflet of "Exitel Plus-Tabletten für Hunde" 2019; "Zipyran Tabletten für Hunde"; "Prazitel-Plus Tabletten für Hunde" 2019; "Anthelmex Forte Kautabletten für Hunde" 2020; "Cazitel Tabletten für Hunde" 2019; "Endogard Plus Flavour Tabletten für Hunde" 2016).

Other than that, patient information leaflets also state that in rare cases (less than 1 out of 10.000 treated animals) patients showed signs of hyperactivity (patient information leaflet of "Drontal Plus Tasty Tabletten für Hunde" 2020).

It must be considered that some medications are combination drugs with other agents. Consequently, the mentioned side effects could be the cause of one agent or the other.

5.2.1.3. Flubendazole

Flubendazole is orally administered and has a broad spectrum of efficacy against nematodes and cestodes. It is available in form of a suspension and has good efficacy against helminth infections (Löscher et al. 2010).

This agent presents great tolerability; in toxicity studies, no side effects were noted, neither neurologically, nor clinically, histologically and pathologically (Thienpont et al. 1978).

In Austria, only Flubenol® (Flubenol KH 44mg/ml Paste zum Eingeben für Katzen und Hunde, 44mg Flubendazol, Elanco GmbH, Deutschland), an anti-endoparasitic drug in form of an oral suspension for cats, small dog breeds and puppies up to 5 kg bodyweight, is available. There is no medication currently available which is also suitable for larger dog breeds.

5.2.2. Tetrahydropyrimidines

Tetrahydropyrimidines are used as broad-spectrum anthelminthic agents against gastrointestinal nematodes. They are nicotinic receptor agonists and act on the muscle cells of nematodes. Thus, contraction is induced following spastic paralysis and nematodes are not able to attach to the intestinal wall (Riviere and Papich 2018; Vardanyan and Hruby 2016). Overall, tetrahydropyrimidines essentially act by mimicking the paralytic effects of excessive amounts of acetylcholine. This action is similar to the paralytic effects of nicotine, which are also described as “nicotine-like effects” (Riviere and Papich 2018).

5.2.2.1. Pyrantel

Pyrantel is orally administered in form of a tablet or a suspension to control gastrointestinal nematodes including ascarids, hookworms and stomach worms. (Löscher et al. 2010; Riviere and Papich 2018).

When pyrantel is given at RTD, side effects are unlikely to occur. Only debilitated animals and those with lesions in the intestinal walls can be affected. It is not recommended to administrate pyrantel in these patients, because its cholinergic effect may be intensified. Toxic symptoms like muscle tremors, salivation, tachypnoea, diarrhea and decreased activity due to acetylcholinesterase can then occur (Löscher et al. 2010; Riviere and Papich 2018).

Pyrantel has got a moderate margin of safety. Toxic symptoms can be seen in dogs when given a chronic dosage of 50 mg/kg/d over three months. They showed increased respiratory rates, profuse sweating, ataxia, and other cholinergic effects (Plumb 2005; Riviere and Papich 2018).

Patient information leaflets do not state any neurological side effects (patient information leaflet of "Banminth-Paste zum Eingeben für Katzen" 2017).

5.2.2.2. Oxantel

Oxantel is an orally administered anthelminthic drug in form of a tablet, which is only available for dogs in combination with pyrantel and praziquantel (Austria Codex, access 23.02.2021).

This agent eliminates gastrointestinal nematodes and high drug concentrations can be found in the colon. Oxantel is well tolerated and hardly toxic because of its low absorption rate in the upper part of the gastrointestinal tract (Brander 1991; Riviere and Papich 2018).

Patient information leaflets state that only gastrointestinal adverse effects could be seen when oxantel was used in combination with praziquantel. Overdoses of this drug, i.e. five times higher than the RTD, have not shown any side effects (patient information leaflet of "Dolpac Tabletten für kleine Hunde" 2018).

5.2.3. Macrocyclic Lactones

Macrocyclic lactones increase the membrane permeability of nematode neurons and pharyngeal muscle cells by binding to glutamate-gated chloride-channels. The opening of these channels happens very slowly and irreversibly, which leads to a long-lasting hyperpolarization. Thus, further functions of the parasites are blocked (Wolstenholme and

Rogers 2005). In dogs and cats, a reduction of the function of the P-glycoprotein transporter at the blood-brain-barrier could be the reason why macrocyclic lactones can reach the central nervous system and cause neurotoxic effects (Löscher et al. 2010).

5.2.3.1. Avermectins

Avermectins have a broad spectrum of antiparasitic effects, which include endoparasitic nematodes and also some ectoparasite infestations, and are usually well tolerated by dogs and cats (Löscher et al. 2010).

Nematodes have a central nervous system with GABA acting as a neurotransmitter. Avermectins act as GABA-agonists, which means that these drugs potentiate the effects of GABA. The main effect of GABA is the opening of glutamate-activated chloride-channels, which allows chloride ions influx. This influx leads to a long-lasting hyperpolarization, so signals are no longer registered by the recipient cells. No excitatory stimuli can be transferred, so the muscle cells do not function and paralysis is induced, followed by death of the parasite (Campbell 1981).

Dogs and cats do not have any glutamate-controlled chloride-channels and the effect of macrocyclic lactones on mammals are 100-times lower. The blood-brain barrier in healthy vertebrates is rarely permeable for avermectins. Nevertheless, side effects because of administration of avermectins can occur due to different mechanisms (Löscher et al. 2010).

The side effects caused by avermectin in mammals can be related to the neurotransmission of GABA. These adverse reactions include central nervous system depression and coma, sometimes resulting in death. In dogs and cats, these depressive effects are commonly seen, but most likely include more complex mechanisms and multiple drug interactions. On the one hand, avermectins penetrates the blood-brain-barrier quite easily and can hereby enter the central nervous system. On the other hand, avermectins induce agonistic actions on the GABA-receptor, which are responsible for the depression and anticonvulsive effect, depending on the concentration. Moreover, a reduced efficacy of the P-glycoprotein-pump at the blood-brain-barrier to remove different drugs from the central nervous system, can also be an explanation for the accumulation of toxic substances in the brain and therefore causing neurologic side effects. In a study, convulsions were induced by strychnine/lidocaine and by pentylenetetrazole. These seizures were then relieved after the administration of avermectins. This action proves the agent’s anticonvulsive effect. A few authors reported gastrointestinal dysfunctions when animals or humans are poisoned with avermectins, which can indicate a

possible action on neuronal tissue in the gastrointestinal tract. Additionally, there is some evidence, that avermectins can interact with the binding sites of benzodiazepines at the GABA-receptor. The interaction of avermectins with different GABA receptors has not yet been clearly investigated, but the effect of this agent on the central nervous system of rats imply similar effects of benzodiazepines. (Trailovic and Nedeljkovic 2011)

However, the depressive adverse effects of avermectins cannot only be explained by the effect of GABA. A potent GABA receptor antagonist, picrotoxin, was administered after an ivermectin intoxication, but only had a partial effect during treatment (Trailovic and Nedeljkovic 2011).

In multidrug-resistant-gene-1 (MDR-1)-mutant dogs, macrocyclic lactones are especially risky, as this agent is a good substrate for the P-glycoprotein-efflux-pump and can penetrate the blood-brain-barrier quite easily. Neurotoxic overdose-symptoms of avermectins due to a defect efflux transporter include somnolence, ataxia, hyperexcitability, tremor, salivation and mydriasis (Löscher et al. 2010).

Selamectin

Selamectin is a licensed antiparasitic drug, which is applied as a spot-on solution to treat fleas, ear-scabies in cats, sarcoptic-mange in dogs, as well as intestinal nematodes and it is also used for heartworm-prevention (Löscher et al. 2010).

This agent is well tolerated by many dog breeds as well as MDR1-mutant dogs. After overdoses, no side effects were observed (Novotny et al. 2000). In a study, Collie-breed dogs with a sensitivity to ivermectin were identified and these dogs were then used for another study, testing the symptomatology of selamectin and milbemycin oxime. The results show that the agent selamectin was tolerated better than milbemycin oxime (Bishop et al. 2000).

In another study, young dogs received large doses of selamectin. Even at exceedingly high doses, no adverse side effects could be observed (Novotny et al. 2000).

When using selamectin, reversible neurological deficits could very rarely (less than 1 of 10.000 patients) be observed in dogs and cats. (patient information leaflet of "Stronghold Lösung zum Auftropfen für Hunde" 2019).

5.2.3.2. Milbemycins

The effect mechanism of milbemycins is similar to avermectins: the agent induces a paralysis of neuronal and neuromuscular transmission of nematodes and arthropods due to an increase of anion influx through glutamate- and GABA-mediated chloride-channels (Löscher et al. 2010).

Moxidectin

Moxidectin is used to treat fleas, gastrointestinal nematodes, *Sarcoptes*-mites, *Demodex*-mites, ear-mites and is also used for prevention of heartworm infections. It is available as a combination drug with imidacloprid (Löscher et al. 2010). In Austria, only spot-on agents and orally administered tablets are registered (Austria Codex, 2021). Nevertheless, in other countries, subcutaneous injections are licensed as well (Plumb 2005).

The most often described side effects after administration of moxidectin in dogs are ataxia, lethargy, inappetence, emesis, diarrhea, pruritus etc. These symptoms are described when applied subcutaneously rather than orally (Wagner and Wendlberger 2000).

Moxidectin has a wide margin of safety in dogs when administered orally. Overdosages of up to 300-times higher than the RTD showed little to no side effects. In a clinical study, dogs were treated with unintentional high doses and demonstrated signs of hypersalivation, mydriasis, fasciculation and ataxia of the hind limbs (Plumb 2005).

Licking of the applied spot and an accidental oral administration of the dermal spot-on solution should be avoided. After accidental oral administration of the spot-on solution in MDR1-defect dogs, central-nervous intoxications symptoms occurred (Löscher et al. 2010).

The main adverse effects described in patient information leaflets are dermatological and gastrointestinal problems, which disappear by themselves without any treatment. If the animal licks the treated, dermally applied spot, neurological deficits can be seen in rare cases. Due to the bitter taste of this agent, salivation can also be seen after licking which disappears on its own. (patient information leaflet of "Advocate-Lösung zum Auftropfen für Hunde" 2019)

Adult dogs showed adverse effects when dosages of 10-times higher the RTD was given. For example, mydriasis, salivation, and emesis occurred. After accidental oral administration of the dermal solution, dogs demonstrated neurological symptoms including ataxia, generalized tremor, mydriasis, nystagmus, etc. Oral intake of 40% of the topic solution lead to severe neurological disorders, whereas the oral intake of 10% of the topic solution did not lead to any adverse effects. (patient information leaflet of "Advocate-Lösung zum Auftropfen für Hunde" 2019). As Advocate® (Advocate Lösung zum Auftropfen für Hunde und Katzen, Imidacloprid + Moxidectin, Bayer Animal Health GmbH, Deutschland) is a combination drug with imidacloprid, no exact information can be given if these symptoms are caused by one agent or the other.

Milbemycin Oxime

Milbemycin oxime is administered orally in form of tablets and is licensed in combination with lufenuron or praziquantel. It is used to prevent flea and heartworm infections and to treat gastrointestinal nematode infections (Löscher et al. 2010).

When milbemycin oxime is administered in therapeutic doses, adverse effects are negligible. At higher dosages, for example when treating demodicosis, Collies with a MDR-1 mutation can show neurologic deficits. (Plumb 2005) In those dog breeds, milbemycin oxime leads to characteristic central-nervous symptoms like depression, mydriasis and salivation (Löscher et al. 2010).

8-week-old puppies which received high dosages up to 5-times higher than the RTD, showed no symptoms on the first day of application but the following days they showed ataxia and trembling (Plumb 2005). However, milbemycin toxicosis is suspected to be dose-dependent (Tranquilli et al. 1991). In MDR1-mutant dogs, overdosages of milbemycin oxime lead to neurological symptoms like ataxia, mydriasis, depression and salivation (Jaham and Henry 1995).

Patient information leaflets of drugs including milbemycin oxime and praziquantel state that neurologic symptoms like muscle tremor, ataxia and convulsions can occur in rare cases (less than 1 of 10.000 treated patients) (patient information leaflet of "Milbactor-Tabletten für Hunde" and "Milbactor Filmtabletten für Katzen " 2017; "Milbemax Kautabletten für Hunde" and "Milbemax Filmtabletten für Katzen" 2018; "Milpro-Filmtabletten für Hunde" and "Milpro Filmtabletten für Katzen" 2018).

Patient information leaflet of milbemycin oxime and lufenuron, does not state any neurological adverse effects. Only when overdosed, neurological deficits like ataxia, tremors, lethargy, salivation and mydriasis can occur (patient information leaflet of "Program Plus Tablette für Hunde" 2019).

5.2.4. Organophosphates and Carbamates

Organophosphates and carbamates inhibit the activity of cholinesterase. They cause muscarinic effects such as salivation, emesis, diarrhea, bronchospasms, miosis, and nicotinic effects like muscle fasciculations and weakness. Moreover, neuropathies can develop days to weeks after exposure (O'Malley and O'Malley 2020).

Generally, organophosphates are suspected to be irreversible inhibitors of the cholinesterase-activity, whereas carbamates are suspected to be slowly reversible inhibitors (Fikes 1990).

Usually, when organophosphate- or carbamate-toxicosis occurs, clinical symptoms of the muscarinic type are first observed, including hypersalivation, gastrointestinal hypermotility, bronchoconstriction, etc. Following these symptoms, nicotinic neuromuscular signs can be observed: muscle stiffness, fasciculations, tremors, weakness, and paralysis. Accumulation of acetylcholine in the central nervous system expresses itself with restlessness, anxiety, hyperactivity, seizures and mental depression (Fikes 1990).

5.2.4.1. Emodepside

Emodepside is available in combination with praziquantel in form of a spot-on solution for cats and in form of tablets for dogs to treat nematodes and cestodes (Gaens et al. 2019a).

This agent interferes with latrophilin receptors and calcium-activated potassium channels, which lead to muscle paralysis, inhibition of locomotion and also egg-laying of the parasites. This drug also interferes slightly with GABA-receptors. What is more, emodepside has low acute toxicity in dogs and cats and does not enter the central nervous system because of the P-glycoprotein-transporter at the blood-brain-barrier (Gaens et al. 2019a).

The main side effects of the combination drug with emodepside and praziquantel are primarily neurological. With increasing doses, muscle tremors occur and can get more severe and frequent, accompanied by incoordination and behavioral changes. These effects were transient, dissipating by themselves within eight hours (EMEA 2008).

As part of the approval of Profender® (Profender Tabletten mit veränderter Wirkstofffreisetzung für Hunde, Emodepsid + Praziquantel, Bayer Animal Health GmbH, Deutschland), the drug was tested in MDR1-mutant (-/-) Collies. Even though adverse neurological effects could not be observed at a dosage 2-times higher than the RTD, these agents were licensed with a strict note in the package information leaflet that these MDR1-mutant patients should be treated with particular caution (Elmshäuser et al. 2014).

In a new toxicity study for emodepside, male dogs showed neurological symptoms after overdosages of this agent including tremor and ataxia. Females additionally showed staggering gait, incoordination and a reduced overall health status at 20 mg/kg (EMEA 2008).

The patient information leaflet of the spot-on solution states that in very rare cases (less than 1 out of 10.000 treated patients) neurologic deficits like ataxia and tremors can occur. This

reaction is probably caused by licking of the applied spot right after treatment. After administering overdosages to cats, occasionally salivation, emesis and neurologic symptoms like tremors can be seen. These symptoms are only temporary and probably caused by licking of the affected area after the treatment (patient information leaflet of "Profender Lösung zum Auftropfen für Katzen" 2020).

After oral administration of the tablet, rare cases of mild neurologic disorders are described including tremors and coordination-disorders. Beyond that, dogs with a MDR-1-gene-defect can demonstrate more severe neurological disorders, including convulsions. After overdosing, temporary muscle tremors, coordination-disorders and lethargy were noted. These symptoms dissipated without any further treatment (patient information leaflet of "Profender Tabletten für Hunde" 2010).

In a case report, a 3-year-old Australian Shepherd was described to have suffered neurological toxicity following the administration of Profender® at RTD. Neurologic toxicity was shown as generalized tremor, panting and agitation, which resolved after symptomatic treatment. The dog was then tested regarding its MDR1-gene and revealed a homozygous mutation. Moreover, the Australian Shepherd was fed around the time of drug administration, which increases the release of the active substance and leads to an increased plasma drug level. Thus, overnight fasting is recommended by the manufacturer when dogs are treated with Profender® (Gaens et al. 2019a).

5.2.4.2. Praziquantel

Praziquantel is available for dogs and cats in form of a tablet, spot-on solution, and an injection solution. It is currently the most effective agent on the market against cestodes and trematodes (Riviere and Papich 2018).

The mechanism of action is a rapid paralytic muscle contraction and depends on the tegument destruction of the helminths (Fort 1998; Löscher et al. 2010).

Praziquantel is well tolerated in dogs and cats and toxicity studies indicate a wide margin of safety. Up to 50 mg/kg are well tolerated without any symptoms. Exceeding the dose of 50 mg/kg only led to emesis. Other than that, no adverse effects are described after oral administration of the tablet (patient information leaflet of "Droncit Tablette für Hunde und Katzen" 2020; Löscher et al. 2010; Plumb 2005). Subcutaneous injections in cats at doses of 50-100 mg/kg induced transient ataxia and depression, 200 mg/kg were lethal (Plumb 2005; Riviere and Papich 2018).

The patient information leaflet of the subcutaneously injectable solution states that the included benzyl alcohol can cause apathy, salivation, tremor, and ataxia in cats. Product descriptions of spot-on agents of praziquantel do not describe any neurological adverse effects. (patient information leaflet of "Droncit Spot-on zum Auftropfen auf die Haut für Katzen" 2020).

5.3. Anti-ectoparasitic agents

The effect mechanism of anti-ectoparasitic agents is generally a neurotoxic effect: larvae, nymphs and adult forms of arthropods are paralyzed. These toxic, neurologic effects lead to an immobilization and paralysis after an adequate time of application, and the parasites start to die off. If the application time is not adhered to, parasites can recover from the immobilizing effect and reinfest the host. Ectoparasites are principally treated locally at the infected spot. In some cases, ectoparasites can also be treated systemically (Löscher et al. 2010).

Oral ectocides are advantageous for pet owners, as they do not have to take care that the treated area is touched by human family members including children, or that other animals in the household lick the fur on which the drug has been applied. Other than that, antiparasitic drugs with a long lasting effect can also improve a continuous flea- and tick-treatment and most often, the animals' and the owners' compliance are thought to be better, when the frequency of the treatment can be reduced (Pirk 2015).

A consequent protection against ectoparasites is especially important in some regions and countries in specific seasons. When treating ectoparasites, the rapid mechanism of action and an uninterrupted speed of kill are important. Also, systemic anti-ectoparasitic agents decrease or prevent the transmission of tick-borne diseases. Thus, long-lasting agents are often needed and helpful in protecting dogs and cats against ectoparasites and pathogens vectored by them (Little 2017; Löscher et al. 2010).

5.3.1. Pyrethroids

Pyrethroids are deducted from the natural and insecticidal rapid-acting contact poison "pyrethrin" and are highly effective on all major arthropods. Their neurotoxic effect is based on the inhibition of sodium-channels. Thus, nerves fire constantly because of the absence of depolarization. The axonal stimulus is then disturbed, and consequently, loss of coordination, paralysis and death of the parasites occur (Dymond and Swift 2008; Löscher et al. 2010). Their high toxic activity on insects, but low toxic activity in dogs and cats is due to a rapid metabolism in mammals (Calore et al. 2000).

The effect on sodium channels is based on a negative temperature coefficient, which favors the cold blood of insects over the warm blood of dogs and cats. Consequently, pyrethroids have a greater impact on insects rather than dogs and cats (EMEA 2002).

Commonly used pyrethroids have a low acute toxic effect when applied topically. When cats accidentally get in contact with this agent, a high risk of intoxication is given, because cats are only poorly able to detoxify the drug by glucuronidation, which is responsible for the species' toxicity. Symptoms of pyrethroid-toxicity in cats include tremor, ataxia, convulsions, but they do not have anything to do with epileptic diseases (Löscher et al. 2010).

5.3.1.1. Permethrin

Permethrin is licensed for dogs as a spot-on agent in Austria and is used to treat flea-, tick-, and sand fly-infestation. (Austria Codex, access 2021).

Permethrin is an effective anti-ectoparasitic agent with low toxicity to dogs and has a wide safety margin when applied correctly (Dymond and Swift 2008).

Cats are particularly susceptible for toxicosis with pyrethroids due to their deficiency in glucuronidase. A study found out that most commonly (75 %), cats were intoxicated accidentally after dermal application of products, which are intended for large dogs (Dymond and Swift 2008).

Patient information leaflets of permethrin state that restlessness, tremors, convulsions, or ataxia can occur when treating animals with this agent. However, these reactions disappear after several hours when the agent is washed out of the fur (patient information leaflet of "Exspot Lösung zum Auftragen auf die Haut für Hunde 2012).

Patient information leaflets state that in combination with fipronil, transient neurologic symptoms like hyperactivity, restlessness, lethargy, depression, muscle tremors, convulsions, ataxia, etc. can occur. These side effects were transient and disappeared after 1 – 2 days (patient information leaflet of "Frontect Lösung zum Auftropfen für Hunde" 2019; "Effitix Lösung zum Auftropfen für Hunde" 2019).

Patient information leaflets state that in combination with imidacloprid, neurologic adverse effects can be observed. These symptoms are milder than other combination drugs, and include staggering gait, twitching and lethargy. Toxic reactions after accidental oral intake of the drug is unlikely, but can cause neurologic symptoms like tremor, lethargy, and incoordination (patient information leaflet of "Advantix Spot-on Lösung zum Auftropfen auf die Haut für Hunde" 2020; "Ataxxa Lösung zum Auftropfen für Hunde" 2018).

Patient information leaflets of the pharmaceutical drug combination of permethrin with dinotefuran and pyriproxyfen state that neurological adverse effects like hyperactivity, anxiety,

lethargy, muscle tremors, staggering gait and ataxia can occur. However, ataxia is only registered in very rare cases (less than 1 of 10 000 treated patients) (patient information leaflet of "Vectra 3D Lösung zum Auftropfen auf die Haut für Hunde" 2020).

Patient information leaflets of permethrin combined with indoxacarb, gives similar information: adverse effects include gastrointestinal and reversible neurologic symptoms like tremors, ataxia, lethargy and are generally transient and disappeared within 24 – 48 hours (patient information leaflet of "Activyl Tick Plus Lösung zum Auftropfen auf die Haut für Hunde" 2020).

5.3.1.2. Deltamethrin

Deltamethrin is licensed as a collar for dogs and is used to treat flea and tick infestations (Austria Codex, access 18.02.2021). Deltamethrin is supposed to be the most toxic pyrethroid for vertebrates (Toś-Luty et al. 2001).

In a study in anesthetized dogs, the median lethal dose of deltamethrin was tested after intravenous administration. Dogs were first given 1 mg/kg, where mild clinical signs were observed. At 3 mg/kg, convulsions could be noted. Approximately one hour later, death or recovery followed. Moreover, adverse effects like hypersalivation, abdominal spasms, irregular breathing, body tremors and twisting movements could be observed (Valentine 1990).

Patient information leaflets of deltamethrin state that in very rare cases (less than 1 of 10 000 treated animals) neurologic symptoms like ataxia and muscle tremor can be observed. However, these symptoms disappear on their own within 48 hours after taking off the collar. An accidental oral intake can lead to acute intoxication symptoms like incoordination, tremor, salivation, vomiting and stiffness of the hind limbs (patient information leaflet of "Scalibor Protectorband für Hunde" 2020; "Deltatic wirkstoffhaltiges Halsband für Hunde" 2019; "Prevendog wirkstoffhaltiges Halsband für Hunde" 2019).

5.3.1.3. Flumethrin

Flumethrin is licensed as a collar for dogs and cats and is used to treat flea and tick infestations (Austria Codex, access 18.02.2021).

Patient information leaflets do not record any neurological adverse reaction when flumethrin was used in combination with propoxur. Only dermatological or mild gastrointestinal side effects are noted. Moreover, these leaflets state that overdosages are not to be expected. In controlled tests, two collars were administered simultaneously, but no local or systemic adverse effects could be found (patient information leaflet of "Frento forte Zecken- und

Flohschutzband Halsband für Katzen und Hunde" 2020; "Kiltix Halsband für Katzen und Hunde" 2020; "Frento forte Flohschutztropfen Lösung zum Auftropfen für Katzen" 2020).

However, prescribing information of flumethrin combined with imidacloprid states that in very rare cases (less than 1 of 10 000 treated animals) neurologic symptoms were observed including ataxia, convulsions and tremors. In such cases, the collar shall be removed immediately. Nevertheless, patient information leaflets describe that overdosage-symptoms are unlikely to occur (patient information leaflet of "Seresto Halsband für Hunde" 2020; "Seresto Halsband für Katzen" 2020).

5.3.2. Carbamates

The effect mechanism of carbamates is the inhibition of cholinesterase which leads to a disturbance in neuro-muscular transmission of the cholinergic nervous system of insects. Thus, paralysis of the parasites follows. When extensive skin lesions are treated with carbamates, parasympathomimetic adverse effects can occur (Löscher et al. 2010).

5.3.2.1. Propoxur

Propoxur is licensed in Austria as a collar and spraying solution for dogs and cats and a shampoo for dogs. The collar is used against fleas and ticks and the shampoo to treat fleas and lice (Austria Codex, access 18.02.2021).

Patient information leaflets of propoxur state that no neurological side effects are suspected when this agent is administered. Only mild gastrointestinal and dermal adverse reactions were observed. When this drug is accidentally taken in orally, it can lead to signs of carbamate poisoning with the following symptoms: salivation, miosis, vomiting and diarrhea (patient information leaflet of "Bolfo Zecken- und Flohschutspray für Hunde und Katzen" 2019; "Bolfo Flohschutz-Shampoo für Hunde" 2020; "Bolfo Zecken- und Flohschutzband für Katzen und Hunde" 2020). Drugs combined with flumethrin do not describe any neurological side effects (see 5.3.1.3. Flumethrin).

5.3.3. Macrocyclic Lactones

As already mentioned, macrocyclic lactones are effective against gastrointestinal endoparasites as well as ectoparasites. Information about the effect mechanism of macrocyclic lactones can be found in chapter 5.2.3.

5.3.3.1. Ivermectin

Even though ivermectin has not been approved for dogs and cats in Austria, the agent is listed in this thesis, as it can be used against antiparasitic infections in dogs and cats. Moreover, accidental use and overdoses of this agent in small animals often occurs. For example, large doses of accidental intake of equine products in cats has resulted in neurological toxic consequences like severe ataxia, disorientation, whole body tremors, mydriasis, blindness, walking into walls, head pressing, loss of most reflexes, coma and death (Lovell 1990).

Only the ear ointmemt Otimectin® (Otimectin vet. 1 mg/ml Ohrengel für Katzen, 1 mg Ivermectin, Le Vet B.V., Niederlande), a licensed anti-ectoparasitic agent against ear mites in cats, will be discussed in this chapter. Otimectin® is the only pharmaceutical drug which contains ivermectin and is licensed for cats only in Austria. When the ear ointment is used to treat ectoparasitic infections in defect ear drums, adverse reactions, which inhibit the central nervous system, can occur. Neurologic deficits like apathy, anorexia, mydriasis, ataxia, tremor, and salivation are observed (patient information leaflet of "Otimectin vet. 1 mg/g Ohrengel für Katzen" 2003).

5.3.3.2. Spinosad

Spinosad is a mixture of two compounds of macrocyclic lactones: spinosyn A and spinosyn D and belongs to the group of tetracyclic macrolides. This agent does not belong to the group of macrocyclic lactones, but as this agent is related to this class, this agent will be described in this following paragraph. Spinosad is administered orally in form of tablets and has an insecticidal effect. This agent is used to treat flea infestations. Its effect mechanism is an activation of nicotinic acetylcholine-receptors, where the spinosyns bind on another site than the neonicotinoids. Additionally, spinosad causes hyperpolarization due to a prolonged opening of GABA-controlled chloride-channels. After initial excitation of the parasites, paralysis and necrosis follows (Austria Codex, access 18.02.2021, Löscher et al. 2010; Vo et al. 2010).

In a study, spinosad was tested at overdoses in adult ivermectin-sensitive Collies. As a result, vomiting and mild salivation were noted as side effects. Other than that, no adverse reactions, including neurological ones, could be observed. The results show that spinosad at the given dosages does not induce signs of toxicosis in ivermectin-sensitive Collies (Sherman et al. 2010).

In studies, performed in Europe, two dogs with a history of epilepsy suffered from seizures while being treated with spinosad. This event could be incidental, but precautions should be taken when animals with neurologic diseases are treated with this agent (EMEA 2011).

Patient information leaflets of spinosad state that gastrointestinal symptoms like vomiting are commonly observed. Occasionally (more than 1, but less than 10 out of 1 000 treated animals) lethargy, anorexia, diarrhea and in rare cases (less than 1, but more than 10 out of 10 000 treated animals) muscle tremors, ataxia and convulsions could be observed (patient information leaflet of "Comfortis Kautabletten für Hunde und Katzen" 2020).

5.3.4. Isoxazolines

Isoxazolines have been licensed in Austria since 2014 and have acaricidal and insecticidal effects. The effect mechanism is a blockage of specific GABA- and glutamate-gated chloride-channels, which inhibit the intake of chloride ions. Due to this, nerves are stimulated, parasites are initially hyperexcited, then paralyzed and die off (Löscher et al. 2010).

The safety of isoxazolines in mammals is based on a selectivity for neurons that are only present in the central nervous system of insects and not in mammals (Kuntz and Kammanadiminti 2017). Most of the registered isoxazolines are claimed to have an adequate safety margin and are thought to be insect specific (Palmieri et al. 2020). Nevertheless, it cannot be ruled out completely that these agents really do not target those channels in vertebrates (Gaens et al. 2019b). A survey conducted on veterinarians and owners showed that the neurotoxicity of isoxazolines in dogs is not arthropod-specific and can work as an intrinsic neurotoxin across species. Dogs were given an isoxazoline for tick- and flea-treatment and the following adverse reactions were then compared with the numbers of side effects published by the US-Food and Drug Administration (FDA) and the European Medicines Agency (EMA). What is more, not all dogs showing neurological signs like ataxia, tremors, or seizures, progressed to death, but 21 - 31% of the dogs which died, also suffered from seizures. Based on the results, the survey concludes that the neurotoxicity of isoxazolines was not flea- and tick-specific and studies across species should be surveyed in the future (Palmieri et al. 2020).

The FDA claims that neurological side effects can occur in dogs and cats after treatment with isoxazolines, but nevertheless, they consider these products to be safe and effective at their recommended therapeutic doses. Pet owners and veterinarians should be alerted to the fact that neurological reactions can be experienced, even without a medical history. Manufacturers

of isoxazolines and the FDA are working together to produce new label information to highlight neurological adverse effects because these events occur regularly (Palmieri et al. 2020).

5.3.4.1. Afoxolaner

Afoxolaner is an anti-ectoparasitic agent which is licensed as an oral tablet for dogs to treat flea and tick manifestations, demodicosis and sarcoptic mange. This agent is also licensed in combination with milbemycin oxime, which additionally treats gastrointestinal nematodes. (EMEA 2013; Löscher et al. 2010).

At standard dosages, afoxolaner is safe in dogs and is also well tolerated. In a study, administration of 5-times higher than the RTD only lead to mild gastrointestinal symptoms. In another pharmacokinetic study, afoxolaner was given to ivermectin-sensitive Collies. Generally, this agent was tolerated well, and it has been confirmed that the P-glycoprotein-transporter did not play any role in the transport of this agent (EMEA 2013).

Patient information leaflets of afoxolaner state that adverse effects like mild gastrointestinal and neurologic symptoms can occur. Neurologic side effects include convulsions, ataxia, tremors, and were transient and only occurred in very rare cases (less than 1 of 10 000 treated animals) (patient information leaflet of "Afoxolaner Merial Kautabletten für Hunde 2019"; "NexGard Kautabletten für Hunde 2019").

5.3.4.2. Fluralaner

Fluralaner has an acaricidal and insecticidal effect on ticks, fleas, mites, and is available in form of tablets for dogs and in form of a spot-on solution for dogs and cats (Austria Codex, access 18.02.2021).

Fluralaner is generally well tolerated in dogs, but it has been stated that neurological disorders occurred in individual animals. Nevertheless, these cases have not been documented adequately and just a few of them is reported or discussed in any literature (Gaens et al. 2019b).

As already mentioned, fluralaner inhibits glutamate- and GABA-gated chloride channels in arthropods (Walther et al. 2014). Experiments on several membranes show that the binding affinity to vertebrate receptors is much lower compared to arthropod receptors. However, it cannot be completely ruled out that fluralaner also binds to vertebrate receptors which are exclusively expressed in the central nervous system. Based on the localization of the receptors, they can cause neurological symptoms (Löscher et al. 2010).

One case report stated that a seven-month-old female Kooikerhondje dog suffered neurologic symptoms after 24 hours of treatment with fluralaner. Those neurologic signs included generalized ataxia, myoclonic jerks, tremor, muscle twitching and oral dysphagia. However, it cannot be determined whether this event was incidental or fluralaner induced. (Gaens et al. 2019b).

In clinical studies fluralaner has been well tolerated in dogs, but recently more cases of neurological adverse drug reactions were reported. These neurological signs included tremors, ataxia and seizures (Gaens et al. 2019b). However, the Committee for Veterinary Medicinal Products (CVMP) stated that these neurologic symptoms are reported very rarely and it is considered that fluralaner is safe when administered correctly. Nevertheless, dogs with pre-existing epilepsy should be treated with caution (Gaens et al. 2019b).

Patient information leaflets of fluralaner for cats state that neurologic signs right after treatment are recorded in 0,9 % of treated patients and included apathy and tremor (patient information leaflet of "Bravecto Lösung zum Auftropfen auf die Haut für Katzen 2019).

Patient information leaflets of fluralaner for dogs state that mild gastrointestinal symptoms can occur. Neurological adverse effects are seen in very rare cases (less than 1 of 10 000 treated animals) and included convulsions and lethargy. (patient information leaflet of "Bravecto Kautabletten für Hunde" 2019; "Bravecto Lösung zum Auftropfen auf die Haut für Hunde)" 2019). Overall, oral administration of the chewable tablet is well tolerated in dogs and has a safe therapeutic margin (Walther et al. 2014).

For additional information regarding the effects and side effects of fluralaner, the Diploma Thesis by Magdalena Potocnik (2021) “Effects and suspected adverse effects of fluralaner (Bravecto®) and their representation on social media” can be recommended.

5.3.4.3. Lotilaner

Lotilaner is an anti-ectoparasitic agent which is administered orally in form of tablets for cats and dogs (Austria Codex, access 18.02.2021). When given in higher doses, no adverse reactions could be observed. Field trials with lotilaner prove that flea infestations are eliminated successfully and flea allergy dermatitis is reduced significantly (Little 2017).

In a study, the agent was tested on beagle puppies, which were treated with overdoses. Overall, no lotilaner-related adverse effects could be observed. In conclusion, this agent was well

tolerated in beagle puppies and did not cause effects of toxicological concern (Kuntz and Kammanadiminti 2017).

Lotilaner is also one of the few oral formulation for cats to treat parasites. In cats, this agent is rapidly absorbed and has a good safety profile, which is important, as cats are particularly susceptible to toxic effects of some antiparasitic drugs due to their weakness in glucuronidation (Wright 2018).

Lotilaner is licensed as a flavored chewable tablet and is rapidly absorbed (Kuntz and Kammanadiminti 2017; Cavalleri et al. 2017). Scientific reports of the European Medicine Agency state that neurologic side effects such as ataxia, tremor or convulsion can occur in very rare cases and are, most often, transient. When overdosed in puppies and kittens no side effects could be observed (patient information leaflet of "Credelio Kautabletten für Katzen" 2018; "Credelio Kautabletten für Hunde" 2018).

5.3.4.4. Sarolaner

Sarolaner is an anti-ectoparasitic agent which is licensed as a tablet and as a spot-on agent in dogs and cats (Austria Codex, access 18.02.2021).

In a safety study, signs of neurological disorders including tremor, ataxia and convulsions could be overserved when the agent was overdosed (Gaens et al. 2019a).

The European Medicines Agency states that adverse effects with sarolaner are uncommon and seen in less than one dog in 10 000, and include mild gastrointestinal symptoms, tremor, ataxia, or convulsions. These signs usually disappeared without any treatment. (EMEA 2015)

The safety of sarolaner has been investigated in several studies, which results are listed below:

- Sarolaner was given to beagle puppies in an overdose once monthly. In this study, the agent was generally well tolerated, but neurological effects were noted, including tremors and ataxia, and at higher doses convulsions, tremors, and ataxia.
- A safety study in dogs reports that a high oral dosage (62 mg/kg) caused effects on the nervous system.

To summarize, neurologic disorders appear in dogs at dosages of 3-times higher the maximum RTD, and generally expressed as tremors. At higher dosages, signs are more severe and include convulsions. Furthermore, increased plasma exposures are associated with neurological signs, but this is not necessarily predictive of neurologic adverse effects. It is suspected, that certain individual dogs are more sensitive than others (EMEA 2015).

Patient information leaflets of sarolaner state that in very rare cases (less than 1 of 10 000 treated animals) affected patients showed mild gastrointestinal adverse effects and neurological symptoms like tremor, ataxia and convulsions. All animals recovered from the symptoms without any treatment (patient information leaflet of "MiPet Easecto Kautabletten für Hunde" 2020; "Simparica Kautabletten für Hunde" 2019).

5.3.5. Phenylpyrazoles

The effect mechanism is a non-competitive blockage of GABA-controlled chloride-channels in the nervous system of arthropods. As a result, hyperexcitability and uncontrolled central nervous activity occurs, following necrosis of the parasites (Löscher et al. 2010).

5.3.5.1. Fipronil

Fipronil is licensed in Austria as a spraying solution for a full body treatment and as a spot-on-formulation to treat fleas, ticks, and lice. (Austria Codex, access 18.02.2021).

Clinical side effects are expected to be mild and self-limiting and include drooling and intermittent vomiting. When high doses are administered, seizures can be expected (Hovda and Hooser 2002).

After dermal administration of fipronil, the drug is only resorbed in small amounts, so the bioavailability after accidental licking of the treated spot, is also very low. Using this agent at standard dosages, no side effects were observed. Even after application of dermal overdoses no noticeable adverse effects are described. However, after repeated oral overdoses of the pure substance, dogs showed reversible neurologic signs of hyperexcitability, tremors and convulsion (Löscher et al. 2010).

Patient information leaflets of fipronil state that increased salivation can occur when the treated site is licked. In rare cases, dermatological reactions and reversible neurologic adverse effects like hypersensitivity, depression and other neurological symptoms could also be observed (patient information leaflet of "Bob Martin Clear Spot on Lösung zum Auftropfen für Hunde" 2016; "Flevox Spray zur Anwendung auf der Haut, Lösung für Katzen und Hunde" 2014; "Flevox Spot-on Lösung für Katzen" 2019; "Flevox Spot-on Lösung für Hunde" 2019; "Eliminall Spray zur Anwendung auf der Haut, Lösung für Katzen und Hunde" 2015; "Eliminall Lösung zum Auftropfen für Hunde" 2016; "Effipro Spray zur Anwendung auf der Haut, Lösung für Katzen und Hunde" 2017; "Effipro Lösung zum Auftropfen für Katzen" 2017; "Effipro Lösung zum Auftropfen für Hunde" 2017; "Pestigon Lösung zum Auftropfen für Katzen" 2019;

"Pestigon Lösung zum Auftropfen für Hunde" 2019; "Frontline Pumpspray für Hunde und Katzen" 2020; "Frontline Spot on Hund Lösung zum Auftropfen auf die Haut für Hunde" 2020; "Frontline Spot on Katze Lösung zum Auftropfen auf die Haut für Katzen" 2020).

However, prescribing information of the Frontline® Pumpspray (Frontline 1,5 ml Pumpspray für Hunde und Katzen, 0,25 g Fipronil/100 ml, Boehringer Ingelheim, Deutschland) states that neurologic side effects like tremors, ataxia, mydriasis, and paresis of the hind limbs are possible. The drug's safety was tested on dogs at a dose of 5-times higher the RTD. In single cases, vomiting, ataxia, tremor, and depression were recorded. In cases of extreme overdoses, deaths could not be excluded (patient information leaflet of "Frontline Pumpspray für Hunde und Katzen" 2020).

Combined drug formulations with permethrin also recorded neurologic adverse effects (See 5.3.1.1. Permethrin).

5.3.5.2. Pyriprole

Pyriprole is licensed in Austria as a spot-on solution for dogs and is used to treat fleas and ticks (Austria Codex, access 18.02.2021).

At standard dosages, only dermatological side effects could be observed. Licking the treated spot right after applying the agent led to salivation for a short time. After overdosages of 3- to 5- times higher than the RTD, reversible neurologic symptoms like restlessness and mild incoordination could be noticed (Löscher et al. 2010).

After a single topical administration of 10x the RTD, this agent caused neurological symptoms like muscle tremors, ataxia, seizures, convulsions, inability to control limbs, weakness and unsteadiness (patient information leaflet of "Prac-tic Lösung zum Auftropfen für Hunde" 2018; EMEA 2012).

The Committee for Medicinal Products for Veterinary Use (CVMP) states that the adverse effects of pyriprole correlates with the interaction of GABA receptors. Pyriproles can inhibit the GABA-gated chloride channels, which lead to a blockage of the transfer of chloride ions resulting in uncontrolled activity of the central nervous system including incoordination, muscle tension, ataxia, tremors, and convulsions (EMEA 2012).

Patient information leaflets of pyriprole states that dermatologic reactions on the treated area, gastrointestinal symptoms and neurologic adverse effects like ataxia, incoordination and convulsions can occur. These symptoms were transient and disappeared within 24 hours. Mild

neurological symptoms like restlessness and mild incoordination were observed in single animals. After a one-time overdosage of 10x higher than the RTD more severe symptoms occurred including muscle tremors, restlessness, convulsions, and strained breathing. All these symptoms disappeared on their own 48 hours after treatment (patient information leaflet of "Prac-tic Lösung zum Auftropfen für Hunde" 2018).

5.3.6. Neonicotinoids

Neonicotinoids are nicotinic agonists, which bind on postsynaptic cholinoceptors in the nervous system of insects. Its mechanism of action is the binding to nicotinic acetylcholine receptors (nAChR), which leads to an influx of natrium and calcium and efflux of potassium. Consequently, a permanent depolarization of the neurons is given, which leads to paralysis and death of the parasites (Löscher et al. 2010; Vo et al. 2010).

Neonicotinoids are particularly toxic against insects and are well tolerated by dogs and cats, because these agents only have a low affinity to nicotinic receptors in vertebrates. The effect on vertebrates is 100-times lower and only lasts for a short time. In brains of vertebrates no specific binding sites for neonicotinoids could be found (Löscher et al. 2010; Vo et al. 2010).

5.3.6.1. Imidacloprid

Imidacloprid is licensed for dogs and cats in form of a spot-on solution which is applied topically and kills adult fleas rapidly. Imidacloprid is also licensed in combination with permethrin against additional tick infestation or in combination with moxidectin to prevent heartworms and to kill gastrointestinal nematodes and mites (Austria Codex, access 18.02.2021; Vo et al. 2010).

When administered dermally at standard dosages, imidacloprid is well tolerated by dogs and cats. When the treated spot is accidentally licked, transient salivation can be observed (Löscher et al. 2010).

Overdosage symptoms after accidental oral intake include signs of central nervous hyperexcitation up to convulsions, locomotory incoordination, ataxia, tremor, mydriasis and affected breathing (Löscher et al. 2010).

Patient information leaflets of imidacloprid state that signs of restlessness and disorientation could be observed after taking the drug. In single cases, increased salivation and nervous symptoms like incoordination, tremors and depression were also recorded. When overdosed or when the treated spot is accidentally licked, central nervous disorders like twitching, tremors, ataxia, mydriasis, miosis and lethargy can occur (patient information leaflet of "Exidot Lösung

zum Auftropfen für Hunde" 2019; "Advantage Lösung zum Auftropfen auf die Haut für Hunde" 2020; "Frento forte Flohschutztropfen Lösung zum Auftropfen für Katzen" 2020).

Neurologic adverse effects are also described when combined with the agent permethrin and flumethrin (see 5.3.1.1. Permethrin, 5.3.1.3. Flumethrin).

Patient information leaflets state that in combination with moxidectin, accidental oral intake of the spot-on solution or after overdosages, neurologic symptoms like lethargy, salivation, ataxia, and generalized tremor can occur (less than 1 of 10 000 treated animals). However, most of the symptoms were only transient. Ivermectin-sensitive Collies tolerated monthly treatments with dosages up to 5-times higher than the RTD without any unwanted side effects. However, when 40 % of the topical spot-on solution was taken in orally by Collies, severe neurologic symptoms were recorded (patient information leaflet of "Prinocate Lösung zum Auftropfen für Hunde" 2020; "Advocate-Lösung zum Auftropfen für Hunde" 2019).

5.3.6.2. Nitenpyram

Nitenpyram is administered in form of tablets against flea infestations for dogs and cats. This agent is licensed as an oral tablet for short-term control of fleas. Nitenpyram is commonly used in combination with an insect development inhibitor to provide continuous flea control (Austria Codex, access 18.02.2021).

The effect mechanism is a binding to specific nicotinic acetylcholine receptors, which interfere with nerve transmission in the insect and die off (Dobson et al. 2000).

Nitenpyram is well tolerated by dogs and cats at standard dosages: no side effects, except for transient itching at the application site, are noted. Overdosage symptoms could be seen when dosed 100-times higher than the RTD. These symptoms included: salivation, vomiting, tachypnoea and convulsions. However, these symptoms disappeared on their own after 24 hours (Löscher et al. 2010).

This agent has a low toxicity for mammals, as nitenpyram is highly selective for nicotinic receptors of insects and only has low affinity for mammalian receptors (Dobson et al. 2000).

Patient information leaflets of nitenpyram state, that this agent is well tolerated by dogs and cats. Adverse effects, when a higher dosage than the RTD is given include salivation, vomiting, diarrhea, tremors, ataxia, convulsions, and in very rare cases (less than 1 of 10 000 treated animals) lethargy. The severity increases with higher dosages, but the symptoms disappear rapidly. The animals recover within 24 hours after the overdose, as nitenpyram is eliminated

quickly by the body (patient information leaflet of "Capstar Tabletten für Katzen und Hunde" 2019).

5.3.6.3. Dinotefuran

Dinotefuran is licensed as a spot-on agent and prevents fleas for at least 30 days. In combination with permethrin, it is licensed for dogs and has an additional property to treat ticks. In combination with pyriproxyfen, it is licensed for cats to break the life cycle of fleas (Austria Codex, access 18.02.2021; Vo et al. 2010).

Patient information leaflets state that besides dermatological problems, behavior disorders like hyperactivity, anxiety, and neurological adverse effects like muscle tremors could be observed in rare cases (more than 1 but less than 10 out of 10 000 treated animals) when dinotefuran was used in combination with pyriproxyfen and permethrin. Neurological signs like ataxia and insecure gait were recorded in very rare cases (less than 1 out of 10 000 treated animals). (patient information leaflet of "Vectra 3D Lösung zum Auftropfen auf die Haut für Hunde" 2020).

Patient information leaflets of the combined drug with pyriproxyfen for cats state that no neurological signs were observed, after administration of the spot on agent (patient information leaflet of "Vectra felis-Lösung zum Auftropfen auf die Haut für Katzen" 2019).

5.3.7. Indoxacarb

Indoxacarb is an anti-ectoparasitic agent which is licensed to treat adult and larval stadiums of fleas in form of a spot-on formulation for cats and dogs. For dogs, also a combination with permethrin is licensed, which also treats ticks (Austria Codex, access 18.02.2021).

There are only few adverse reactions described, for example pruritis, skin irritations and after accidental oral intake, transient salivation (Löscher et al. 2010).

Patient information leaflets of indoxacarb state that in rare cases neurologic adverse effects like incoordination, tremor, ataxia, convulsions, and mydriasis can occur. After repeated overdosages in puppies, only signs of hypersalivation could be seen (patient information leaflet of "Activyl Lösung zum Auftropfen auf die Haut für Hunde" 2020).

5.4. P-glycoprotein-transporter (P-gp), Multidrug-resistance-gene-1 (MDR1)

The permeability glycoprotein (P-gp) or ABCB1 (ATP-binding-cassette-transporter-1) which is encoded by the multidrug-resistance-gene (MDR1), is an efflux transporter which pumps potentially harmful chemicals out of cells. It is an ATP-dependent efflux pump and plays an important role at the blood-brain-barrier. There, it prevents the transit of potentially toxic substances in the brain. This efflux pump protects the animals from high drug concentrations which could cause neurological toxicity. Until today, more than 100 pharmacological substances are known, which are transported by MDR1 or substances which block this transporter (Potschka 2010). Multidrug-transporters are expressed in all cells of the body to protect the organism from endogenous and exogenous toxins. In various studies, it was proven, that antiepileptic drugs are substrates of the P-glycoprotein-transporter. In investigations of drug-resistant epilepsies, the inhibition of P-glycoprotein was successful and the intake of antiepileptic drugs in the brain was clearly increased (Unkrüer 2008).

When treating epilepsy, there is a chance, that drug resistant patients do not respond to their therapy. Those patients have tried at least two different anticonvulsive drugs and still suffer from epileptic seizures. The effect mechanism of drug resistances is quite controversial, but the most common thesis is the “multidrug-transporter hypothesis”. It is suspected that an overexpression of efflux transporters at the blood brain barrier prevents sufficient concentrations of antiepileptic drugs reaching neuronal tissue. Investigations in human and animal models show, that in drug resistant individuals, an increased expression of the multidrug transporter P-glycoprotein is detected. This knowledge could help prevent these drug resistances. Researchers could already prevent epileptic seizures through inhibition of certain enzymes and thus, the inhibition of the overexpression of p-glycoprotein (Bauer et al. 2008).

In dogs, the MDR1-protein can lose its full function due to a 4-bp-deletion in the gene. Dogs with a homozygous mutation of the MDR-1-gene (MDR1 -/-) do not have a sufficient amount of the MDR-1-transporter at the blood-brain-barrier, thus they have increased levels of pharmaceutical substances in the brain and consequently, more drug intolerances can occur. Especially antiparasitic agents can increasingly cross the blood brain barrier, when the MDR1-protein is defect. For example, avermectins can exceed the plasma levels 30-times and since this agent is known to be a neurotoxic drug, it reaches neurotoxic concentration even at low doses (Elmshäuser et al. 2014; Löscher et al. 2010).

The MDR1-defect is responsible for neurologic adverse effects in dogs with a mutation in this gene, but it has got nothing to do with the disease “epilepsy”. Epileptic patients can randomly have a MDR-1-defect, but epilepsy-diseased patients are not predisposed for this gene mutation. Therefore, not all epileptic patients suffer from this gene mutation, but epileptic patients, which suffer from this gene disease, do have a higher risk of neurologic side effects.

This hypersensitivity is suspected for mostly avermectins and milbemycins, but as ivermectin is more potent for the MDR-1-P-glcoprotein-transporter, even low dosages lead to overdosing symptoms. Over 50% of overdosed patients suffered death, whereby increased ivermectin-concentrations could be proved in the brain (Löscher et al. 2010).

In Collies with a MDR1-defect, low ivermectin doses (100-500 µg/kg) already caused side effects, so it is supposed that ivermectin penetrates their blood-brain barrier more than in other dog breeds. 1 ml of subcutaneous injection in a young Collie lead to mydriasis, ataxia, depression, blindness, spastic movements etc. In a study, seven out of 14 Collies expressed seizure-like activity, non-responsiveness, recumbency and coma after oral administration of ivermectin. In another study, three out of 14 Collies after an oral dose of ivermectin suffered from hypersalivation, vomiting, confusion, ataxia, and tremors (Lovell 1990).

Emodepside and praziquantel are also transported by the MDR1-protein, but when this protein is defect, high concentration of these substrates can accumulate in the brain. In a retrospective study, drug intolerances after administration of emodepside/praziquantel (Profender®) was tested in MDR1-mutant (-/-) dogs. The most frequent adverse effects were ataxia, salivation, shivering, tremors and in some cases convulsions. Other adverse effects included paralysis, depression, apathy, mydriasis, nystagmus, vomiting and diarrhea. These symptoms lasted between two hours and several days. Most of these adverse reactions affected Collies, Australian Shepherds and Shetland sheepdogs. However, almost 80 % of the dogs with a homozygous MDR-1 defect were affected by drug intolerances. In the same study, one MDR1-mutant-dog (-/-) was an epileptic patient, but only with one to two convulsions per year. In this dog, the course and the characteristics of adverse reactions did not differ from the other animals. It is also advised, that dog should be examined and evaluated before administration of Profender® if a MDR1-defect exists (Elmshäuser et al. 2014).

In a study in laboratory mice, emodepside was injected in MDR1-defect and MDR1-intact animals. A part of the mice was euthanized two hours after application: the MDR-1 intact mice did not show any plasma concentration of emodepside, whereas MDR-1-defect mice showed

twice as high emodepside-concentrations in the plasma. This fact speaks for a good brain penetration of emodepside at the blood-brain barrier in MDR-1-defect animals. Another part of the mice were examined after application of emodepside and clinical symptoms could be observed including, ataxia, anxiety, loss of orientation, etc. (Elmshäuser et al. 2014).

5.5. Cytochrom-P-450-enzymes

Cytochrome-P-450-enzymes are proteins which are bound to the membrane and are a part of the “heme-containing” proteins. These enzymes can be found in bacteria, fungi, plants, and animals and are named after their ability to absorb light at 450 nm (Waigner 2019).

These enzymes can appear in all organs but are especially predisposed in liver cells and are common in the membrane of the endoplasmic reticulum. Cytochrom-P-450-enzymes are involved in oxidation of endogenous and exogenous substances (particularly drugs). For example, pharmaceutical drugs can be converted by cytochrom-P-450-enzymes to substrates. Depending on how much the enzymes are influenced, whether the enzymes are degraded rapidly or slowly, different drug interactions can occur (DocCheck; access 31.01.2021).

In case of antiparasitic drugs, particularly praziquantel is metabolized in the liver by cytochrome-P-450 enzymes. When this drug is given to treat gastrointestinal parasites in dogs and cats, interactions with patients under treatment of phenobarbital occurs, as phenobarbital is an inducer of this enzyme. Consequently, serum blood levels of praziquantel can be decreased in these patients, thus there will be less to no effect of this antiparasitic agent (Waigner 2019).

Moreover, patient information leaflets of praziquantel describe drug interactions with antiepileptic drugs when taken in at the same time, as this combination leads to decreased serum concentrations of praziquantel. Drugs, which increase the effects of cytochrome-P-450 enzymes, i.e. phenobarbital, decrease the plasma levels of praziquantel. (patient information leaflet of "Canifelmin-Injektionslösung für Hunde und Katzen" 2013; "Zipyran Tabletten für Hunde").

5.6. Owners' adverse drug experiences on internet websites – selected examples

In my thesis, I also want to present some webpages on the internet, where a lot of neurological side effects and even deaths are being discussed because of antiparasitic agents. A lot of these websites resemble conspiracy theories, nevertheless, we must take the fact seriously that neurologic adverse reactions after administration of antiparasitic treatment are possible in dogs and cats.

For example, the website "https://www.isbravectosafe.com/index.htm" (access 05.02.2021) tells a story of a 12-years-old dog which dies one months after the administration of Bravecto® (Bravecto Kautabletten für Hunde, Fluralaner, Intervet International B.V., Niederlande). The author puts the blame on the antiparasitic treatment. In her story she tells that the dog already suffered from heart problems and after administration of fluralaner, the dog developed a fever, which is very uncharacteristic for this agent. The owner also refused an examination in a specialized clinic at the costs of the manufacturer MSD and did not mention any visits or examinations or treatments by a veterinarian. Also, no pathologic examination was performed to prove that Bravecto® was the cause of the dog's death.

Other cases have been uploaded on this website by owners from all over the world. Most of the dogs in these stories suffered from neurologic side effects or died, with the antiparasitic treatment Bravecto® being blamed. All these patients who died after the administration of fluralaner, were suffering from other systemic diseases as well. So, these case reports are to be treated with great caution, as in most of the cases, the death of the pets are associated with other systemic diseases and not associated with antiparasitic treatment. Again, more information regarding this topic, the Diploma Thesis by Magdalena Potocnik (2021) "Effects and suspected adverse effects of fluralaner (Bravecto®) and their representation on social media" can be recommended.

Another controversial webpage is the group "Does Nexgard Kill Dogs" https://www.facebook.com/groups/704330073037200/ (access 05.02.2021) on Facebook. A lot of owners tell their story about their dog who suffered from neurologic side effects or dies after administration of the tablet. A lot of these reports also reveal that the pets suffered from other diseases as well after taken in the antiparasitic treatment. One owner told that the veterinarian had suspected a systemic disease but the owner did not have enough money to pay for more examinations regarding to his pet's neurological disease, so he blames the tablet Nexgard® (NexGard Kautabletten für Hunde, Afoxolaner, Boehringer Ingelheim Vetmedica

GmbH, Deutschland) to have killed his dog. In this group, very strong and negative opinions towards Nexgard® are described by pet owners although most of their pets are suffering from other systemic diseases.

A petition website against Simparica® (Simparica Kautabletten für Hunde, Sarolaner, Zoetis Belgium SA, Belgien) https://www.change.org/p/petition-for-the-immediate-withdrawal-of-simparica-flea-tick-treatment-from-the-market (access 05.02.2021) states that an owner's dog passed away after the administration of the antiparasitic agent sarolaner. This was the reason why the author started a petition for the withdrawal of Simparica®. However, when reading this owner's story, it was revealed that the dog had already been suffering from liver disease, acute pancreatitis, Cushing disease and kidney problems. Nevertheless, the owner is very sure that Simparica® killed her dog because her pet's condition started to worsen when the tablet was administered.

With cases like these, the given information has to be assessed very carefully, as the owners tell their stories very subjectively and only associate their pets' death with the administration of a tablet a few days or weeks prior to that. What they do not see is that other systemic diseases may already have progressed. Also, in all these cases no pathologic examination was conducted and not one article has been written by a professional. These stories and articles are mostly composed by emotional, partly hurt and angry pet owners, who are grieving the loss of their pets. However, the possibility of neurologic side effects that can occur after administration of isoxazolines have to be taken seriously.

6. Discussion

Until today, no specific statements can be made about which antiparasitic agents are safe to use in epileptic dogs and cats. There is no literature available, which gives explicit recommendations or instructions about the choice as to which antiparasitic agent to use for epileptic patients in terms of its possible proconvulsive effects.

The problem when writing this review was the lack of information about this issue. Just a small number of publications could be found and moreover, papers, studies and reviews on this precise topic were hard to find in scientific literature. With the aid of numerous patient information leaflets and the limited scientific information, the issue on antiparasitic treatment in epileptic dogs and cats was examined. Nevertheless, it is hard to find an answer in literature which antiparasitic treatment is suitable for epileptic dogs and cats.

No package information leaflet and no reports of the European Medicines Agency state that any of the discussed antiparasitic agents are not licensed for epileptic dogs and cats. Not even recommendations concerning neurologic diseased animals regarding the use of antiparasitic drugs are provided in literature. Only the scientific report for spinosad of the European Medicines Agency state that precaution in dogs with a history of epilepsy should be taken. However, antiparasitic agents are not prohibited, on the contrary, they may also be necessary for neurologic diseased dogs and cats and therefore, the application of these products is allowed for these patients. Nevertheless, an individual benefit-risk assessment for epileptic dogs and cats should be evaluated in each case. Again, the benefit and risks of neurological side effects should be thoroughly assessed and in case of doubt, only antiparasitic agents with no/low risk regarding neurologic adverse effects should be chosen.

This thesis is based on the effect mechanism and possible neurologic side effects of conventional antiparasitic agents. Research has also been done whether antiparasitic agents are selective for parasites' receptors or whether they can overlap on the receptors of vertebrates. Most antiparasitic agents have a high selectivity for parasitic receptors, but indeed, in rare cases, some agents could overlap on the receptors of vertebrates. Moreover, overdosages of antiparasitic drugs were revised and it turned out that the majority of them can induce neurologic adverse effects including convulsions, epileptic seizures, and signs of excitations when an overdose was given.

What is more, this thesis also deals with different kinds of application regarding the administration of antiparasitic agents. When spot-on agents are being administered on a pet's fur and if more than one animal lives in a household, it should be taken into account that the applied spot can be licked by one animal or the other, which could cause severe neurologic side effects. Spot-on agents declare a higher dose of active substances to ensure a total dermal absorption, but because of this high dose of antiparasitic agents, neurologic side effects can be induced. Furthermore, new formulations of isoxazolines provide long-lasting efficacy for up to three months, indicating high plasma levels of the compounds for a long period of time.

Finally, it can be stated that epileptic dogs and cats should be administered the correct recommended therapeutic dosage when using antiparasitic agents and if other animals live in the household, spot-on agents should be avoided.

Interactions with licensed antiepileptic drugs in Austria including phenobarbital, potassium bromide, imepitoin and antiparasitic agents were tried to find, but there was also only little information given on this topic. Phenobarbital describes an interaction with praziquantel, as phenobarbital increases the effects of the P-450-enzymes, so no effective plasma levels of praziquantel can be reached. To sum up, praziquantel is less effective, when phenobarbital is taken simultaneously, but no proconvulsive effects are described with these two agents (Waigner 2019).

Moreover, correlations between the P-glycoprotein-transporter/Multidrug-Resistance-Protein-1 (MDR1) and possible proconvulsive effects in correlation with antiparasitic agents were investigated. Dogs, especially Collie dogs and similar breeds, with a mutation of the MDR1 experienced proconvulsive interactions after administration of antiparasitic drugs. However, the MDR1-defect has got no connection with the disease epilepsy. Even though epileptic patients have a more permeable blood-brain barrier, no connection with this gene mutation and antiparasitic agents, could be found.

The recommendations listed in this thesis are based on possible proconvulsive or neurologic side effects described in different literature, papers, reviews, and patient information leaflets. The collected and summarized information on this topic aims to give veterinarians a better understanding of handling conventional antiparasitic agents for epileptic dogs and cats. This thesis shall give information about which agents could act proconvulsive and should be avoided in neurologic diseased animals.

In the future, more investigations must be done in terms of antiparasitic drug-relating convulsions in epileptic patients. One approach for further investigation could be a prompt blood sampling right after the occurring seizure, to detect significant serum levels of antiparasitic agents. Studies with a large enough amount of test animals could help find a significance between the intake of antiparasitic drugs and the following seizures.

Overall, more studies and research need to be carried out in terms of this issue. To find out more about the interaction of antiparasitic drugs and epileptic patients, further investigations are needed. Consequently, no exact data on antiparasitic treatment for epileptic dogs and cats can be given, only recommendations can be made, as precise studies and evidence are missing.

6.1. Suggested recommendation regarding endocides

When treating epileptic patients against endoparasites, it should be taken into account that some drugs could have proconvulsive effects when taken in in a high dose. So, these patients should be treated with an exact dose according to their weight.

6.1.1. Benzimidazoles

Fenbendazole is assumed to be a very safe anti-endoparasitic agent, even at higher dosages, as no neurological side effects are described in any literature. We assume that epileptic patients are not predisposed to suffer from neurologic adverse reactions after administration of fenbendazole.

Febantel is a safe drug for patients with central nervous diseases, as no neurological adverse effect is described in any literature.

We can assume that flubendazole is a safe drug for neurologically diseased patients, including epileptic patients, as no side effects, especially neurological ones, are described. The currently licensed product Flubenol® is only available for cats, small dog breeds and puppies. As flubendazole is an agent, which does not cause any neurological side effects, it would be optimal, if a medication of this agent could also be produced for larger dog breeds.

6.1.2. Tetrahydropyrimidines

Unfortunately, not a lot of information of pyrantel regarding neurotoxic adverse effects and overdosage symptoms can be found in literature. Only gastrointestinal side effects are described after administration of this agent. Pyrantel is often combined with other agents and

in these combination drugs, it cannot be ruled out if side effects are due to one agent or the other. The licensed anti-endoparasitic drug Banminth® (Banminth-Paste zum EIngeben für Katzen, 40 mg/g Pyrantel, Zoetis Österreich Gesellschaft m.b.H., Österreich), which is available and licensed in Austria, only includes pyrantel, and does not cause any neurological symptoms. When administering pyrantel to epileptic dogs and cats, it must be considered, that overdosages can induce effects of acetylcholinesterase and thus neurological side effects are provoked. Therefore, we need to pay attention when using pyrantel as an antiparasitic agent in neurologically diseased patients because of the cholinergic effects given. Given in the RTD this agent is normally well tolerated.

In Austria, oxantel is not available as a single agent in antiparasitic medications, only as a combination drug with other agents. Therefore, only little information about its side effects and overdosage symptoms are reported. Neurological symptoms after oral administration of this drug are not stated in any literature.

6.1.3. Macrocyclic Lactones

Generally, macrocyclic lactones should be avoided in epileptic patients, as this agent can be a cause of a wide range of neurologic adverse effects.

In epileptic patients, ivermectin should be avoided, as this agent can cause neurotoxic effects when the efflux transporter at the blood-brain barrier is not working properly. Neurologic adverse effects and even deaths are observed when using this agent in high dosages. What is more, this agent is not licensed in Austria, except for dermal use against ear mites, and consequently not recommended and allowed for any other use. Especially ivermectin can induce proconvulsive effects when overdosed, so the only licensed product noawadays is the ear ointment “Otimectin®”, which only contains 1 mg/g ivermectin. When using this agent, especially the intactness of the ear drums has to be examined, otherwise, ivermectin can induce systemic adverse effects and neurologic deficits. Thus, epileptic patients should be treated with extreme caution and the intactness of the ear drums should be checked when using this product.

Selamectin does not cause severe adverse effects when treating parasitic infections in healthy animal patients. Owner of epileptic patients should note that in rare cases this agent can cause convulsions, but generally, the occurrence of side effects is very low.

Moxidectin can induce a wide range of neurological adverse effects even in healthy animals. Thus, epileptic patients have a higher risk when this agent is administered, as their brain

conformation is more susceptible to neurological side effects. Moreover, subcutaneous injections, which are not licensed in Austria, should be avoided, as the number of adverse effects is higher when using this form of application. In addition to this, accidental licking of the applied spot is risky as central nervous symptoms are described in several literatures. Overall, moxidectin is not advised to be used in epileptic patients, as this agent can cause a number of side effects, especially neurologic adverse reactions. Thus, when using moxidectin in epileptic patients, correct doses of this agent are important, as overdoses show neurologic adverse effects even in healthy dog.

Epileptic patients should be treated with greater caution, when using milbemycin oxime, as this agent can cause neurologic side effects in rare cases or when overdosed. Especially the recommended therapeutic dosages should not be exceeded, as even healthy patients can suffer from adverse effects when this agent is administered in high doses.

In epileptic patients, when antiparasitic treatment is needed, spinosad should be avoided, as this agent can induce neurologic adverse effects like muscle tremors, ataxia, and convulsions at recommended therapeutic doses. Furthermore, two case reports stated that epileptic patient suffered from seizures during a therapy with spinosad. Overall, spinosad is not considered suitable for epileptic patients, as convulsions are commonly observed and recorded in literature.

To sum up, when using macrocyclic lactones, it must be considered whether dogs have a mutation in the MDR-1-gene because especially these dogs can suffer from neurological side effects.

6.1.4. Organophosphates

Epileptic dogs and cats should avoid emodepside as an antiparasitic agent, as neurologic side effects are commonly described when this agent is administered. Dogs and cats can suffer from neurologic adverse effects, including convulsions. Especially cats show neurologic side effects, when the applied spot-on solution is accidentally licked and orally absorbed. Also, canine patients with a defect in the MDR-1-gene should avoid emodepside, as these patients are predilected to suffer from adverse effects. Overall, neurologically diseased patients are advised to use other antiparasitic agents than emodepside.

6.1.5. Praziquantel

We can assume that praziquantel is a safe agent to use when recommended therapeutic doses are administered. However, when overdosed, neurologic adverse effects are described, especially, when the injection solution is used. Thus, dogs and cats with epilepsy or other neurological diseases should strictly keep the RTD and avoid the injection solution.

6.2. Chart of anti-endoparasitic agents

	Neurologic adverse effect	Neurologic overdosage symptoms	Recommended for epileptic patients
Benzimidazole			
Flubendazole	-	-	recommended - low risk/safe
Fenbendazole	-	-	recommended - low risk/safe
Febantel	-	-	recommended - low risk/safe
Tetrahydropyrimidines			
Pyrantel	unlikely, only when intestinal wall has lesions: muscle tremors	ataxia, cholinergic effects	mild risk - recommended when no lesions in intestinal wall
Oxantel	-	-	unknown, limited information
Macrocyclic Lactones			
Selamectin	- convulsions - MDR-1-defect dogs: tremors, ataxia, mydriasis	convulsions	not recommended for MDR1-defect- patients, epileptic patients with high risk
Moxidectin	- ataxia, lethargy, inappetence - accidental oral intake of the topic solution: ataxia, lethargy, generalized tremor, nystagmus - MDR-1-defect dogs: ataxia, depression	hypersalivation, mydriasis, fasciculation, ataxia of the hind limbs	
Milbemycin Oxime	muscle tremor, ataxia, convulsions, lethargy, salivation, mydriasis	- ataxia, periodic recumbency - MDR-1-defect-dogs: ataxia, central nervous-depression, mydriasis, salivation	
Cyclooctadepsipeptides			
Emodepside	- muscle tremors, incoordination - accidental oral intake of the topic solution: neurologic symptoms, tremors - MDR-1-defect dogs: convulsions	tremor, ataxia, staggering gait, incoordination, salivation, depression	not recommended – high risk

	Neurologic adverse effect	Neurologic overdosage symptoms	Recommended for epileptic patients
Isochinolin-Derivates			
Praziquantel	subcutaneous injection: apathy, salivation, tremor, ataxia	subcutaneous injection: ataxia, depression, death	subcutaneous injections are not recommended (high risk), oral formulations (mild risk): recommended doses should strictly be adhered to

6.3. Suggested recommendation regarding ectocides

When using anti-ectoparasitic agents which are applied topically, the treated area should be observed by the owners when other animals are living in the household, as the licking of the applied agent can cause severe adverse reactions. Those drugs for dermal application are then taken in systemically, thus, neurological side effects can occur. Especially epileptic patients should be treated with caution due to proconvulsive adverse effects of these drugs when dermal spot-ons are applied.

6.3.1. Pyrethroids

Due to literature, permethrin should be avoided when treating epileptic patients, as this agent can cause a wide range of neurologic adverse effects and overdoses can even lead to acute neurologic symptoms. Especially cats are predisposed to toxic effects, as they have a weakness of glucuronidation, so this agent is prohibited for cats. Eventually, it is advised that the recommended therapeutic doses are strictly adhered to, and overdoses should be avoided at any rate. Finally, if possible, epileptic patients should be treated with other antiparasitic agents, as permethrin can be the cause of various neurologic side effects.

In epileptic patients, deltamethrin should be avoided, as this agent can induce a wide range of (partly severe) neurologic side effects. In addition to this, accidental licking of the treated spot can be risky, as neurological adverse effects are described in several patient information leaflets. When more than one dog lives in a household, where epileptic patients are included, this agent should definitely not be administered, as severe intoxication symptoms can occur after licking of the treated spot, even in healthy patients. However, epileptic patients are more susceptible to suffer from neurologic adverse effects due to their altered brain conformation. Overall, deltamethrin should be avoided in epileptic patients due to their neurologic side effects.

In Austria, flumethrin is only available in form of a collar and can induce neurologic side effects, but only in very rare cases. When using this agent, it must be taken into account, that neurologic dysfunction can be induced in epileptic patients. Thus, other antiparasitic agents should be administered in these patients, as flumethrin can be the cause of ataxia, tremors, and convulsions.

6.3.2. Carbamates

We can assume that propoxur is a moderately safe drug for epileptic patients, as no side effects of neurologic origin are described in any literature. It must be taken into account, that

extensive skin lesions can cause parasympathomimetic effects. Moreover, not a lot of information and not a lot of agents are available for propoxur. Due to this limited information, neurologic side effects could not be found in literature. Other than that, propoxur is only available in form of a collar, spraying solution or shampoo, which means that no systemic protection can be reached with this agent.

6.3.3. Isoxazolines

Afoxolaner can induce neurologic side effects as described in patient information leaflets. Therefore, epileptic patients should avoid this agent. Optimally, neurologic diseased patients should be treated with other agents.

Fluralaner is well tolerated in dogs and cats, as well as in MDR1-gene-mutant dogs. When administered correctly, no acute or heavy adverse reactions are suspected. Neurologic side effects are described to come up rarely, but neurologically diseased patients, e.g. epileptic patients, should take caution, when taking this agent, as fluralaner can have a proconvulsive effect. As already mentioned, one case report states that a seven-month-old dog suffered from neurologic symptoms after 24 hours of treatment with fluralaner (Gaens et al. 2019b). To confirm if these convulsions are drug related or incidental, plasma levels or levels of the cerebrospinal fluids of this agent could be quantified in the blood of the patients. In the future, the approach of testing plasma or cerebrospinal fluids could be useful in distinguishing between drug-related seizures and seizures due to other causes. Overall, epileptic patients should be treated with higher caution when using fluralaner, as several neurologic adverse reactions can be induced.

Patient information leaflets of lotilaner do not record any neurologic side effects, and no neurological deficits are described in any literature. Due to limited information relating to this agent, no adequate statement can be made regarding its neurotoxicity. Although no neurologic adverse reaction is known for lotilaner, epileptic patients should be treated with caution, as this agent belongs to the group of isoxazolines, which can stimulate GABA- and glutamate-gated chloride-channels in vertebrates. This stimulation can be the cause of neurologic adverse reactions, as these receptors are localized in the brain and cause proconvulsive effects.

It is advised that epileptic patients should not be treated with sarolaner, as this agent can cause a wide range of neurologic side effects. Especially when overdosed (e.g. three times higher than the RTD), the agent can cause convulsions, even in healthy patients. As neurologic

diseased patients have a higher risk of suffering from proconvulsive effects, sarolaner should be avoided for antiparasitic treatment in epileptic patients.

6.3.4. Phenylpyrazoles

Epileptic dogs and cats should not be treated with fipronil, as neurologic side effects are commonly described. When extensive skin lesions exist, the spraying solution should not be used, as it can reach systemic levels and cause neurologic adverse effects. Especially when overdosed, studies describe neurologic disorders, including convulsions. As epileptic patients are more susceptible to these symptoms because of an impaired brain conformation, fipronil should be avoided when treating ectoparasites.

When treating epileptic patients against ectoparasites, pyriprole should be avoided, as this agent can cause various neurologic adverse effects. Overdosages of this agent can lead to severe neurologic deficits including ataxia, tremors, convulsions and also strained breathing. Consequently, pyriprole as antiparasitic treatment is not advised in neurologic diseased patients, including epileptic dogs and cats.

6.3.5. Neonicotinoids

Imidacloprid can induce several neurologic disorders, particularly when the agent is overdosed. Especially accidental oral intake of the spot-on solution can lead to severe neurologic deficits, including ataxia, generalized tremor and convulsions. Even the breathing can be affected, when overdosed. Consequently, in households with more than one dog and of which one is an epileptic patient, the spot-on solution should be avoided to prevent oral intake by licking the applied spot-on solution. Overall, imidacloprid should be avoided in epileptic patients as this agent can be a cause of various neurologic side effects. Thus, the use of other antiparasitic agents is advised.

Nitenpyram is suspected to be well tolerated in dogs and cats at standard dosages. Only mild dermatological side effects are described at standard dosages. However, overdoses can lead to severe neurological adverse effects like tremors, ataxia, and convulsions. Therefore, epileptic patients should be treated with great caution when nitenpyram is chosen as an antiparasitic treatment and standard dosages should strictly be followed. If possible, other antiparasitic agents should be applied in epileptic patients.

It is difficult to say, if dinotefuran is suitable for epileptic patients, as not a lot of information is given in literature for the single agent. There is currently no drug available which only contains

the agent “dinotefuran”, so it is hard to say if this agent is responsible for the possible neurologic side effects described in the patient information leaflets. The combination drug Vectra3D® (Vectra 3D Lösung zum Auftropfen auf die Haut für Hunde, 54 mg Dinotefuran + 4,84 mg Pyriproxyfen + 397 mg Permethrin, Ceva Sante Animale, Frankreich) for dogs which consists of dinotefuran, pyriproxyfen and permethrin does describe neurologic side effects, but the combination drug for cats VectraFelis® (Vectra Felis Lösung zum Auftropfen auf die Haut von Katzen, 423 mg Dinotefuran + 42,3 mg Pyriproxyfen, Ceva Sante Animale, Frankreich) does not state any adverse neurologic reactions. Due to this, these neurologic symptoms can be the cause of one agent or another, but it cannot be ruled out which one is responsible for these neurologic symptoms, as we do not have any comparison to reported adverse effects for dinotefuran itself. Due to this lack of information, it cannot be ruled out that dinotefuran might be suitable for epileptic patients.

6.3.6. Indoxacarb

Various literature states that when treating dogs and cats with indoxacarb, no neurologic adverse reactions are to be suspected. Only dermatological side effects are described in patient information leaflets. Unfortunately, not a lot of information is given in literature regarding this agent. Due to this, epileptic patients should be treated with greater caution when using this agent, as not a lot of information concerning neurologic side effects have been described so far.

6.4. Chart of anti-ectoparasitic agents

	Neurologic adverse effects	Neurologic overdosage symptoms	Recommended for epileptic patients
Pyrethroids			
Permethrin	muscle fasciculation, hyperesthesia, restlessness, tremor, convulsions, ataxia	unlikely	not recommended - mild/high risk agent is often used with other proconvulsive antiparasitic agents
Deltamethrin	ataxia, tremor	incoordination, hypersalivation, tremors, convulsions	not recommended, accidental oral intake should be avoided (high risk)
Flumethrin	ataxia, convulsions, tremor	unlikely	not recommended - mild/high risk agent is often used with other proconvulsive antiparasitic agents
Carbamates			
Propoxur	not described	not described, parasympathomimetic effects when overdosed	unknown - limited information available
Macrocyclic Lactones			
Ivermectin	apathy, mydriasis, ataxia, tremor, salivation	severe ataxia, disorientation, hyperexcitability, tremors, rowing motions, mydriasis, head pressing	not recommended - high risk, also no local use when ear drums are defect (high risk)
Spinosad	lethargy, ataxia, convulsions, salivation, tremors	not described	not recommended (high risk): case reports state that epileptic patients suffered from seizures while being treated with spinosad
Isoxazolines			
Afoxolaner	convulsions, ataxia, tremor	-	all isoxazolines with high risk, accidental oral intake of topic solutions should be avoided
Fluralaner	- ataxia, tremors, muscle twitching, myoclonic jerks, convulsions, lethargy - MDR1-defect-patients: depression, mydriasis, salivation, tremor, ataxia	salivation, apathy, tremor	

	Neurologic adverse effects	Neurologic overdosage symptoms	Recommended for epileptic patients
Lotilaner	tremor, ataxia, convulsions	-	
Sarolaner	lethargy, tremor, ataxia, convulsions	tremor, ataxia, convulsions, mydriasis	
Phenylpyrazoles			
Fipronil	salivation, depression, hypersensitivity, tremor, ataxia, paresis of the hind limbs	seizures, hyperexcitability, tremor, convulsions, ataxia, tremor, depression, death	not recommended - high risk
Pyriprole	ataxia, incoordination, convulsions, twitching	restlessness, incoordination, muscle tremors, convulsions, unsteadiness, ataxia, weakness	not recommended - high risk
Neonicotinoids			
Imidacloprid	restlessness, disorientation, salivation, incoordination, tremor, depression, lethargy, mydriasis	salivation, hyperexcitation, convulsions, incoordination, ataxia, tremor, mydriasis, lethargy	not recommended (high risk), accidental oral intake and overdoses should be absolutely avoided
Nitenpyram	ataxia, tremor, convulsions	salivation, vomiting, convulsions, restlessness, lethargy	not recommended - high risk
Dinotefuran	hyperactivity, anxiety, tremors, ataxia, insecure gait	not described	mild risk, not a lot of information available
Oxadiazine			
Indoxacarb	incoordination, tremor, ataxia, convulsions, mydriasis	salivation	mild risk, not a lot of information available

7. Conclusion

According to the investigations discussed, following conclusions can be drawn:

Patient information leaflets do not state that any antiparasitic agents are not licensed for epileptic dogs or cats. Therefore, all antiparasitic drugs can basically be administered to these neurologic diseased patients. Nevertheless, an individual benefit-risk assessment should be carried out to avoid neurologic side effects.

What is more, most antiparasitic agents are selective for parasitic receptors, but when given in an overdose, some agents can also target vertebrates' receptors and cause neurologic adverse effect. Therefore, it is important that the recommended therapeutic doses, especially in epileptic dogs and cats, are adhered to, to avoid neurologic side effects.

Additionally, in households where more than one dog or cat is living, owners should be cautious when spot-on agents are administered. Spot-on agents usually declare a higher dose of antiparasitic agents than oral formulations, which is necessary for total dermal absorption. Thus, when the treated spot on the pet's fur is licked by an epileptic dog or cat, neurologic overdosage symptoms can occur. Therefore, spot-on agents in households with more than one animal, spot-on products should be avoided, especially when one of them is suffering from epilepsy.

Furthermore, Collies and similar dog breeds, with a mutation in the Multidrug-Resistance-Protein-1, often suffer from neurologic side effects after administration of antiparasitic drugs. However, this gene defect has got no correlation with the neurologic disease epilepsy.

To conclude, the research of this thesis is based on different literature, papers, reviews, studies, scientific reports, and patient information leaflets. The information presented here shall give veterinarians a better overview of various antiparasitic agents and their possible proconvulsive and neurologic side effects. In the future, more investigation regarding this topic should be made. However, this thesis should facilitate the choice of the appropriate antiparasitic treatment for epileptic dogs and cats.

8. Summary

The aim of this thesis is to provide an optimal recommendation for antiparasitic treatment in epileptic dogs and cats, based on neurologic side effects and overdosage symptoms of different antiparasitic agents. The research is based on different literature, papers, reviews, and patient information leaflets. In this thesis, antiparasitic agents, which are often and commonly used in veterinary medicine, are listed. The focus is laid on their possible proconvulsive effects which could affect the altered brain conformation of epileptic patients and cause convulsions. Based on different literature, the effect mechanism of antiparasitic agents was revised.

The aim was to find out if antiparasitic drugs also have an effect on vertebrate's receptors or if they are parasite-specific. Some agents demonstrate a high selectivity on parasitic receptors, but other drugs are indeed thought to overlap on vertebrate's receptors.

Furthermore, a brief abstract about P-glycoprotein-transporters/MDR1-mutations relating to epileptic dogs and cats is worked out, but no connection to the neurologic disease and the mutation in MDR1 genes could be found.

In addition, different websites and internet groups of lay people, on which antiparasitic treatments are discussed or accused of causing convulsions or even deaths are revised. Subjective inputs by grieving pet owners, whose animals died supposedly due to an antiparasitic drug, were analyzed. Finally, all stories about dogs and cats in these forums, who apparently died because of an antiparasitic agent, were suffering from other severe systemic diseases, which more probably led to the pet's death.

In conclusion, the proposals made in this thesis regarding the right choice of antiparasitic drugs for epileptic dogs and cats are only a recommendation and are not scientifically proved. However, this thesis should give veterinary practitioners a guidance, on which antiparasitic treatment to use on epileptic dogs and cats, based on scientific literature research.

9. Zusammenfassung

Das Ziel dieser Diplomarbeit ist es, praktizierenden Veterinärmedizinern eine Übersicht über antiparasitische Behandlungen bei epileptischen Katzen und Hunden zu erstellen. Diese Empfehlungen basieren auf Recherchen bezüglich neurologischer Nebenwirkungen und Symptome einer Überdosierung nach der Gabe von verschiedenen Antiparasitika. Die Recherche stützt sich auf verschiedene Literaturen, Papers, Reviews und Beipackzetteln. In dieser Arbeit werden verschiedene Wirkstoffgruppen von herkömmlichen Antiparasitika aufgelistet, welche häufig in der Veterinärmedizin angewendet werden. Der Fokus dabei liegt auf mögliche prokonvulsive Wirkungen, welche mit der veränderten Gehirnfunktion von epileptischen Hunden und Katzen interagieren und somit auch Anfälle auslösen können. Verschiedene Literaturstellen wurden herangezogen, um die Wirkmechanismen der verschiedenen Antiparasitika zu erklären.

Das Ziel hierbei war es, herauszufinden, ob die Wirkstoffe insektenspezifisch wirken, oder auch auf Rezeptoren von Vertebraten Einfluss nehmen können. Einige der antiparasitischen Medikamente weisen eine hohe Spezifität auf Insektenrezeptoren auf, aber tatsächlich gibt es auch Medikamente, die auf Rezeptoren der Vertebraten übergehen können.

Außerdem wird in einem kurzen Kapitel auf MDR1-Mutationen in Bezug auf epileptischen Katzen und Hunden eingegangen. Es konnte allerdings keine Verbindung zwischen der neurologischen Krankheit Epilepsie und MDR1-Mutationen gefunden werden.

Es wurden auch verschiedene Internetseiten und Internetgruppen von Laien überprüft, welche behaupten, dass Antiparasitika Anfälle oder sogar den Tod verursachen können. Subjektive Äußerungen von trauernden Besitzern, deren Tiere mutmaßlich durch die Gabe eines Antiparasitikums gestorben sind, wurden analysiert. Aus allen Erzählungen, geht hervor, dass diese Haustiere auch an anderen, schweren systemischen Erkrankungen litten. Diese Systemerkrankungen waren in den meisten Fällen eher der Grund für den Tod der Tiere.

Abschließend lässt sich sagen, dass die hier angeführten Vorschläge zur richtigen Wahl eines Antiparasitikums für epileptische Hunde und Katzen, nur Empfehlungen sind und diese nicht wissenschaftlich überprüft wurden. Diese Arbeit soll, basierend auf wissenschaftlicher Literaturrecherche, praktizierenden Veterinärmedizinern eine Orientierungshilfe geben, welche antiparasitischen Mittel an epileptischen Patienten angewendet werden sollen.

10. Abbreviations

CVMP	Committee for Veterinary Medicinal Products
FAD	flea allergy dermatitis
FDA	US-Food and Drug Administration
GABA	gamma-aminobutyric acid
MDR1	multidrug-resistenace-protein-1
nAChR	nicotinic acetylcholine receptor
RTD	recommended therapeutic dose

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