



Management of specific fears and anxiety in the behavioral medicine of companion animals: punctual use of psychoactive medications

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Abstract: A growing body of research has recently focused on the use of psychoactive medication for the short-term management of specific fear and anxiety in pet cats and dogs, i.e. triggered by well-identified and predictable stimuli. Such medications are used short-term and administered as needed to prevent the symptoms of fear and anxiety associated with specific situations. Noticeably, in the last few years two medications have been approved in the US and Europe for the treatment of noise fear in dogs. Furthermore, literature from the past decades provides evidence of the anxiolytic effect following the administration of several other medications used in various situations such as travelling and veterinary examinations. This review provides a summary of the most appropriate medications for punctual use in case of specific fear and anxiety in cats and dogs. The authors recommend the use of psychoactive medications providing a clear anxiolytic effect, especially in association with environmental management and humane behavioral procedures, such systematic desensitisation and counterconditioning. Combination treatment with non-psychoactive medications is also discussed.

Key Words: anxiety, psychopharmacology, acepromazine, dog, cat.

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Introduction

The recent years have seen a growing body of research on the application of psychoactive medication for the temporary management of fear and anxiety in pet cats and dogs. These medications are usually indicated for short term, punctual use, i.e. to alleviate the symptoms of fear and anxiety associated with specific situations. Historically, acepromazine (ACP) has been for a long time the sole psychoactive drug, originally approved in several countries “as an aid to control intractable animals” and “as an antiemetic agent to control vomiting due to motion sickness in dogs and cats” (Plumb, 2018). With time, acepromazine has become also commonly used in various situations that caused increased reactivity in the animal or were associated with symptoms of anxiety and fear; such as the exposure to thunderstorms and fireworks. Despite such common use of this medication, acepromazine is a phenothiazine derivative, which does not alleviate the animal's emotional state of fear and/or anxiety (Sümegei et al., 2014); in fact, the tranquilliser effect is rather dependent on motor inhibition mechanisms. The mechanism of action of acepromazine relies on the blockage of dopaminergic receptors situated in the basal ganglia and in the limbic system, whose activation is associated with CNS depression, sedation, and motor incoordination.

Nowadays, authors agree that phenothiazines are not the drug of choice for the treatment fearful or phobic behaviors (long or short term), because they have poor anxiolytic activity, they induce marked sedation and even heighten the animals' sensitivity to stimuli, while they have no means to escape due to the motor inhibition effects. This combination of effects induces an aversive experience that might lead to worsening of the behavior problems by increasing the sensitivity to the

triggering stimuli (sensitization) (Clough, 1982). According to some authors dogs may become more reactive to noise after treatment with ACP (Landsberg, 2003; Overall, 1997; Overall, 2002). On the contrary, dissociative agents, such as acepromazine, reduce the animal's general ability to process and elaborate environmental stimuli, which is likely to increase rather than decrease the animal's anxious response to the triggering stimulus (Overall, 2013). Furthermore, the duration and degree of sedation may vary among individuals and might be breed dependent (Thompson, 1998). It should also be noted that paradoxical reactions and aggressive dis-inhibition have been observed after acepromazine administration, which poses a risk for humans and other animals that are in contact with the treated individual (Crowell-Davis, Murray & de Souza Dantas, 2019).

Overall, it is therefore clear that phenothiazines are not appropriate medications for the treatment of anxious, fearful, or phobic animals because they have poor anxiolytic effect and produce marked sedation and potential sensitisation to the triggering stimuli (Thompson, 1998). The use of acepromazine in dogs and cats that show signs of distress during specific situations (e.g. car transport, sudden noises) not only is not related to long term improvement of the emotional and behavioral signs, but it might even further compromise the welfare of the animal. For these reasons the authors agree that the use of ACP should be avoided, especially as a sole or preventive medication, for the treatment of animals that show signs of distress associated with specific events, such as travel, exposure to loud noises or during veterinary examinations. Likewise, the authors disagree with the use of any strategy based on coercive methods (e.g. physical punishment) or flooding (i.e. the continuous exposure of an animal to an aversive stimulus). The authors recommend the use of psychoactive medications with a clear anxiolytic effect, especially in association with environmental management and humane behavioral procedures, such systematic desensitisation and counterconditioning.

General overview of the behavioral signs related to specific fear and anxiety in cats and dogs

Cats and dogs manifest their discomfort in situations such as travel by car, airplane, or train, or during the exposure to loud noises through behaviors that are commonly associated with anxiety and fear of various intensity, depending on the individual. Such behaviors include vocalizations, shaking, mydriasis, polypnea, tachycardia, drooling, hyperactivity and pacing, escape attempts, searching for hiding places, inappropriate urination and/or defecation (Anon, 1998; Beaver 1999; Bergeron, 2002; Blackwell et al., 2005; Bower and Youngs 1994; Crowell-Davis, 2019; Dale et al., 2010; O'Farrell 1992; Mariti et al., 2012; Mugford, 1991; Schwartz, 1997; Storengen & Lingaas, 2015).

Car travel

Owners often travel by car with their pets for short journeys (e.g. few minutes to reach a park) or long journeys (e.g. long hours to arrive to a holiday destination). Various behavioral responses to distress in these situations have been described in cats and dogs: some manifest signs of motion sickness (nausea, vomiting), others manifest signs of distress or simple over excitement in anticipation of the event following the travel or the journey itself (Anon, 1998; Beaver, 1999; Bower & Youngs, 1994; O'Farrell, 1992; Mugford, 1991; Schwartz, 1997).

Airplane travel

Acepromazine has been widely prescribed in occasion of airplane journeys; however, evidence indicates that stress signs during the journey do not change in dogs treated with ACP (Bergeron,

2002). Furthermore, the International Air Transport Association recommend to not use any drug to tranquilise pets prior to transport, due to health and safety reasons for the animal itself.

Noise sensitivity

Several studies indicate that nearly half of the pet dog population may be fearful or anxious when exposed to various of auditory stimuli, such as storms and fireworks (Blackwell et al., 2005; Crowell-Davis, 2019; Dale et al., 2010; Mariti et al., 2012; Storengen & Lingaas, 2015). It is however possible that these figures underestimate the real frequency of occurrence of the issue. Furthermore, the problem poses a considerable risk for the animals, which may become seriously injured or lost while attempting to escape from the triggering stimuli.

Drugs indicated for punctual use in case of specific fear and anxiety in cats and dogs

Given the considerations above, veterinary practitioners should consider other alternatives to the use of ACP to provide short-term support (i.e. punctual use) for anxious, fearful and phobic cats and dogs in the case of specific triggering situations. All the dosages and formulations discussed below are for oral administration (i.e. *per os*) except when differently specified.

Overall, the successful treatment of fearful and anxious pets aims to: a) relieve the distress and the negative emotional state during the triggering situation (stressful event) and consequently improving the behavioral responses of the animal; b) support a long term behavioral modification programme that aims to modify the emotional response to the triggering situation (these include desensitisation and counterconditioning).

Labelled products

Dexmedetomidine

Dexmedetomidine oro-transmucosal gel (Sileo®) is a drug approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to reduce acute anxiety and fear associated with noise aversion in dogs. The active ingredient is an alpha-2 adrenoceptor agonist which reduces the signs of acute anxiety and fear associated with noise in dogs when administered at the dose of 125 micrograms/m² - please note that the formulation requires oro-transmucosal absorption (Dean, 2017; Korpivaara et al., 2017). Clinical studies have found the drug to be effective to reduce anxiety during travel (Landsberg et al., 2018) and veterinary examinations (Jonckheer-Sheehy & Zaal, 2018). Owners must be informed about the correct administration of the medication, i.e. in the buccal area. The gel is not for oral administration and should not be swallowed; the effects following oral administration of this formulation are not predictable.

The anxiolytic effect of dexmedetomidine is linked to the alpha-2 adrenoceptor agonist action in the *Locus coeruleus* (Aantaa et al., 1993; Murrell & Hellebrekers, 2005). Sileo® should be administered 30-60 minutes before the triggering event; the effect lasts for 2-3 hours. The administration can be repeated up to 5 times in 24 hours, which should be taken into account for long travel or during hospitalization. There is no information in the literature about the use of Sileo® in cats.

No information is available on the interactions between Sileo® and other drugs. However, the use of Sileo® in combination with sympathomimetic amines is highly discouraged. The use of the product during pregnancy, cardiovascular and systemic pathologies, and in senior pets is not recommended (BSAVA, 2017).

Imepitoin

Imepitoin (Pexion®) has been recently approved by the EMA for the reduction of anxiety and fear associated with noise phobia in dogs. Imepitoin has an anxiolytic effect, due to the partial activation of the receptors for the neurotransmitter GABA-A and weak blocking effect on calcium channels (Denenberg & Bräm Dubé, 2018; Engel et al., 2018). The anxiolytic effect of Pexion® starts after a few days of administration, therefore some authors suggest that the treatment should start a few days before the triggering event (Denenberg & Bräm Dubé, 2018; McPeake et al., 2017).

A series of case studies has found that, in dogs, Pexion®, administered at the dose of 10-30 mg/kg BID, reduces signs of distress and induces a positive emotional state in case of fear and anxiety related problems (McPeake et al., 2017). The results were further confirmed by a placebo-controlled clinical trial indicating that Pexion®, administered at the dose of 30 mg/kg BID starting 2 consecutive days before the expected triggering noise event, significantly reduces the behavioral signs of fear and anxiety, when compared to a placebo (Engel et al., 2019). In the literature, the use in cats is suggested at a dose of 10-30 mg/kg BID, starting 5-10 days before the triggering event (Denenberg & Bräm Dubé, 2018). It should be noted that the use of Pexion® for cats is not yet approved by the EMA or the FDA.

Overall, it is recommended for the treatment to start at the lowest dose and titrate upward if needed until the effect has been reached (Denenberg & Bräm Dubé, 2018; McPeake et al., 2017). In case of side effects, doses should be reduced (McPeake et al., 2017).

Off-label products

In Europe, a number of psychoactive medications are used off-label based on evidence in the literature and may be prescribed taking into account the principles of the Cascade. The Cascade is a risk based decision-tree aiming veterinary surgeons in the decision process to select the product to use when there is no authorised veterinary medicine available for a specific condition or species. In certain countries (e.g. Italy) the use off-label may be approved based on scientific evidence where a given product is available but proves not to be effective in a certain individual. Without the Cascade, veterinary surgeons could only prescribe veterinary medicines that are authorised for a given species and for a given condition.

Benzodiazepines

Various Benzodiazepines are reported in literature to be effective in case of anxiety and fear in small animals: for example, Lorazepam 0.02–0.1 mg/kg PO every 8-12 hours. Benzodiazepines increase the effect of GABA on the GABA-A receptors, with anxiolytic, relaxing, antiepileptic, and muscle-relaxing effects (Dodman & Shuster, 1994). Owners should be warned that benzodiazepines might have dis-inhibitory effect, therefore they may disinhibit aggressive behavior (Crowell-Davis, Murray & de Souza Dantas, 2019).

Gabapentin

Gabapentin has been recently discussed in the literature as a safe and effective treatment for cats to help reduce stress during transportation and veterinary examination, and for trap-and-release procedures in feline colonies (van Haften et al., 2017; Pankratz et al., 2017).

The anxiolytic mechanism of Gabapentin is not well understood, although it is suspected to be related to the effect on calcium channels in the neural tissue (Cheng & Chiou, 2006; Davies et al., 2007). Additionally, Gabapentin is an effective medication for the management of neuropathic pain both in cats and dogs (e.g. Siao et al., 2010; Moore, 2016).

In cats, Gabapentin has been used to reduce stress and aggression and increase compliance dur-

ing transportation and veterinary examination, when administered in a single dose of 50-100 mg / animal, 90-120 minutes prior to placing the cat into a carrier. In smaller cats Gabapentin might be administered at the lowest dose in order to avoid sedative effect (van Haaften et al., 2017; Pankratz et al., 2017).

Suggested doses for dogs range from 2-5 mg/Kg BID to 10-20 mg/Kg BID or TID (Overall, 2013). The effect of Gabapentin lasts for about 8 hours and should not be repeated more than 3 times within 24 hours. The authors have found the 10-20 mg/Kg dosage to be effective, especially in combination with other medications (e.g. Trazodone).

Trazodone

Trazodone is classified as a Serotonin Antagonist and Reuptake Inhibitor (SARI) and in humans is used as antidepressant, anxiolytic, and for the treatment of OCDs.

This psychoactive drug has a complex pharmacologic mechanism, which includes an antagonist action on the 2A serotonergic receptors and the post-synaptic reuptake of serotonin (Stahl, 2009). The use of Trazodone has often been reported in the literature for its anxiolytic effect in dogs (e.g. Gruen & Sherman, 2008; Gruen et al., 2017). The medication has also been used for the treatment of nocturnal activity both in cats and dogs, especially when associated with anxiety, due to its mild sedative effects (Gruen et al., 2014; Orlando et al., 2016).

The suggested dosage for Trazodone in dogs ranges between 1.7 and 9.5 mg/kg in a single dose to be administered 90 minutes prior to the stressful event. The administration may be repeated for a maximum of 3 administrations in 24 hours (Overall, 2013).

In cats, Trazodone has been suggested in the literature to reduce the symptoms of stress during transportation and veterinary examinations (Stevens et al., 2017). The suggested dose is 50 mg/cat to be administered 60-90 minutes before the triggering event. It has been reported that in a few cases trazodone had a dis-inhibitory effect, which might lead to increased aggressive response (Gruen & Sherman, 2008). Therefore, the use of Trazodone in animals with a history of aggressive behavior should be considered cautiously.

Combined use of psychoactive and non-psychoactive medication

Anxiety and fear-related responses to certain stimuli might be related to physical causes of distress for the animal (Reaney et al., 2017). These might be unrelated with the triggering situation, such as acute and chronic pain (Affenzeller et al., 2017; Barcelos et al., 2015; Camps et al., 2012; Lopes Fagundes et al., 2018), or they might be event-related consequences, such as motion sickness. Therefore, it is recommended that pain-relief or other relevant medication is used in combination with psychoactive drugs, in order to alleviate the symptoms associated with the triggering situations.

For example, recent evidence in the literature lead to the recommendation that pets that presenting with noise sensitivities (anxious, fearful, phobic or over-reactive responses to noises) should be assessed and treated for pain related problems (Lopes Fagundes et al., 2018). The authors would like to stress that adequate pain management (especially in the case of musculoskeletal pain) should also be a key aspect of the long and short-term medical treatment of pets showing signs of distress associated to travel, due to the continuous solicitations on the joints and musculoskeletal system associated with transport.

Another aspect may lead to distress and consequent sensitisation, especially during travel and transportation, may be motion sickness. The management of gastrointestinal effects caused by motion sickness is associated with a less stressful experience for the pet during travelling. Maropitant citrate, an NK1 antagonist is indicated for the prevention and treatment of acute vomit-

ing during travel (Benchaoui et al., 2007; Hickman et al., 2008). The medication does not induce behavioral inhibition that is associated to other drugs such as ACP. In order to prevent motion sickness, Maropitant is administered at a minimum dose of 8 mg/kg once 1 hours prior to travel (Benchaoui et al., 2007). It should be noted that the dosage needs to be adjusted in cardiopathic animals since Maropitant affects calcium channels.

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Trattamento della paura e dell'ansia in medicina comportamentale: corretto uso di psicofarmaci

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Sintesi

Numerose ricerche sono state effettuate sull'uso di psicofarmaci per il trattamento a breve termine di casi specifici di paura ed ansia nel cane e nel gatto, ovvero scatenati da stimoli ben evidenti e prevedibili.

Questi farmaci sono utilizzati per breve tempo e somministrati al bisogno per prevenire i sintomi della paura e dell'ansia associate a particolari situazioni.

Negli ultimi anni due farmaci sono stati approvati negli Stati Uniti ed in Europa. La letteratura degli ultimi dieci anni fornisce evidenze di effetti ansiolitici conseguenti alla somministrazione di altri farmaci usati in varie situazioni come ad esempio i viaggi e le visite veterinarie.

Questa review elenca i farmaci più appropriati per un uso corretto in casi specifici di paura ed ansia in cani e gatti.

Gli autori raccomandano l'uso di psicofarmaci che forniscano un chiaro effetto ansiolitico, specialmente in associazione con gestione dell'ambiente di vita e delle relazioni con l'uomo, come la desensibilizzazione sistematica ed il controcondizionamento. È inoltre presentato l'uso combinato con altri farmaci non psicoattivi.