Advances in Behavioral Psychopharmacology

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KEYWORDS

• Psychopharmacology • Behavioral drugs • Behavioral therapy
• Psychoactive medication • Canine • Feline

KEY POINTS

- Recent findings focusing on such drugs as trazodone, clonidine, and gabapentin have revolutionized how clinicians handle and treat dogs and cats.
- The results of these studies should be applied in the clinical setting with caution and with a full understanding of the potential pros and cons of using these medications.
- Despite promising results, additional research is desperately needed regarding pharmacokinetics, frequent and infrequent side effects, long-term behavioral impact, and the most clinically appropriate and effective use of these drugs.

INTRODUCTION

Research in the area of veterinary behavioral psychopharmacology is in its infancy. Only clomipramine (separation anxiety), selegiline (cognitive decline), and dexmedetomidine (noise phobia) are approved for use in dogs in the United States. There are no approved behavioral drugs for cats. Using any of the previously mentioned medications for purposes other than the indications listed on the label and the use of any psychoactive medication not listed previously is considered extralabel use and falls under the rules of the Animal Medicinal Drug Use Clarification Act of 1994 and its implementing regulations.

Extralabel use refers to the use of an approved animal or human drug in a manner that is not in accordance with the label directions and is limited to situations where the animal's health is at risk and/or suffering or death may result from lack of treatment[1]: "Actual use or intended use of a drug in an animal in a manner that is, not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease and other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from labeled withdrawal time based on these different uses" (21 CFR 530.3[a]). Client consent should always be obtained before proceeding with extralabel drug use.

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Recent studies have led to some groundbreaking findings regarding the use of medications for the support of behavioral health. Despite tantalizing results, these studies should be viewed in light of their limitations. Behavioral studies typically involve small numbers of animals often maintained in nonstandardized condition.[2] Most are open trials or retrospective studies. Many rely on owner or veterinarian observation opening up the possibility of placebo effect, which can reach 45%.[3] Consequently, the results of these studies should be applied in the clinical setting with caution and with a full understanding of the potential pros and cons of using these medications.[4]

α_2-ADRENERGIC AGONISTS

α_2-Adrenergic agonists bind to presynaptic α_2 receptors (negative feedback receptors) in the brainstem causing a decrease in calcium levels; inhibiting the release of norepinephrine (NE); and resulting in a subsequent decrease in sympathetic tone, sedation, analgesia, and anesthesia.[5] Drugs in this class include clonidine, detomidine, and dexmedetomidine. Hypotension, cardiac depression, and atrioventricular block can occur with higher doses. Sedation, ataxia, bradycardia, and blanching at the site of oral transmucosal (OTM) administration may also occur. Species vary in the type, number, density, and distribution of α receptors so response to these medications varies.[6] One advantage of the use of α_2-adrenergic agonists is that atipamezole (Antisedan-Zoetis) is an effective reversal agent.[6]

Clonidine

Clonidine is a hypertension medication that has been used in human medicine for decades. It is a centrally acting α_2-adrenergic agonist. It is nonselective, acting on α_{2A}, α_{2B}, and α_{2C} adrenergic receptors and the imidazoline receptor.[5]

There is a single research study published on the efficacy of this medication in dogs.[7] In this study 22 dogs were divided into two groups of 11 each, one with separation anxiety, noise phobias, and storm phobias, and the second group with fear-aggression and/or fear-based territorial aggression. According to assessments made by owners, 70% of owners in the first group indicated that clonidine was more effective than previously administered medication, whereas 92% of the owners in the second group indicated that clonidine reduced the intensity of their dog's aggressive response. Previously administered medications included propranolol, alprazolam, or buspirone alone or in addition to baseline sertraline, fluoxetine, or clomipramine. Adverse side effects were limited to a single dog with noise phobia reporting increased sensitivity to noise while on the medication. Clonidine was administered 1.5 to 2 hours before the fear-inducing event. The optimal median dosage of clonidine ranged from 0.017 mg/kg to 0.026 mg/kg orally on an as-needed basis (PRN) up to twice daily. Duration of efficacy was 4 to 6 hours. Pharmacokinetics for clonidine were extrapolated from human use because data in dogs are lacking.[7] In humans, clonidine is administered two to three times daily. Drowsiness, sedation, fatigue, hypotension, bradycardia, and respiratory depression are all potential side effects but are dose dependent and were not observed in this study at these dosages.

Takeaway points

PRN use of clonidine seems to be effective in the treatment of fear-based behaviors in dogs, especially in situations where alprazolam or propranolol provided no benefit. Side effects at these dosages were not observed (increased sensitivity to noise was reported in one dog). The optimal median dosage of clonidine was 0.017 mg/kg to 0.026 mg/kg orally PRN administered 1.5 to 2 hours before the fear-inducing event up to twice daily.