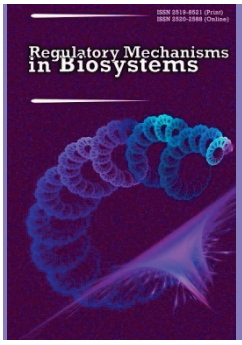

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The use of anxiolytic drugs for the correction of behavioral disorders in mammals

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The issue of stress and behavioral disorders are growing significantly in the contemporary word in humans and animals alike. Various drugs are used to modify affected behavior, including psychotropic, anticonvulsant, antihistamines, hormones, analgesics, and neuroleptics. Psychotropic drugs are prescribed for animals with behavioral disorders, signs of anxiety or hypersensitivity. Improving the methods of diagnosing and treating behavioral disorders in animals can enhance animal welfare and optimize animal husbandry technology. Future research should be aimed at improving and optimizing the use of psychotropic drugs for behavioral disorders of various animal species. The main indication for the use of anxiolytic drugs is behavioral disorders associated with anxiety in wild and domestic animals. When anxiolytic drugs are used in mammals their pharmacological properties, the dependence of their action on the route of administration, age and species of the animal, and the ability to selectively affect the central nervous system should be taken into account. The most commonly used drugs for the treatment of behavioral disorders in animals are fluoxetine, amitriptyline, escitalopram, haloperidol, zuclopentixol and azaperone. Fluoxetine is an effective drug for the treatment of dogs with behavioral disorders associated with psychological changes. An important component of escitalopram's pharmacological effect is the psychomotor influence, when the animal's behavior changes are due to improved motor activity. Zuclopentixol has a wide range of anxiolytic, sedative and analgesic effects when used in wild cloven-hoofed animals. Amitriptyline along with antidepressant properties, has a local analgesic impact. Azaperone has a pronounced anxiolytic and sedative effect on animals. It is widely used as an antistress agent to overcome anxiety caused by weaning, regrouping or veterinary manipulations. Azaperone is often used to control aggressive behavior in group housing, especially in the pig industry. The psychotropic drugs surveyed in this paper, along with direct anxiolytic action, are able to manifest additional physiological effects, which should be taken into account when developing treatment protocols for animals with behavioral problems. Further targeted studies are required to assess the pharmacological effects of anxiolytic drugs in animals.

Keywords: animals; behavior; treatment; fluoxetine; amitriptyline; escitalopram; haloperidol; zuclopentixol; azaperone.

Introduction

Behavioral disorders are a fairly common pathology in animals (Rapoport, 1990; Rothman, 1991; Mondino et al., 2021). A variety of drugs are used to modify behavior, including psychotropic, anticonvulsant and antihistamines, hormones, analgesics and neuroleptics (van Zeeland, 2018). Many drugs from these groups are controlled substances, which increases the responsibility of the veterinarian for their proper and safe use (Anand & Hosanagar, 2021). It should also be taken into consideration that only 3% of such veterinary drugs are intended for use only in animals and more than 61% are also approved for use in human medicine (Avram, 2023). The clinical assessment of affective states, which mainly determine the course of behavioral reactions in animals, is a difficult but important task for a clinician when developing treatment protocols for animals with behavioral disorders (Schmidt et al., 1998; Irimajiri et al., 2009; Rutherford et al., 2012).

Psychotropic drugs, which include anxiolytic drugs, are prescribed for animals with behavioral disorders, signs of anxiety or increased reactivity (Demontigny-Bédard & Frank, 2018). While doing so, veterinarians must take a thorough behavioral history, understand and properly justify the use of a particular class of medication, and accordingly provide information and discuss possible consequences and prognosis with animal owners.

Changes in behavior are often associated with the development of disease states in animals. These changes are often seen as abnormal behavior, indicating the presence of pain or discomfort in certain organs or tissues (Frank, 2014). In our opinion, the appropriate correction of behavioral parameters in such cases can be considered as a means of pathogenetic therapy. Thus, improved methods of diagnosing and treating behavioral disorders in animals can optimize care for animals and increase their welfare. Future research should be aimed at improving and optimizing the use of psychotropic drugs for behavioral disorders in animals of various species. The purpose of this study was to provide physiological and pharmacological justification for the use of anxiolytic drugs for the correction of behavioral disorders in mammals based on the analysis of the scientific literature. We searched, selected and analysed publications related to the research topic in 1990–2023 in accordance with the methodology for systematic literature reviews (Gupta, 2018). The Web of Science Core Collection and PubMed were used to search for scientific articles.

The following keywords were used in the search: animals, behavioral disorder, anxiolytic drugs, azaperone, amitriptyline, fluoxetine, aripiprazole, escitalopram, haloperidol, clopixol, zuclopenthixol.

Using the electronic database PubMed, the key words – behavioral disorders, anxiolytic drugs and animals – since 1955, there were found 8245 scientific articles, of which 2691 or 32.6% were published in the last ten years. Similar studies on the use of separate anxiolytic drugs in veterinary medicine show that over the past ten years, 65.3%, 49.6%, 49.2% and 36.7% of the articles have been published on the use of escitalopram, aripiprazole, fluoxetine and azaperone, respectively. Since 1960, more

than 13,000 articles have been published on the effects of haloperidol, including 1,259 over the past 10 years. Since 1962, 2593 scientific articles have been devoted to the study of the efficacy of amitriptyline in animals.

These data indicate that the relevance of the use of psychotropic substances in veterinary medicine has increased significantly over the past decade. In this paper, we have drawn attention to scientific publications that reveal the physiological and pharmacological rationale for the use of anxiolytic drugs in the correction of behavioral disorders in animals.

The use of fluoxetine for the treatment of behavioral disorders in animals

Fluoxetine is an effective drug in the treatment of animals with behavioral disorders associated with psychological changes.

Kaur et al. (2016) conducted a survey among the veterinary practitioners on the use of fluoxetine in small animals. It was found that the most common indications for the use of this drug in dogs were anxiety, aggression, compulsive disorders and phobias, and in cats – elimination problems, anxiety, aggression and excessive grooming.

Fluoxetine has been shown to be effective for stereotypic behavior in Asian black bears (0.25–1.00 mg/kg, by mouth, every 24 hours, for 91 days) (Jeong, 2017). At doses that cause maternal behavioral disturbances (1, 10 and 20 mg/kg, for 21 days postpartum), fluoxetine did not affect offspring behavior or brain development during the dosing and thereafter (Zaccarelli-Magalhães, 2020).

Holman (2015) describes a case of treatment of an adult male snow leopard (*Uncia uncia*) that was raised in captivity. During continuous use (more than 3 years) of fluoxetine, this animal was treatedfor anxiety associated with the presence of visitors and exposure to an unknown female. The pathological behavior included panting, trembling, tail gnawing, panic, attacks on the sight glass, constant pacing and avoidance of the female. As a result, all signs of anxiety disappeared; the leopard no longer required medication, and successfully inseminated unfamiliar females. The author also noted that there were no signs of negative side effects during the long-term use of fluoxetine.

Fluoxetine in combination with clorazepate Pineda et al. (2014) was used for the treatment of dogs with anxiety-related behavioral disorders. The drug was administered orally at a dose of 1.0 mg/kg, every 24 hours for 10 weeks. Improvement was observed in 25 out of 36 experimental dogs. Other authors (Karagiannis, 2015) used fluoxetine in dogs for behavioral disorders associated with human separation (separation anxiety or separation stress). The affected animals showed destruction of property, vocalisation (barking, howling), urination or defecation in inappropriate places. A significant improvement in the behavior and psychological state of the dogs was found, which, according to the authors, also indicates an increase in the level of animal welfare.

Thus, fluoxetine is an effective anxiolytic agent used for the treatment of behavioral disorders associated with anxiety in various species of wild and domestic animals. The mechanism of anxiolytic action of fluoxetine often goes beyond serotonergic effects. For example, Ramsteijn et al. (2019) found changes in the composition and functional activity of the gastrointestinal microbiota in animals after treatment with this drug. According to the authors, since microbial metabolites affect the homeostasis and development of the macroorganism, disruption of the maternal microbiome under the influence of fluoxetine may have certain consequences for the health of the female and her offspring.

Fluoxetine does not adversely affect the appetite of pregnant ewes (Lingis, 2012). However, according to Nguyen et al. (2011), motor hyperactivity of lambs under antenatal fluoxetine exposure may indicate an increased rate of brain maturation. At the same time, electrocardiogram, blood pressure, heart rate, pH and gas composition of arterial blood, cortisol, glucose, and lactate levels, and sleep cycles did not change significantly. The authors believe that the altered rate of brain development may be the cause of poor neonatal adaptation of lambs exposed to fluoxetine while in the ewe's womb.

As a selective serotonin reuptake inhibitor, fluoxetine is one of the drugs widely used to treat aggression in dogs. The serotonergic system and the hypothalamic-pituitary-adrenal (HPA) axis are believed to play an important role in the control of aggression. In this regard, plasma concentrations of serotonin, cortisol and dehydroepiandrosterone (DHEA) were analysed in aggressive and non-aggressive dogs. A trend towards an increase in the DHEA/cortisol ratio after fluoxetine treatment was found in both groups of dogs (Rosado et al., 2011). The authors believe that, given these features of fluoxetine pharmacodynamics, the determination of serotonin levels and the DHEA/cortisol ratio in the blood may have important clinical applications. In particular, it can help to decide which animals may benefit from fluoxetine treatment, as well as to monitor the course of the disease.

The aim of Field et al. (2021) was to characterize the role of fluoxetine in glucose and insulin metabolism in dairy calves. It was found that fluoxetine-treated calves had fewer islets in the pancreas per microscopic field and reduced insulin staining intensity. According to Marrero et al. (2021), fluoxetine affects gene expression and serotonin receptors of immunocompetent cells in calves. In our opinion, these data indicate important pharmacological features of fluoxetine's effect on the body of animals, which should be taken into account, especially in the case of long-term use of the medicine and the others drugs of this group.

Marsh et al. (2020) tested the usefulness of cortisol as an indicator of the effectiveness of fluoxetine hydrochloride on the brain of pigs. It was found that the mean plasma cortisol level of animals in anxious states increased significantly ($P = 0.048$) with the highest cortisol concentrations in fluoxetine-treated pigs. However, individual profiles of cortisol levels after fluoxetine treatment showed a high individual variation in response, which, according to the authors, may hinder the use of this approach in pigs. Thus, the pharmacological action of fluoxetine is characterised by a multidirectional mechanism of anxiolytic and somatic effects. Along with direct neurotropic serotonergic action, fluoxetine has an effect on the hypothalamic-pituitary-adrenal axis, gastrointestinal tract, glucose metabolism, reproductive and protective functions of animals. In fetuses and newborn animals, fluoxetine may affect the development and functional activity of certain parts of the brain. However, most researchers emphasise that further targeted scientific studies are required for a more specific and objective assessment of the pharmacological effects of fluoxetine and other serotonergic anxiolytic drugs on the animal body.

Meanwhile it is widely believed that the pharmacological effects of fluoxetine in animals depend on the route of administration, age and species of the animal. That is why an important condition for the effective use of the medicine is to take into account its pharmacokinetics and the dependence of its effect on the route of administration, etc. The aim of the study by Eichstadt et al. (2017) was to compare fluoxetine serum concentrations after transdermal (lipoderm liniment) and oral (fluoxetine tablets) administration. It was found that the concentrations of fluoxetine and norfluoxetine in the blood were significantly different for oral and transdermal administration. Fluoxetine concentrations were consistently higher when administered orally. The authors noted that the lack of knowledge regarding physiologically effective blood levels of fluoxetine did not allow them to determine whether a clinically effective response will be achieved at the found blood concentrations of the drug with both routes of administration.

The effect of rumen passage on fluoxetine bioavailability and serum concentrations was studied by Yates et al. (2010). It was found that a higher oral dose may be required to overcome the partial loss of fluoxetine bioactivity during passage through the forestomach compared to the dose for animals with a single chamber stomach.

An *in vivo* assessment of fluoxetine metabolism and its disposition in various tissues of lambs from birth to one year of age was conducted by Chow et al. (2019). It was found that renal elimination of fluoxetine metabolites was low. The rate of drug elimination increased nonlinearly during the first year of life. The metabolism and excretion of fluoxetine products in plasma and urine were selective, which the authors explain by both selective binding of the drug to proteins and peculiarities of its metabolism. Therefore, when using fluoxetine in animals, its pharmacokinetics should be taken into account depending on the route of administration, age and species of the animal, and the ability to selectively bind to proteins of various organs and tissues.

The pharmacological characteristics of fluoxetine determine the directions of its use in the treatment of behavioral disorders in different animal species. The most common indications for fluoxetine in dogs are various

compulsive disorders, aggression and certain somatic pathologies. For example, according to Yalcin (2010), fluoxetine (1 mg/kg, orally, for 12 weeks) was effective in the treatment of dogs with tail chasing. D'Angelo et al. (2022) reported that three months after pharmacological treatment with fluoxetine and α-s1 casozepine, they observed a decrease in the intensity and frequency of obsessive states (tail chasing) in experimental dogs. At the same time, studies conducted by Mosallanejad et al. (2015) showed that hypericin is more effective than fluoxetine in controlling the signs of tail chasing in dogs.

One of the most common behavioral disorders in dogs is aggression. The use of anxiolytic drugs is one of the mostly used options in the treatment of dogs with this pathology. The results of the study by Odore et al. (2020) showed that fluoxetine (1.5 mg/kg/day) in combination with behavioral therapy, effectively controlled dog aggression over a six-month period. The authors note that the level of norfluoxetine in the blood of dogs can be a reliable indicator for monitoring and predicting clinical efficacy. Other authors (Sacchettino et al., 2023) reported that after treatment with fluoxetine (0.8 mg/kg, daily, for 9 months) in combination with oral α-s1 casozepine and behavioral rehabilitation, a significant reduction in the intensity and frequency of aggressive behavior was observed.

Wrzosek et al. (2015) reported one hundred per cent efficacy of fluoxetine in the treatment of dogs with fly-catching syndrome.

Fluoxetine is also widely used for the treatment of psychological disorders or somatic effects in many other animal species. For example, a meta-analysis done by Mills et al. (2011) allowed the authors to suggest that fluoxetine, clomipramine and pheromone therapy may be effective in overcoming the problem of urinary marking in cats. In ewes, fluoxetine causes a decrease in milk production (Harrelson et al., 2018), which the authors consider to have the potential to facilitate the transition to dry period. Administration of fluoxetine to calves helped to normalise the heart rate, increase red blood cell and haemoglobin levels in the blood, and serotonin bioavailability in the body. The experimental calves had a higher average daily weight gain (Marrero et al., 2019). Fluoxetine partially or completely reversed the negative behavioral and somatic effects of chronic stress in pigs (Menneson et al., 2019). In a retrospective assessment of the clinical effects of fluoxetine in horses, most owners perceive it as an effective means of preventing stereotypical behavior during prolonged stalling (Fontenot et al., 2021).

Thus, fluoxetine is an effective pharmacological agent in the treatment of dogs with behavioral disorders associated with psychological disturbances. At the same time, attempts to use this drug for the treatment of somatic diseases (Fujimura et al., 2014; DiCiccio et al., 2022) have not yet been successful.

The use of haloperidol for the correction of behavioral disorders in animals

Haloperidol enhances the effect of neuroleptics and is capable of providing long-term sedation in animals. Haloperidol can selectively affect certain forms of animal behavior (Osacka et al., 2022). As a dopamine D2 receptor blocker, haloperidol negatively affects the development of conditioned and unconditioned feeding reflexes in chickens (Moe et al., 2014). Mow et al. (2015) found that haloperidol has an active antiarrhythmic effect on pharmacologically induced arrhythmia in animals. According to the authors, this effect is mediated by their high affinity for α1-adrenergic receptors.

The oxidative and degenerative effects of haloperidol and its effect on the inflammatory processes were studied by Bahrambeigi et al. (2021). It was found that haloperidol can adversely affect the regenerative component of inflammation and cause hepatocyte degeneration. According to the authors, the effect of haloperidol on the immune system needs to be further studied, and higher doses should be prescribed with caution. Chiejina et al. (2023) studied the effect of haloperidol on peripheral red blood cells and neurotransmitter levels in the brain of the African sharp-toothed catfish (*Clarias gariepinus*). It was found that haloperidol is toxic to these fish and its use in the environment should be cautious to avoid adverse effects on non-target species, including fish.

Other authors (Chiejina et al., 2022) studied the effects of haloperidol on freshwater African catfish by dissolving it in water at doses of 0.12, 0.24 and 0.48 mg/L. The volume of blood cells, red blood cells, haemoglobin, reticulocytes and lymphocytes significantly decreased in fish exposed to the drug. The number of neutrophils increased, whereas the number of monocytes, basophils and eosinophils was not affected. The activity of aspartate aminotransferase, alkaline and acid phosphatase, alanine aminotransferase, as well as bilirubin, creatinine, and bile acid in the blood serum increased, while fibrinogen activity decreased. It was concluded that haloperidol was toxic to fish at the doses and regimens studied, but that this effect was short-lived, as it disappeared already in 5 days after drug discontinuation. Martelli et al. (2021) describe the successful use of haloperidol (in combination with Zoletil) for long-term (20 days) sedation of an orangutan with pneumonia. Haloperidol has also been shown to be useful in reducing stress during the capture and trapping of spotted deer (Martelli & Oh, 2021).

Thus, haloperidol is an effective anxiolytic agent in animals. It is capable of potentiating the effects of neuroleptics and, if necessary, providing long-term sedation of animals. However, it should taken into account that even when used in therapeutic doses, haloperidol may adversely affect the course of the inflammatory processes and the function of other organs and systems of the body.

The use of zuclopentixol for the treatment of behavioral disorders in animals

Zuclopentixol has a wide range of anxiolytic, sedative and analgesic effects, especially when used in wild cloven-hoofed animals. One of the promising drugs with anxiolytic effect is zuclopentixol. The drug belongs to the thioxanthene group. Its antipsychotic effect is associated with dopamine receptor blockade, 5HT receptor blockade, affinity for both dopamine D1 and D2 and 5HT2 receptors and α1-adrenoceptors (https://compendium.com.ua/uk/akt/90/44/zuclopenthixol). Zuclopentixol is able to reduce aggressive behavior and produce a transient dose-dependent sedative effect (Johns et al. 2020).

The pharmacokinetics of zuclopentixol depends on both the solvent and the chemical composition of the drug. Aaes-Jørgensen et al. (1989) studied the pharmacokinetics of three different zuclopentixol preparations. These were zuclopentixol dihydrochloride in aqueous solution, zuclopentixol acetate in oil and zuclopentixol decanoate in oil. It was found that the pharmacokinetic profiles of these injectable formulations are very different. Maximum serum levels were reached after approximately 1 hour for zuclopentixol dihydrochloride, 36 hours for zuclopentixol acetate and one week for zuclopentixol decanoate. It is obvious that the different pharmacokinetics of the three injectable drugs affect the clinical properties of zuclopentixol, which should be taken into account when using it in animals.

The effect of zuclopentixol on the physiological functions and behavior of animals is pronounced. Thus, according to Fick et al. (2005), zuclopentixol (5 mg/kg) significantly reduced nighttime body temperature and activity of rats in a cage, and in doses of 1 and 5 mg/kg significantly reduced feed intake 5–17 hours after injection ($P < 0.05$). Significant analgesic effect was observed in rats treated with 5 mg/kg of zuclopentixol within 40 hours after injection, and their motor function was also impaired. Taking into account the effects of zuclopentixol on body temperature, feeding and behavior, the authors noted that such effects were short-lived and should not prevent the use of the drug in wild animals.

Laubscher et al. (2016) studied the effects of the slow-release zuclopentixol acetate (Acunil®) on captive blue wildebeest (*Connochaetes taurinus*). Antelopes treated with Acunil spent more time lying down, eating and standing with their heads down, and spent less time being alert and exploring while walking. Less grooming activity was observed in the treated animals and they shook their heads less and spent less time making rapid movements when stimulated (the person entering their pen). The average respiratory rate was lower ($P = 0.02$) in animals treated with Acunil (before the drug administration 14.5 ± 0.82; after administration – 12.5 ± 0.83 breaths/min). Due to its pharmacological properties, zuclopentixol is used for the prevention of fixation stress and myopathy in deer (Read et al., 2000) and in complex protocols for anaesthesia of wild animals (Woodbury et al., 2001).

At the same time, the use of zuclopentixol acetate at a dose of 0.6 mg/kg alone or in combination with perphenazine enanthate in chee-

tahs caused loss of appetite, ataxia, extrapyramidal reactions (hypokinesia, involuntary movements, oscillatory rhythmic jerks), akathisia (restlessness, anxiety and agitation, which makes the animal unable to stand or lie still) and eyelid prolapse (Huber et al., 2001). Therefore, the authors of the study noted that zuclopentixol acetate should not be used in cheetahs, and that further scientific research is needed to determine whether it can be used in other wild cats.

Thus, zuclopentixol has a wide range of anxiolytic, sedative and analgesic effects. However, its mechanism of action and clinical efficacy has not yet been sufficiently described in different animal species. Today, there are sufficient grounds to recommend its use in wild cloven-hoofed animals. At the same time, the results of some studies indicate a significant number of adverse complications when used in certain species of wild cats.

The use of azaperone for the correction of behavioral disorders in animals

Azaperone has a pronounced calming and anxiolytic effect on animals. In veterinary practice, azaperone is often used to reduce emotional or physical stress in animals during various stressful situations. It is also used in animals in combination with anaesthetic drugs during surgical interventions (Schmidt et al., 2012).

The purpose of the research done by Rutherford et al. (2012) was to study the effect of azaperone on the emotional state of pigs. The experimental animals were injected with azaperone and the control animals with saline, after which they were subjected to an open field and maze test. The qualitative assessment of behavior was carried out using two parameters. The first parameter was positively associated with such terms as "confident" and "inquisitive" and negatively associated with "uncertain" and "nervous" states; the second parameter was positively associated with "calm"/"relaxed" and negatively – with "agitated"/"angry" states. In both tests, pretreatment with azaperone was associated with more positive emotionality (higher scores on the first parameter), and more pronounced confident/inquisitive behavior was observed in azaperone treated pigs. There was no effect of azaperone on the second parameter.

Weaning piglets always causes emotional stress in sows. The effect of azaperone on sow behavior during weaning was studied by Schwarz et al. (2018a). Sows were injected with azaperone (Stresnil) at a dose of 2 mg/kg body weight immediately before weaning. It was found that sows treated with azaperone had a significantly longer interval from weaning to estrus and a significantly larger piglet nest size. The researchers also identified the specific effects of azaperone on the reproductive behavior of sows depending on the season. In particular, the use of azaperone at weaning increased sow productivity and the development of winter farrowing piglets, but significantly reduced it in summer. In general, according to the researcher's conclusion, additional costs due to the delayed onset of estrus may negate any reproductive benefits of azaperone treatment.

Schwarz et al. (2018b) also showed that azaperone affects endocrine and sexual activity of sows. It was found that the intervals from weaning to the onset of estrus and ovulation were longer in sows treated with azaperone (by ~12 hours) than in control sows. Temporary suppression of cortisol release was observed 10 and 30 minutes after azaperone injection. Also, the experimental animals showed a pre-ovulatory increase in luteinising hormone, but the secretion of estradiol slowed down. The researchers, based on the analysis of changes in hormone levels, concluded that the administration of azaperone during weaning had a significant effect on the pre-ovulatory secretion of luteinising hormone (LH), as well as on the growth kinetics and activity of ovarian follicle estrogenesis. However, according to the authors, the causal relationship between different levels of pre-ovulatory LH secretion, ovarian and adrenal secretion requires further study. Azaperone in combination with other drugs is used to immobilize various species of wildlife. In studies conducted on rhinos, bears and raccoons, it was found that the use of azaperone as an additional drug for immobilizing animals is clinically safe and effective. The average induction time for rhinos decreased from 8.9 min for etorphine alone to 6.3 min with the addition of azaperone. No changes in physiological parameters during the recovery period, including arterial blood gas analysis, were observed (Buss et al., 2022; Johnson et al., 2023; Sheldon, 2023; Somers, 2023). Thus, azaperone has a calming influence on animals due to its effect on serotonin receptors. It is used to control stress caused by weaning, regrouping and aggression of older and larger animals and during veterinary manipulations.

The use of amitriptyline for the treatment of behavioral disorders in animals

Amitriptyline, in addition to its antidepressant properties, can have a local analgesic effect. Amitriptyline is one of the antidepressant drugs used to treat behavioral disorders in animals. It is used for pathologies such as generalised anxiety and separation anxiety in dogs, as well as excessive self-grooming, urine spraying ("marking") or anxiety in cats.

Norkus et al. (2015a) evaluated the pharmacokinetics of oral amitriptyline and its effect on feeding behavior in dogs. It was found that the relative bioavailability of amitriptyline in fasted dogs compared to fed dogs was 69–91%. It has also been found that amitriptyline can induce vomiting in pre-fed dogs. In their other work the researchers (Norkus et al., 2015b) found that oral administration of amitriptyline at a dose of 4 mg/kg was well tolerated by the animals, but the authors claim that the plasma concentrations of amitriptyline and nortriptyline probably did not rise enough for pharmacological effects. The mean maximum concentration of amitriptyline in blood plasma was 27.4 ng/mL after 1 hour, and its mean terminal half-life was 4.33 hours, with oral amitriptyline bioavailability of 6%. The authors concluded that this dose of amitriptyline (4 mg/kg) is not effective in dogs. Ratajczak-Enselme et al. (2015) studied the pharmacokinetics of amitriptyline after intrathecal, epidural and intravenous administration in sheep. The results of the study indicate that amitriptyline is a lipophilic tricyclic antidepressant with analgesic properties that can be used for epidural analgesia.

Batle et al. (2019) describe cases of amitriptyline in combination with other drugs in the treatment of hyperesthesia syndrome in cats. The animals showed skin twitching in the dorsal lumbar region, excessive vocalization, periods of jumping and running, tail chasing, and self-injury. It was found that the clinical signs were alleviated and aggressive behavior was reduced. At the same time, the use of amitriptyline for the treatment of post-traumatic stress disorder, a debilitating condition that includes constant anxiety, obsessive repetitive behavior and several physiological disorders in animals, has not yielded a positive effect (Zoladz et al., 2013).

Thus, for effective action of amitriptyline in animals, its route of administration, dose, pharmacokinetic properties and interaction with other drugs should be taken into account.

The use of escitalopram for the correction of behavioral disorders in animals

The psychomotor effect of escitalopram is accompanied by its influence on motor activity parameters. For many years, selective serotonin reuptake inhibitors have been taking the leading position in the treatment of emotional disorders in animals. Among them, a prominent place is occupied by escitalopram, which acts by blocking the serotonin transporter (Taylor et al., 2017).

The aim of the study done by Abdelwahab et al. (2021) was to investtigate the effect of escitalopram on the behavior of rats with depression caused by separation from their mother. It was found that the drug alleviates depression in rats by positively affecting the serotonergic and oxytocinergic systems. Escitalopram caused an increase in plasma oxytocin levels, a decrease in adrenocorticotropic hormone, and a restoration of oxytocin and serotonin release in the hippocampus. Clinical data (Hudson et al., 2017) confirm that escitalopram has antidepressant properties as a selective serotonin reuptake inhibitor and its effect is exerted by improving psychomotor functions in animals.

The use of escitalopram as a preventive strategy for the treatment of spasticity after spinal cord injury in rats was studied by Ryu et al. (2021). It was noted that in most animals with spinal cord injury, spasticity develops subacutely and chronically due to hypertension of the corporal muscles. This condition is based on the increased expression of 5-HT receptors on spinal cord motoneurons due to enervation, which is considered to be one of the crucial factors in the hyperexcitability of the spinal cord.

The authors concluded that escitalopram, as a 5-HT signalling modulator and a selective serotonin reuptake inhibitor, effectively prevents spasticity resulting from spinal cord injury. Thus, the psychomotor effect of escitalopram is achieved by improving the animal's motor activity, but in combination with other drugs, a better antidepressant effect can be obtained.

The use of aripiprazole for the correction of behavioral disorders in animals

The antidepressant effect of aripiprazole is due to its ability to increase the survivability of nerve cells in the brain. Aripiprazole is one of the common drugs that are used for the treatment of mental disorders in animals. The results obtained by Scheggi et al. (2018) show that aripiprazole alleviates stress-induced motivational anhedonia in rats. Anhedonia is considered to be an important feature of depression and psychosis, which is associated with a deficit in mesolimbic dopaminergic sensitivity. The authors note that aripiprazole can be used as an adjunctive therapy for the treatment of persistent depression as it can stabilise the dopaminergic system in animals.

The neuroprotective effects of aripiprazole in depression-like behavior caused by stress were studied by Dashti et al. (2022). It was found that aripiprazole can promote synaptic plasticity by improving the expression of BDNF and GAP-43 genes. In addition, reducing inflammation and downregulating CACNA1C expression may be among the mechanisms by which aripiprazole delays and prevents hippocampal cell death caused by chronic stress, thus playing its key antidepressant role.

Concomitant and side effects of anxiolytic drugs

Diagnosing and treating behavioral disorders in animals is an important task for veterinarians. The impact on the central nervous system is often accompanied by various additional effects. In this regard, the scientific literature is widely represented by studies aimed at improving and optimizing the use of anxiolytic drugs in different animal species.

When prescribing anxiolytic drugs, it is important to take into account both the peculiarities of the pathogenesis of behavioral pathology and the special features of the pathogenetic and pharmacological effects of the drugs. Such information will help the veterinarian to prescribe treatment with proper justification.

Frank (2014) also notes that changes in behavior are often secondary consequences of the development of disease states of other organs and systems of the animal. In our opinion, in such cases, changes in behavior should be considered as an important means of early diagnosis of somatic pathology, and correction of behavioral parameters should be considered as a means of pathogenetic therapy.

The activation of the stress response accompanied by behavioral disorders in animals is similar to that in humans. In both cases, it leads to immune suppression, gastrointestinal, cardiovascular and skin diseases, delayed wound healing, changes in pain perception and neurological disorders (Lefman & Prittie, 2019). The relevance of studying the effects of anxiolytic drugs on animal behavior is also high due to the use of many animal species (dogs, sheep, pigs, horses) to model mental and behavioral disorders in humans (Stein et al., 1994; LeBlanc et al., 2014; Danek et al., 2017; Dewey et al., 2019).

Most anxiolytics are easy to monitor pharmacologically. They are retained in blood plasma for up to 1 week. Caution should be exercised when determining them in serum or in the presence of haemolysis (Fisher et al., 2013). Some anxiolytic drugs can have an antispastic effect on the smooth muscles of the urinary tract, which is often used in the treatment and prevention of urolithiasis in animals (Li, 2015; Uno et al., 2017; Obara et al., 2019).

An overdose of anxiolytic drugs leads to an increase in the level of serotonin in the central nervous system. Clinically, such poisoning is manifested by nausea, vomiting, mydriasis, hypersalivation and hyperthermia. In severe cases, ataxia, tremors, diarrhoea, or even convulsions are observed. However, with proper detoxification, symptomatic treatment and observation of the animal for 12–24 hours, the prognosis for full recovery is good (Fitzgerald et al., 2013; Pugh et al., 2013). One of the undesirable side effects of anxiolytic drugs is a possible negative impact on reproductive function in females (Read et al., 2002; Ince et al., 2021).

The main indication for the use of anxiolytic drugs is behavioral disorders associated with anxiety in various species of wild and domestic animals. When anxiolytic drugs are used in animals, their pharmacological properties, the dependence of the action on the route of administration, age and species of the animal, and the ability to selectively affect the affective serotonergic zones of the central nervous system should be taken into account.

Conclusions

Fluoxetine, amitriptyline, escitalopram, haloperidol, zuclopentixol and azaperone are widely used for the correction of behavioral disorders in animals. Fluoxetine is an effective drug used for the treatment of dogs with behavioral disorders associated with psychological changes. An important component of escitalopram's pharmacological effect is the psychomotor effect, when the animal's behavior changes due to improved motor activity. Improvement of the antidepressant effect of escitalopram is possible when used in combination with other anxiolytic drugs. A special feature of haloperidol is its ability to potentiate the effect of neuroleptics and to provide longer sedation of animals. Zuclopentixol has a wide range of anxiolytic, sedative and analgesic effects when used in wild cloven-hoofed animals. Amitriptyline, along with its classical anxiolytic effects, has local anaesthetic properties, which allows it to be used for epidural analgesia. Azaperone is used as an anti-stress agent in animals to overcome anxiety caused by weaning, regrouping or veterinary manipulations.

The psychotropic drugs reviewed in this paper, along with their direct anxiolytic effect, are capable of producing additional physiological effects, which should be taken into account when developing treatment protocols for animals with behavioral problems. However, we agree with the conclusions of the majority of researchers who emphasise that further targeted scientific studies are required to assess the pharmacological effects of serotonergic anxiolytic drugs in animals.

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