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Melatonin in dogs: mechanisms and applications for behavioral issues. Commentary on current state of art and future perspectives

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Abstract: Melatonin is a multifaceted neurohormone primarily synthesized by the pineal gland. It offers the capacity to enhance the management of behavioral issues in domestic canines. Scientific data supporting its therapeutic value is scarce and varied, despite its widespread off-label clinical application. This commentary summarizes current knowledge regarding the clinical uses and mechanisms of action of melatonin in addressing behavioral disorders in dogs. Clinical evidence supports the potential impact in managing preoperative anxiety, noise phobia, separation-related disorders, compulsive behaviors, and canine cognitive disorders. The recommended dosage is in a range of 1.5 to 6 mg, depending on the dog's weight; the dosage needs to be delivered every 8 to 24 hours, contingent upon the therapeutic circumstances. The safety profile is favorable with negligible side effects. Although melatonin shows promise as an adjuvant treatment for canine behavioral problems, the existing evidence is predominantly based on case reports and anecdotal experiences. To establish evidence-based dose guidelines, long-term efficacy, and safety profiles, thorough randomized controlled trials in dogs are essential.

Key Words: behavior, melatonin, dog, noise phobia.

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Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is a multifaceted neurohormone primarily produced by the pineal gland, with additional contributions to circulating levels from extrapineal sources such as the gastrointestinal tract and retina. Melatonin is generated via intricate enzymatic processes, commencing with the conversion of the amino acid tryptophan. Tryptophan is taken into the bloodstream, conveyed to the pineal gland, and used for the synthesis of proteins essential for melatonin generation (Parmar & Daya, 2001). Melatonin production exhibits a circadian rhythm, reaching its zenith at night due to diminished light exposure, thereby informing the body of alterations in environmental photoperiods and modulating biological rhythms accordingly (Fang et al., 2018; Gao et al., 2022). Melatonin's biological functions primarily occur through the activation of two high-affinity G-protein coupled receptors, MT1 and MT2, which are predominantly expressed in the suprachiasmatic nucleus (SCN) of the hypothalamus, the central circadian pacemaker, as well as in various other brain regions and peripheral tissues. Activation of the MT1 receptor predominantly inhibits adenylate cyclase, leading to a decrease in cAMP levels, whereas the MT2 receptor controls cyclic GMP pathways, each initiating unique intracellular cascades that regulate physiological responses (Gao et al., 2022; Salavati et al., 2023). In addition to receptor-mediated activities, melatonin demonstrates significant antioxidant properties by neutralizing reactive oxygen species (ROS) and enhancing the activity of endogenous antioxidant enzymes, including superoxide dismutase and glutathione peroxidase. This safeguards cerebral tissue from oxidative damage associated with neurodegenerative processes (Paradies et al., 2015). In dogs, melatonin affects the modulation of neurotransmitters like as serotonin, dopamine, and gamma-aminobutyric acid (GABA), which are essential in regulating mood, anxiety, and circadian sleep-wake patterns. Moreover, melatonin regulates the hypothalamic-pituitary-adrenal

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(HPA) axis, diminishing excessive cortisol secretion under stress, thereby aiding in the reduction of anxiety-like behaviors (Salavati et al., 2023; Song & Yoon, 2025). Despite the intricate nature of these systems rendering melatonin a promising therapy option for behavioral disorders in dogs, scientific study remains limited, and data supporting its therapeutic efficacy is derived from model animals, humans, and case reports involving dogs. The heterogeneity in dosage regimens and result measurements hinders broad accord.

Behavioral disorders in dogs and melatonin

Behavioral disorders are a significant welfare concern for domestic dogs and their caregivers, affecting a considerable portion of the global population (Campbell, 1986; Yamada et al., 2019; Dinwoodie et al., 2019; Salonen et al., 2020; Yang et al., 2021). Prevalent disorders encompass generalized anxiety, aggression, noise phobias (such as thunderstorms and fireworks), separation-related disorders, compulsive behaviors, and age-associated cognitive impairment (Landsberg et al., 2023). These conditions frequently indicate dysregulation in neurochemical systems, altered circadian rhythms, and inappropriate stress responses. Anxiety disorders in dogs have similar neurophysiological mechanisms to those in humans, characterized by abnormalities in serotonergic and dopaminergic neurotransmission, together with hyperactivity of the HPA axis, which intensifies sympathetic nervous system arousal. Furthermore, sleep problems exacerbate behavioral dysregulation, establishing a detrimental cycle (Song & Yoon, 2025). Melatonin's capacity to regulate circadian rhythms and influence central neurotransmission provides a biological basis for its therapeutic use in various illnesses. Indeed, melatonin together with adenosine facilitates the restoration of behavioral equilibrium by enhancing synchronization of the sleep-wake cycle and diminishing nocturnal cortisol peaks (Ruiz-Cano et al. 2022; Masson et al., 2024). Experimental and clinical investigations in rodents and animals illustrate melatonin's anxiolytic effects by increasing serotonergic activity and promoting GABAergic inhibitory neurotransmission. This dual action assists in mitigating fear and stress reactions, which are fundamental to numerous canine behavioral issues (Wang et al., 2021; Song & Yoon, 2025).

Clinical use of melatonin in canine behavioral management

In veterinary clinical practice, melatonin is widely utilized off-label to address behavioral issues, owing to its advantageous safety profile and convenience of administration; preoperative anxiety represents a specific situation. Niggemann et al. (2019) performed a clinical trial including 50 dogs to assess the efficacy of melatonin as pre-medication in healthy dogs waiting for elective surgery. Their main goal was dual: to ascertain if oral melatonin administration elicited a calming effect in dogs prior to anesthesia, and to assess whether this effect facilitated a reduction in the required dose of Propofol for anesthesia induction and intubation. The treatment group administered 5 mg/kg of melatonin orally, two hours before to the induction of anesthesia. The researchers discovered that dogs designated as "skeptical" in the melatonin group exhibited more calmness 90 minutes post-administration compared to "skeptical" dogs in the placebo group. This indicates a main advantage for the most anxious animals. Moreover, dogs categorized as "trustful" in the melatonin group necessitated a markedly reduced dosage of propofol for anesthesia induction in contrast to "trustful" dogs in the placebo group. Researchers showed that melatonin is effective in veterinary pre-medication to mitigate alertness and anxiety before to general anesthesia, especially in more agitated dogs, and to decrease the necessary dosage of Propofol for anesthesia induction in calmer dogs (Niggermann et al., 2019).

In 2023, Salavati and colleagues performed a veterinary clinical experiment with 25 healthy dogs to examine the effects of orally administered melatonin on female dogs having ovariohysterectomy (OHE). The study aimed to investigate if melatonin administration may regulate and alleviate post-operative inflammatory and oxidative effects, given its recognized anti-inflammatory and antioxidant properties. The authors administered melatonin at an oral dosage of 0.3 mg/kg. This administration was place on the days preceding and following the surgery (days -1, 0, 1, 2, and 3). To attain the aim, the researchers quantified the levels of various biomarkers in the dogs' blood, including cortisol and serotonin (for the behavioral aspect) and cytokines (such as CRP, SAA, IL-10, for the inflammatory component). The findings indicated that the administration of melatonin (both pre- and post-operatively) resulted in a substantial reduction in cortisol levels and primary inflammatory indicators in the group of female dogs treated with melatonin following OHE, in contrast to those that had surgery without treatment. Furthermore, serotonin levels elevated in females that were administered melatonin. The research concluded that oral administration of melatonin prior to and following ovariohysterectomy is an efficient strategy for managing elevated inflammation and cortisol levels generated by surgery in female dogs.

Although there is an absence of controlled and long-term studies, case reports indicate that melatonin may be beneficial in addressing anxiety, fear of fireworks and thunder, sleep cycle disorders in dogs and cats (Casey et al., 2022; Landsberg, 2005; Landsberg et al., 2023), noise phobia (Aranson, 1999), separation anxiety, compulsive disorder (Sacchettino et al., 2023), and cognitive dysfunction syndrome (Landsberg, 2005; Paradies et al., 2015; Zhao et al., 2024). To the authors' knowledge, the first reported case report in dogs was in 1998, when melatonin was administered in combination with amitriptyline to treat noise phobia at a dose of 0.1 mg/kg per day and up to every 8 hours during fireworks and storms.

In 2023, Sacchettino and colleagues published a case report regarding a 5-year-old mixed-breed dog suffering with a compulsive disorder that was refractory to conventional antidepressant therapies. The researchers employed an interdisciplinary and integrative approach that combined three components: a behavioral program, the administration of cannabis products, and melatonin supplementation (2 mg/day). Clinical observations and owner reports indicated that the integrated strategy resulted in a decrease in the frequency of compulsive episodes and improved overall management of the dog compared to prior therapy with paroxetine, without any short-term side effects reported. Additionally, the authors indicated that sustaining a decrease in dysfunctional behavior to a level deemed acceptable by caregivers was accomplished during a subsequent four-month follow-up period.

Melatonin was recently suggested "by Costa (2023) in the "Chill protocol" for evaluating a pre-visit sedative treatment. This prospective research trial aimed to assess the sedative and behavioral effects of a regimen administered by the caregivers before to a veterinary appointment, referred to as the GMA protocol (gabapentin, melatonin, and acepromazine). The investigation encompassed 45 client-owned dogs exhibiting symptoms of anxiety, fear, and/or aggression during veterinary appointments. Caregivers were instructed to administer gabapentin, melatonin (3-5 mg per dog based on weight), and acepromazine (administered orally-transmucosally) 90-120 minutes prior to the subsequent appointment. Researchers noted a substantial decrease in stress scores and a notable increase in sedation scores following the implementation of the GMA regimen, in comparison to baseline measurements. The GMA technique significantly diminished indicators of anxiety, tension, and fear-induced aggression during visits. The findings indicated that the approach enhanced the manageability of dogs, facilitating the completion of tests on those that were previously too aggressive or fearful to be inspected safely. A notable association was observed between advancing age and diminished post-GMA stress levels, indicating that older dogs may have a more pronounced response. The research indicates that this multimodal approach serves as an extra resource for veterinarians to enhance care quality and mitigate the risk of injury to both staff and animals.

Dosage, safety, and side effects of melatonin in dogs

There is currently no clear consensus regarding the dosage or formulation (e.g., conjugated or not) in behavioral medicine. The authors generally recommend a range of 1.5 mg for small dogs, 3 mg for dogs weighing 15 to 50 kg, and 3-6 mg for dogs weighing more than 50 kg, administered every 8-24 hours (Aranson, 1999; Landsberg et al., 2023). The frequency and timing of treatment are contingent upon the clinical context—typically administered 30 to 60 minutes prior to stimulus exposure or bedtime for anxiety and sleep disturbances, as pharmacokinetic analysis indicates rapid and complete absorption following oral administration, with peak plasma concentrations reached within 30-60 minutes (Sääf et al., 1980; Salavati et al., 2023).

Sharman and Bondy (2016) reported that melatonin has minimal toxicity, even at elevated dosages, rendering it an even safer supplement in comparison to other pharmacological drugs. Its efficacy seems to stem not from a singular mechanism, but from its capacity to implement several neutralizing measures against diverse danger aspects. Pharmacodynamic investigations validated melatonin's dose-dependent effects on calm and sedation, while preserving cardiac and respiratory function, hence promoting its incorporation into multimodal treatment regimens (Peace et al., 2019; Salavati et al., 2023). Even though caregivers may regard melatonin as natural and safe, it contains pharmacologically active compounds that can lead to harmful effects and/or interact with medications. The main interaction issue is drugs that are strong inhibitors of the CYP1A2 enzyme, such as antidepressants (Papagiannidou et al., 2014; Li et al., 2018), which leads to an augmentation of standard treatment. This outcome was additionally emphasized by a clinical case in which a patient exhibited profound sedation following the simultaneous administration of melatonin with two antidepressants (citalopram and nortriptyline) and one opioid analgesic (oxycodone), likely due to the inhibitory effect of melatonin on hepatic enzymes (Foster et al., 2015). Adverse effects are often modest, encompassing fatigue, dizziness, headache, irritability and gastrointestinal disturbances (Seabra et al., 2000). However, due to the presence of excipients harmful to dogs in certain human melatonin products (e.g., xylitol), it is advisable to utilize veterinary-specific formulations.

Conclusion

Melatonin, recognized for its efficacy as a circadian synchronizer and potent antioxidant, has garnered increasing interest in dog behavioral therapy. The physiological mechanism of melatonin in dogs is intricate, involving interactions with the hormonal systems (particularly the hypothalamic-pituitary-adrenal axis) and neurotransmitters. The hormone is hypothesized to affect not only the sleep but also indirectly regulate issues such as separation anxiety, psychogenic alopecia, and compulsive behavior. Specifically, Zhao et al. (2024) highlighted melatonin's role as an antioxidant that mitigates oxidative damage, offering neuroprotective effects in various animal models. This perspective suggests melatonin could be beneficial in elderly dogs suffering from cognitive dysfunction (Landsberg, 2005), also aiding in the regulation of the circadian rhythm—a parallel observed in human patients with cognitive decline (Magri et al., 2004).

Moreover, the association between melatonin and stress management pertains to essential welfare settings, including shelter surroundings. Research on shelter dogs, which generally exhibit heightened stress and cortisol levels, suggests that the administration of agents that regulate the HPA axis may be advantageous (Giuliano et al., 2024). The research by Gazzano et al. (2025), which demonstrated a substantial negative association between oxytocin and cortisol during stressful veterinarian handling, reinforces the notion that hormonal support can mitigate the physiological stress response. Given the proposed antagonistic effect of melatonin on the HPA axis and its ability to reduce stress markers, its incorporation alongside behavioral management

strategies (e.g., environmental enrichment, human interaction) may serve as a beneficial support for enhancing the short-term and long-term welfare of dogs experiencing the persistent stress of shelter.

Despite these optimistic future perspectives, is essential to emphasize that most of the current evidence regarding the use of melatonin in dogs is derived from anecdotal experiences or isolated case reports within an integrated approach (Aronson, 1999; Denenberg, 2021; Sacchettino et al., 2023). Pharmacodynamic research and randomized clinical trials, which are essential for establishing doses, long-term efficacy, and safety, remain scarce.

Future studies must concentrate on accurately delineating specific molecular processes in dogs, including melatonin's impact on serotoninergic, dopaminergic, and GABAergic circuits, as observed in other species (Miguez et al., 1994; Haduch et al., 2016).

However, given the current limitations in evidence-based pharmacological data, a more immediately strategic and functional perspective is required for patient care. Accordingly, an integrated and multidisciplinary strategy for managing canine behavioral diseases is paramount (Sacchettino et al., 2023). This approach, which necessitates robust collaboration among veterinarians, behavior specialists, nutritionists, neurologists, and other relevant experts, ensures that all influencing factors—from stress and physiology to environment and diet—are simultaneously addressed.

Only through this enhanced multidisciplinary framework, supported by ongoing research and scientific rigor, will the full therapeutic potential of melatonin be elucidated, providing clinicians and caregivers with more credible, evidence-based resources to enhance the emotional well-being and behavioral health of dogs.

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Melatonina nei cani: meccanismi e applicazioni per i problemi comportamentali. Analisi sullo stato dell'arte attuale e prospettive future

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Sintesi

La melatonina è un neuroormone multifattoriale sintetizzato primariamente dalla ghiandola pineale, che offre la possibilità di migliorare la gestione dei problemi comportamentali nei cani domestici. Nonostante la sua diffusa applicazione clinica off-label, i dati scientifici a supporto del suo valore terapeutico sono scarsi e disomogenei. Questo commentary riassume le attuali conoscenze relative agli usi clinici e ai meccanismi d'azione della melatonina nell'affrontare i disturbi comportamentali nel cane. L'evidenza clinica ne supporta il potenziale impatto nella gestione dell'ansia preoperatoria, delle fobie da rumore, dei disturbi correlati alla separazione, dei comportamenti compulsivi e della disfunzione cognitive canina. Il dosaggio consigliato è di 1,5 mg per i cani di piccola taglia e di 3-6 mg per i cani di grande taglia. Il dosaggio può essere somministrato ogni 8-24 ore, a seconda delle circostanze terapeutiche. Il profilo di sicurezza è favorevole, con effetti collaterali trascurabili. Sebbene la melatonina si dimostri promettente come trattamento adiuvante per i problemi comportamentali canini, l'evidenza esistente si basa prevalentemente su case report ed esperienze aneddotiche. Per stabilire linee guida basate sull'evidenza per il dosaggio, l'efficacia a lungo termine e i profili di sicurezza, sono essenziali studi randomizzati controllati approfonditi sui cani.