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NegEnt, Micellar CBD for Canine Anxiety and Stress-Related Disorders: Scientific Rationale and Clinical Case Report

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Abstract

Canine anxiety is a widespread behavioural condition that compromises animal welfare and increases the risk of stress-related behavioural dysregulation. Severe anxiety disrupts cognitive processing, sleep regulation, and social functioning, often requiring pharmacological support to enable behavioural rehabilitation. This case report describes the clinical response of a 4-year-old Italian Volpino dog with chronic anxiety, hyperarousal, and stress-related dysregulation treated with a micellar CBD formulation (NegEnt). The treatment produced rapid improvements in sleep continuity, arousal modulation, social behaviour, and impulse control without cognitive or motor impairment.

A planned temporary discontinuation demonstrated the absence of withdrawal or rebound effects, followed by sustained long-term efficacy over a two-month maintenance period. These observations suggest that micellar CBD may facilitate a “window of cognitive plasticity” that supports behavioural therapy. Controlled studies are required to confirm these preliminary findings.

Introduction

Anxiety and stress-related behavioural disorders in dogs represent a major challenge in veterinary behavioural medicine. Conventional pharmacological (“options—primarily”) benzodiazepines and neuroleptics—show significant limitations in chronic emotional disorders. Benzodiazepines may induce paradoxical excitement, disinhibited aggression, and impaired learning. Neuroleptics suppress behavioural output without modulating underlying emotional dysregulation and may cause dysphoria, motor rigidity, and cognitive dulling [1-3].

Cannabidiol (CBD) has emerged as a promising option for emotional disorders in dogs. Pharmacokinetic studies indicate that CBD is well tolerated and clinical observations in epileptic dogs show reductions in hyperarousal and stress-related behaviours. A large survey of U.S. veterinarians reported that CBD is perceived as helpful for anxiety and emotional dysregulation [4-6].

NegEnt contains Terpenolol, a patented CBD-derived micellar molecule; the proposed mechanisms of action, although supported by the CBD literature, must be specifically confirmed for Terpenolol, and further research is underway. NegEnt was previously notified to the Italian Ministry of Health as a Class I Medical Device, based on a physical and reversible mechanism of action, consistent with the European regulatory definition of medical devices, which requires non-pharmacological, non-immunological, and non-metabolic activity (Directive 93/42/EEC; Regulation (EU) 2017/745) [7].

The theoretical rationale of NegEnt proposes a reversible physical mechanism in which micellized terpenolol may modulate CB1 receptor conformational states through supramolecular and electronic interactions. This model remains hypothetical and requires further dedicated experimental validation. This approach aligns with the scientific framework describing medical devices acting through physical mechanisms, where therapeutic activity emerges from physical interactions (adsorption, modulation of molecular energy states, supramolecular structuring) rather than classical pharmacological

receptor binding [8].

Case Description

Leo, a 4-year-old Italian Volpino, was adopted at two years of age and immediately displayed separation anxiety, object possessiveness, and heightened reactivity. At age three, his symptoms escalated into episodes of affective aggression triggered by accidental painful stimuli. His triggers included strangers approaching, loud noises, sudden movements, and proximity to his toys.

Daily signs of distress included growling, rigid posture, ears pulled back, fixed gaze, repeated yawning, and continuous lip-licking. Lip-licking is recognised as a parasympathetic self-soothing behaviour elicited by negative emotional stimuli. Leo's hypervigilance prevented normal sleep; he woke at minimal noises and vocalised repeatedly, generating significant emotional and logistical strain for caregivers [9].

In severe anxiety, neurobiological stimulation surpasses the system's plasticity threshold, leading to reactive allostasis, where cortical computational systems no longer process environmental stimuli. This state prevents the formation of new positive associations, making behavioural rehabilitation ineffective without pharmacological modulation.

Methods

Leo received five drops of NegEnt Micellar CBD three times daily (total: 15 drops/day). Each drop contains 10 mg of micellized terpenolol, resulting in a daily dose of 150 mg, equivalent to 15 mg/kg/day for a 10-kg dog. The approximate volume per drop is 0.05 mL, for a total daily volume of 0.75 mL.

To evaluate potential withdrawal effects or rebound phenomena, a planned 2-day treatment discontinuation was implemented after the first week of administration. This observational pause was conducted without any experimental manipulation, randomisation, or controlled intervention. Following this brief pause, the treatment was resumed and maintained for a total duration of two months.

Composition of NegEnt Drops

Micellized terpenolol (CBD micellar form): "10 mg per drop" Hydrophilic micelles (non-ionic pharmaceutical-grade surfactants) "Terpenic carrier matrix" Purified water CE-approved preservative for medical devices THC: not present No other pharmacological agents were used during the observation period. Behavioural changes were monitored daily by caregivers.

Results

Sleep Restoration

Within days, Leo began sleeping for extended periods in relaxed postures, with near-complete disappearance of nocturnal vocalisations.

Morning Arousal Regulation

Stress-related yawning and agitation upon waking were replaced by calm behaviour and a relaxed facial expression.

Reduction of Stress-Related Reactivity

During the initial week of treatment, no episodes of intra-domestic aggression or biting occurred. Possessiveness and hyperactivity decreased markedly.

Improved Social Behaviour

During walks, anxious barking toward conspecifics was replaced by curious and positive interest.

Impulse Control and Long-Term Follow-Up

The day after the planned 2-day treatment discontinuation, Leo encountered his primary trigger (accidental paw pressure). He growled as a warning but did not escalate to biting, suggesting increased latency between stimulus and reaction. No signs of withdrawal, distress, or rebound anxiety were observed.

Following resumption of the protocol, the treatment was extended for two months and is still active at the time of writing. Over this period, Leo showed stable behavioural consolidation, sustained improvement in sleep quality, and persistent reduction in hyperarousal, with no adverse effects or tolerance.

Cognitive and Motor Integrity

No sedation, confusion, or motor impairment was observed. Leo remained alert, coordinated, and capable of emotional modulation. This observation aligns with published pharmacokinetic and safety data on CBD in dogs.

Discussion

The clinical improvements observed in this case are consistent with emerging evidence supporting CBD as a promising

anxiolytic agent in dogs. Unlike benzodiazepines—which may produce paradoxical agitation, disinhibited aggression, and impaired learning—CBD exerts multimodal emotional regulation without compromising cognition or motor coordination. Neuroleptics, while capable of suppressing overt behavioural responses, do not address underlying emotional dysregulation and may cause dysphoria or cognitive dulling.

Micellar terpenolol CBD offers additional advantages due to its supramolecular structure. Enhanced hydrosolubility and bypass of first-pass metabolism allow rapid absorption at low doses. More importantly, terpenolol may influence CB1 receptors through reversible physical allosteric interactions affecting conformational energy states. This proposed mechanism is theoretical and consistent with the regulatory framework for physical-mechanism medical devices.

Notably, the 2-day experimental discontinuation highlighted the absence of rebound anxiety or withdrawal symptoms, which are common limitations of conventional psychotropic drugs. Furthermore, the excellent safety and tolerability profile observed over the subsequent two months underscores the potential of micellar terpenolol CBD as a viable long-term therapeutic tool.

Although this is a single case report, the findings suggest that micellar terpenolol CBD may represent a valuable adjunct to behavioural therapy in dogs with severe anxiety and stress-related dysregulation. Controlled studies are needed to evaluate its efficacy, safety, and mechanistic profile.

Conflict of Interest Statement

The Authors declare that they have no conflicts of interest related to the conduct of this research. NegEnt Drops were purchased independently and at the dog owner's personal expense. No funding, sponsorship, or commercial support was received.

Ethical Statement

The study adhered to the ethical principles of the Declaration of Helsinki, adapted for non-invasive veterinary behavioural research. No experimental protocols, laboratory procedures, or induced stimuli were applied. The intervention consisted solely of a commercially available Class I Medical Device (NegEnt Drops), purchased at the owner's expense, administered within routine domestic care. All observations were naturalistic, and informed consent for data collection and publication was obtained from the owner. The report complies with European and Italian guidelines for ethical research involving companion animals.

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