



## Combining cannabis and melatonin treatment with a rehabilitation program improved symptoms in a dog with compulsive disorder: A case report

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### ABSTRACT

Compulsive disorder in dogs (CD) is characterized by constant and time-consuming repetition of behaviors, emancipated from the environment, that definitely compromise their everyday life activities. Here, we documented the efficacy of a novel approach to counteract the negative symptoms of CD in a 5-year-old mongrel dog, previously found to be resistant to the conventional antidepressant. The patient underwent an integrated and interdisciplinary approach, based on the cannabis and melatonin co-administration, together with a tailored 5-month-lasting behavioral program. Observational findings showed a lower rate of compulsive episodes and better management of the dog as well, when compared to the previous paroxetine treatment. We followed him for an additional four months of therapy, and the owners reported easier management of the dog, as reduction of abnormal behaviors to a level acceptable to the owners. Overall, our data so far collected in the CD dog may allow us to test more deeply the feasibility and safety of such an off-label approach, at both preclinical and clinical levels.

### 1. Introduction

Compulsive disorder (CD) in companion animals is characterized by the constant repetition of behaviors, generally known as activities emancipated from the environment, which occur to serve no obvious purposes. In this view, patients feel compelled to perform them in response to an obsession or rules that have to be rigorously enforced (Mills and Luescher, 2006). Dogs who suffer from such a psychosocial disorder can experience circling, barking, fly biting, self-mutilation, and acral lick dermatitis, which eventually turn out into an increased anxiety state (Walsh, 2021). These out-of-context activities are generally due to conflict or frustration, that normally appear when animals cannot cope with stressful situations. Unlike humans, the existence of pathological recurrent thoughts in animals is still a matter of debate, since they are ascribed to the people, and not assessed by an external observer (d'Angelo et al., 2022a). Therapeutic interventions aimed at counteracting compulsive disorder in dog mainly rely on the use of the selective

serotonin reuptake and serotonin transporter inhibitors (SSRIs and SERT, respectively), as well as norepinephrine transporter (NET) inhibitors, or noncompetitive glutamate NMDA receptor blockers (Modarresi et al., 2019; Schneider et al., 2009). However, most of them may bring about side effects overlapping those seen in humans, including gastrointestinal and anxiety disorders, fatigue or drowsiness, besides the fact that several dogs with compulsive disorder show to be resistant to such medications, thereby requiring a variety of alternative treatments. In this respect, alongside medical approach, CD dogs are often trained with positive reinforcement to perform a desirable behavior, to mitigate their compulsive attitudes and improve the animal-human relationship. In humans, recent clinical data suggested that the endocannabinoid system seems to play a key role in the pathophysiology of obsessive compulsive disorder (Szejko et al., 2020). In this respect, phytocannabinoids are some of the many biologically active, chemical components of the hemp plants. In human medicine, CBD is being used as a therapeutic option in a variety of clinical indications, such as nausea, seizures,

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chronic pain, neurological and psychiatric disorders mitigate anxiety disorders (Abuhasira et al., 2018). Despite the paucity of clinical trials, the empirical use of phytocannabinoids in dogs, cats, or horses is gaining a growing interest as nutrients, nutraceuticals, or pharmaceutical ingredients (Cunha et al., 2023; Della Rocca and Di Salvo, 2020). In this respect, cannabis has been proven beneficial in some cases of anxiety, pain, type 2 diabetes, inflammatory conditions, epileptic seizures, or digestive issues. Hempseeds as additional food of livestock might be also regarded as a potential source of crude protein and essential fats, with no significant changes in growth performance. In broilers and hens, cannabis and its derivatives were shown to reduce the rate of tibia deformation, have a protective effect on the development of liver diseases, a better serum lipidic profile, and an antimicrobial activity (Della Rocca and Di Salvo, 2020). Among a large number of phytocannabinoids,  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), is responsible for the psychotropic effect of the plant, and cannabidiol (CBD) seems to mitigate the psychotropic activity of  $\Delta^9$ -THC itself (De Petrocellis et al., 2012). Similarly, the less studied cannabigerol (CBG), acts as a precursor molecule for the most representative phytocannabinoids. It generally exhibits affinity and activity characteristics between  $\Delta^9$ -THC and CBD at the cannabinoid receptors (CB1 and CB2), but appears to be unique in its ability to work as a potent agonist of  $\alpha$ -2 adrenoceptors and 5-hydroxytryptamine (5-HT<sub>1A</sub>) antagonist (Cascio et al., 2010; Nachnani et al., 2021). Together with CBD, cannabigerol is able to influence, among different synaptic pathways, the transcriptional changes of genes involved in the GABAergic neurotransmission in the brain. In this respect, through the modulation of the PKC-mediated phosphorylation of the GABA<sub>A</sub> receptor, CBG can potentiate the inhibitory neurotransmission in the adult central nervous system, severely affected in some of the neuropsychiatric disorders, including anxiety, depression, post-traumatic stress disorder and obsessive-compulsive behaviors (Gugliandolo et al., 2020; Noh et al., 2017; Song and Messing, 2005). Moreover, alongside its ability to regulate the circadian rhythm in mammals, melatonin supplementation can also be used to counteract dog behavior disorders, such as fear, anxiety and phobia (Ruiz-Cano et al., 2022). In the present case report, we documented an integrated and interdisciplinary approach in a 5-year-old mongrel CD dog, based on the cannabinoids and melatonin, together with a tailored behavioral rehabilitation.

## 2. Case presentation

We reported the case of a 5-year-old neutered male, mixed terrier breed, 7.8 kg of weight, who underwent behavioral examination, since he showed compulsive behaviors, like tail chasing and biting right hind limb (Table 1). The owners stated that their dog would go out twice a day (40 min in the morning and 15 min in the evening). In addition, he walked on a long leash in a natural park, for a couple of hours (twice a week, on average). The games he normally carried out by the owner consisted of throwing a ball (predatory play, in particular the dog loved chasing balls), chasing lizards in the garden and pull/spring (tug play) as well. He usually slept on the bed together with the owner, although the sleep was light and easy to interrupt. The owners lived steadily in a townhouse, and just occasionally they spent some days in the country house, where the patient used to share the environment with a 14-year-old mongrel spayed female. The first symptoms showed up in the current family the day after the adoption, when the male family member asked for an interaction. Both tail chasing and biting right hind leg occurred more than ten times a day (duration and intensity changed from a few seconds to two minutes). Of note, trying to stop him made the compulsive activities even worse. Symptoms of CD were not particularly associated to specific contexts, since they were triggered most easily by partner's cuddling or interaction with the other family dog. Thus, the family decided to contact the first veterinary behaviorist, who prescribed 5-month-lasting paroxetine treatment (5 mg SID, p.o.) to the patient, associated to a tailored rehabilitation program, mainly based on

olfactory activities and exercise, to enhance self-regulation attitude. However, the therapeutic unsuccessful of this approach led the owners to seek a further opinion, and the case was brought to our attention. To diagnose compulsive condition, we ruled out all factors that do not properly recapitulate such a behavioral disorder, including parasites, skin, bone and joint issues, food intolerance or neurological conditions (Hunthausen et al., 2013). Accordingly, alongside behavioral and physical examinations, neurological assessment by means of computerized tomography (CT) and magnetic resonance imaging (MRI), as well as complete blood count, biochemistry and thyroid hormone parameters were performed, which no significant alterations arose from (see Supplementary materials). Indeed, we failed to find any clinical or neurological alterations during medical examinations. After the canine compulsive disorder diagnosis was drawn, the veterinary behaviorist prescribed a different 5-month pharmacological treatment, based on galenic oil cannabinoid preparation (Bedica 0.1 mg/kg BID + CBD 0.13 mg/kg BID + CBG 0.1 mg/kg BID), co-administered with conjugated melatonin (5 mg BID). Our goal was to minimize anxiety states, restlessness and decrease compulsions as well of the patient, thus reducing suspected pain and enhancing collaboration, exploration and problem-solving activities. Meanwhile, the owners were given tips to adequately manage the patient, mainly relied on (a) the creation of a consistent and predictable environment and daily routine, engaging him in desirable activities (i.e., resting, and playing with objects); (b) use of rewards, to encourage his desirable behaviors, and discourage undesirable ones, providing sufficient enrichment and outlets to meet other dogs; (d) paying attention to the identification and removal (or reduction) of conflict-related stressors (i.e. excessive manipulation and brush use); (e) the reinforcement of desirable alternative behaviors to the compulsive attitude, including resting on a mat or chew on an appropriate chew toy (d'Angelo et al., 2022a). The behavioral therapy session was on a weekly basis for the first three months, becoming bimonthly for the last two months. It was settled through reward methods, both at home and in the outdoor environment, by means of systemic and relational approaches. Starting from olfactory research with the aim to lower the state of emotional activation (d'Angelo et al., 2022b), the dog was then trained to perform tasks with increasing difficulty. In addition, the training focused on problem-solving activities both in home and outdoor contexts. Finally, we implemented Clicker's activities, to teach the patient new attitudes through positive reinforcement (d'Angelo et al., 2022c). Behavioral examinations were performed as reported in the Table 2.

## 3. Discussion and conclusion

Here, we documented the importance of novel approach to treat compulsive disorder in a mongrel dog, based on the cannabis with supplementation of melatonin and a tailored behavioral rehabilitation program. In particular, the patient was resistant to the earlier five-month paroxetine treatment and experienced significant negative effects, such as dysphoria, hyperexcitability, more than one hour of tail chasing activity, even following a single administration of the antidepressant trazodone (10 mg/kg), used to reduce anxiety during medical examinations and diagnostic imaging (Erickson et al., 2021). This evidence is in line with a previous work, displaying that about one third of patients do not benefit from or tolerate such treatments (Naguy and Alamiri, 2018). Given the established interplay between serotonin with endocannabinoid and melatonergic systems, in modulating compulsive-like behaviors and anxiety (De Gregorio et al., 2020; Madsen et al., 2017), we sought to investigate whether such drugs, implemented with a designed rehabilitation program, could have a significant impact upon canine compulsive disorder, in a dog resistant to the conventional therapeutic approach. Our aim was basically to counteract CD symptoms of the patient through the entourage effect of the two different compounds in the hemp plant (Della Rocca and Di Salvo, 2020). The CD dog of the present work experienced substantial and growing improvements

following the five-month-scheduled treatments. The patient was found in the street, as stray dog by the former family and kept until the age of 3 years and 5 months. During that time, he was severely traumatized, constantly abused, thus bringing about a considerable state of generalized anxiety, especially when he asked for interaction with humans and to be handled by them. Therefore, we decided to treat pain-even if suspected-with cannabis, given that pain and compulsive disorders relate to each other. Our therapeutic choice is in line with research of Mills and his colleagues (2020), who reported that is crucial to have an open mind about the potential impact of the pain upon patients in general, whatever the trigger might be (Mills et al., 2020). Thus, based on the notion that anxiety may be associated to cognitive processing impairment, decreased decision-making abilities and behavioral performance alteration in both humans and animals (de Visser et al., 2011), we decided to add melatonin to the cannabinoids treatment, in order to potentiate the behavioral rehabilitation efficacy and synergize the anti-compulsive properties of cannabinoids (Papp et al., 2006; Yu and Rupasinghe, 2021). In this respect, several findings showed that melatonin can modulate mood-related behaviors, as well as sleep, thus improving memory consolidation abilities in both humans and dogs (Haduch et al., 2016; Mogheiseh et al., 2019), with no relevant side effects. In this respect, our last follow up showed that the dog was much calmer and more easily manageable. In humans, previous preclinical and clinical data about the obsessive CD patients highlighted the importance of combining a cognitive behavioral therapy with THC alone or associated to CBD administration, to potentiate the benefits and antagonize the negative side effects as well. Accordingly, data obtained from a small open uncontrolled trial, suggested that using the THC analogue, nabilone, together with the exposure-based psychotherapy is more effective than each treatment alone (Kayser et al., 2020). Overall, data collected from the present CD case report highlighted the importance to further investigate the potential role of combining CBD and melatonin, with a tailored rehabilitation program, in the improvement of CD symptoms in companion animals. For the first time we pointed out the beneficial impact of five-month-integrated approach in a 5-year-old mongrel dog, highlighting the synergic effect of endocannabinoid and melatonin systems, associated with a tailored behavioral program, to improve CD-derived behavioral alterations. We followed the dog's family up to four months from the end of the therapy, and the owners reported easier management of the dog, as reduction of abnormal behaviors to a level acceptable to the owners. Further studies are needed to better address the potential effects arising from combining long-term cannabinoid and melatonin treatments, or tolerance and safety. We recognize that case reports do not provide definitive evidence, but they are useful for highlighting observations of importance to the profession.

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## Author contributions

Dd'A, LM, LS, FN, and CB contributed to the conception and design of the study and wrote sections. Dd'A, LS, LM, LA, and CG wrote the first draft of the manuscript. All authors reviewed and approved the final submitted manuscript.

## Ethics approval

Ethical review and approval were not required for the animal study because this was a retrospective case report.

## Consent for publication

Written informed consent was obtained from the owner for the publication.

## Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rvsc.2023.05.007>.

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