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Case Report

The use of cannabidiol as a novel treatment for oral stereotypic behaviour (crib-biting) in a horse

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ABSTRACT

Behaviour is the response of living things to their environment and external stimulation, and is one of the parameters to be observed when assessing animal welfare. Any alteration from the conditions found in nature can lead to the occurrence of some specific behaviours, called stereotypies which are characterised as repetitive, consistent patterns of behaviour usually defined as having no apparent ultimate or proximal functions. It has been reported that once stabled or subjected to stressful activities, horses have more susceptibility of developing behavioural disturbances; therefore, behavioural disorders in horses are a strong indicator of poor welfare. *Cannabis spp*.-derived molecules have been studied under different medical conditions; the therapeutic potentials of phytocannabinoids are related to the effects of delta-9-tetrahydrocannabinol, cannabidiol (CBD), and other compounds. Cannabidiol has many activities within the central nervous system, such as anxiolytic, antidepressant, antipsychotic, anticonvulsant, and anti-inflammatory activities. Some studies have recently shown the potential and successful therapeutic use of phytocannabinoids in veterinary medicine. This clinical case report described a 22-year-old mare suffering from chronic crib-biting and wind-sucking, and the successful outcome of four weeks-therapy with CBD. This is the first report of the successful therapeutic use of phytocannabinoids in equine behavioural disorders.

1. Introduction

Behaviour is the response of living things to their environment and external stimulation, and is one of the parameters to be observed when assessing animal welfare. Any alteration from the conditions found in nature can lead to the occurrence of some specific behaviours, called stereotypies (ezfouli et al., 2013; Mason, 2006) which are characterised as repetitive, relatively consistent patterns of behaviour, usually defined as having no apparent ultimate or proximal functions. Stereotypies also exist in humans; they can be either psychologically or environmentally induced, and are often associated with developmental disorders, such as autism, neurological disorders, obsessive-compulsive disorder (OCD), Tourette's syndrome, and severe psychiatric disturbances (McBride and Hemmings, 2005).

It has been reported that once stabled or subjected to stressful activities, horses are more susceptible to development of behavioural disturbances, therefore, behavioural disorders in horses are a strong indicator of poor welfare (Lesimple, 2020). The most common behavioural disorders in horses are crib-biting and wind-sucking, weaving and box walking; in Europe and Canada, the prevalence of crib-biting and wind-sucking is 2.4% and 8.4%, respectively (Wickens and Heleski, 2010). Horse owners and veterinarians are often concerned about the stereotypic activities resulting in a reduction in performance, decreased monetary value of the animal, and the development of secondary pathologies, such as gastric ulcers and colic syndrome (Buitrago et al., 2022).

The neurobiological bases of sensitisation may represent a common substrate for different mental and biological disturbances across species (e.g., mouse stereotypies, schizophrenia, and addiction in humans) (Kelly et al., 2021). Primary studies carried out in the 20th century have already shown the role of the basal ganglia in the development of abnormal behaviours (Karler et al., 1997; Smelik and Ernst, 1966). An in-depth investigation by McBride and Hemmings (2009) showed receptor-based alterations in the basal ganglia in crib-biting horses.

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Behavioural frustration and the expression of equine stereotypy are linked with dopamine receptors, i.e., the DRD4 (dopamine D4 receptor subtype) gene (McBride and Hemmings, 2005; Ninomiya et al., 2013).

The expression of cannabinoid receptors types 1 (CBR1) and type 2 (CBR2) and the cannabinoid-related receptors transient receptor potential vanilloid type 1 (TRPV1) and G protein-receptor 55 (GPR55) has been shown in rat and human basal ganglia (Chayasirisobhon, 2019). Chiocchetti et al. (2021a, 2021b) successfully demonstrated the expression of cannabinoid and cannabinoid-related receptors in the dorsal root ganglia and enteric nervous system of horses. Receptors and their ligands are compounds of the endocannabinoid system (ECS) which has evolutionarily been conserved and has been characterised within all vertebrates and many non-vertebrate species (Elphick, 2012). It is currently known that cannabinoid and cannabinoid-related receptors are present in the central and peripheral nervous systems and in peripheral tissues where their balanced expression regulates tissue homoeostasis (Joshi and Onaivi, 2019).

Cannabis spp.-derived molecules (phytocannabinoids) have been studied under different medical conditions; the therapeutic potentials of phytocannabinoids are related to the effects of delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and other *Cannabis* spp. compounds, such as cannabigerol, cannabichromen, etc. Cannabidiol has shown to have benefits in a variety of disorders, such as: autism spectrum disorder, anxiety, psychosis, neuropathic pain, cancer pain, human immunodeficiency virus, migraine, multiple sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, hypoxic-ischemic injury, and epilepsy (Morris et al., 2021; Van der Stelt and Di Marzo, 2003). Some studies have recently shown the potential and successful therapeutic use of phytocannabinoids in veterinary medicine, using CBD as the molecule of choice to treat mechanical allodynia, lower horses reactivity, and improve joint pain (Ellis and Contino, 2021; Sánchez-Aparicio et al., 2020).

Traditional therapies such as cervical collars, environmental enhancement, dietary modification, chemical anxiolytics (e.g. acepromazine) and surgery may not be successful in a significant percentage of cases, therefore new therapies are needed (Houpt and McDonnell, 1993; Nagy and Bodó, 2009).

This case report described the clinical findings of a mare diagnosed

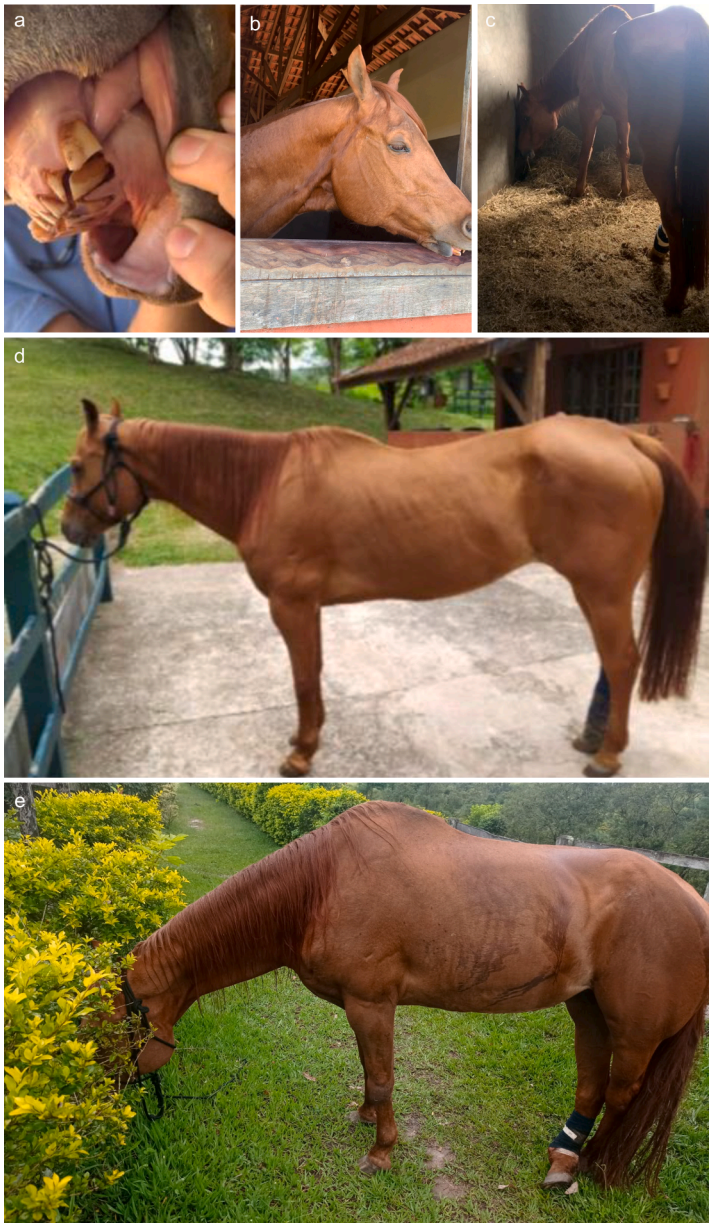

Fig. 1. a) Uneven wear and erosion of the upper and lower incisor teeth due to the habit of crib-biting. b) Mare illustrating the behavioural disorder; she used to stand by the back of the box, supporting her head on the door of the box, crib-biting it, with flexion of the neck and posterior wind sucking. c-e) Body Score evolution of patient pre, during and post CBD therapy; clinical visit 1 week prior to treatment, body score 2 where one can see and feel the bone structures, although there is a thin muscle layer (c); Three weeks after the beginning of CBD oral administration, with visible muscle gain and fat deposit (d); 45 days after the beginning of the treatment, body score grade 4 with notable improvement in weight and coat quality (e).

with chronic crib-biting and wind-sucking, and the successful management and treatment with isolated CBD. To the Authors' knowledge, this is the first report of the successful therapeutic use of phytocannabinoids in equine behavioural disorders.

2. Case report

2.1. Clinical history

A 22-year-old Quarter horse was referred with a history of chronic crib-biting and wind-sucking. According to the owner report, the mare had presented this behaviour for the past 15 years; previous clinical approaches, such as a cervical collar, environmental enhancement, diet change, and chemical tranquilizers (acepromazine 0,1 mg/kg T.I.D) were not successful. At anamnesis, it was revealed that the mare used to be a sport horse with an intensive training routine. Once her sports career was over, the owners retired her and kept her partially in the paddock and partially in the box (average 3 h/day at the paddock). The sport career was over at the age of 10 years old, while the behaviour disorder started at the age of 7 years old, getting progressively worse over the years.

2.2. Clinical findings and diagnostic assessment

The mare showed uneven wear of the upper and lower incisor teeth (Fig. 1a, b), a depressive posture and severe muscular hypotrophy (grade 2/5 body condition score, Fig. 1c, AAEP BSC). Additionally, the hair coat looked dull, brittle, and lacklustre. Values of heart rate and respiratory rate were, respectively, 40 bpm and 20rmm, without abnormalities regarding rhythm and pattern; blood screen showed values within the normal equine parameters (WBC: 8,6 $\times$ 10^3/UL; HCT: 38,6%; FA: 146.7 U/L; ALT: 8.21 U/L; CREAT: 1.1 mg/dL; Urea: 31,17 mg/dL). To assess the behaviour, the patient was observed during 7 days before therapy, inside the box, and in the paddock. When in the box, the mare stood by the back of the box, supporting her head on the door of the box, crib-biting it, with flexion of the neck and posterior wind sucking (Fig. 1b). In addition, the mare showed a lack of interest in the food available. When released into the paddock, within few minutes, the patient used to

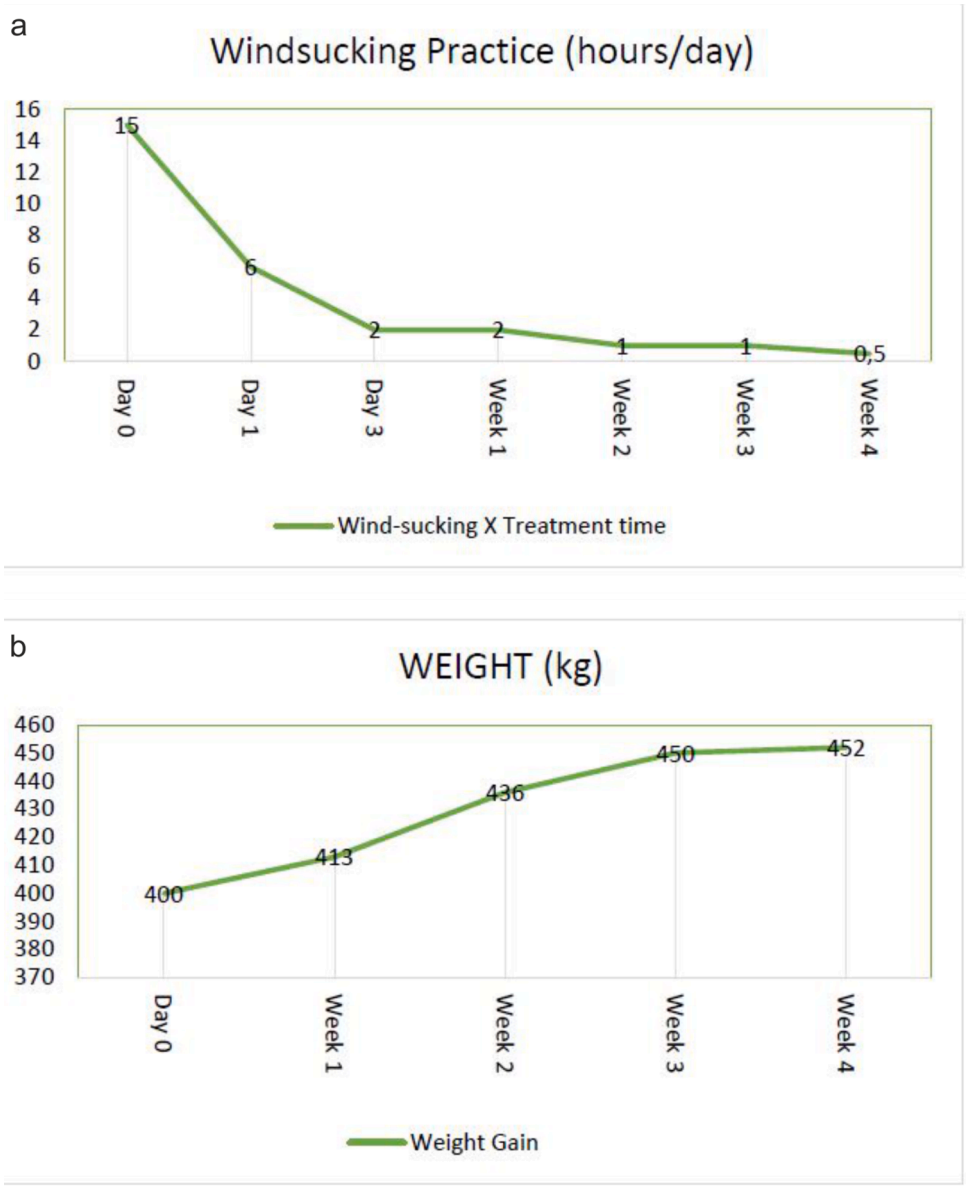

Fig. 2. a) Evolution of the decreased hours spent with the stereotypy pre, during and post administration of CBD. The value of Day 0 is the average of hours spent daily of stereotypy of the 7 days before therapy. b) Line of weight gain during the therapy with cannabidiol.

search for a fence to crib-bit/wind-suck.

The diagnosis was confirmed by clinical examination, analysis of the patient's background and history, and visual confirmation of practicing this oral stereotypy. The horse was placed in therapy with commercially available isolated CBD 200 mg/ml at a dose of 0.5 mg/kg/daily q12h *per os*. The dose and frequency were determinate based on previous case report and veterinary pharmacological studies (Ellis and Contino 2021). During the therapy, there were no changes in food quality/quantity or the daily routine of the mare.

2.3. Treatment and follow-up

To assess the results of the therapy, the mare was followed up under constant observation, for 7 days before the therapy and then during the treatment by the veterinary team divided into shifts, which provided the number of hours spent with the stereotypy (Fig. 2a) pre- and during administration of CBD. The mare was also weighted weekly, with the first weight measured at the start of the 7 days observation period prior to therapy.

One hour after the first administration, the patient showed enhanced appetite and an increase in food-search behaviour. The mare was followed intensively and monitored for colic, lethargy, inappetence, hyperthermia, diarrhoea, sialorrhea, cardiorespiratory disturbances, and ataxia, none were shown. Between the first and second week of the treatment, a significant decrease in the hours spent crib-biting and wind-sucking was observed with a gradual and constant enhancement of appetite. During therapy, no adverse events were reported (colic, lethargy, inappetence, hyperthermia, diarrhoea, sialorrhea, cardiorespiratory disturbances, and ataxia).

At the end of thirty days, visible improvement in the BCS (from grade $^{2}/_{5}$ up to $^{4}/_{5}$, AEEP BCS), and coat quality (presented shiny and silky look) was noted (Fig. 1d, e), and the mare rarely presented the practice of the behavioural disorder in the paddock. More in detail, the patient had gone from 15 hrs/day of stereotypy to less than 1 h/day (Fig. 2a) and had gained 52 kg (from 400 kg to 452 kg) (Fig. 2b). In addition, the groomer and owners reported positive changes in the mare's behaviour, evolving from a down and depressive posture to a bright and alert attitude. After the end of the treatment, the team kept in phone contact with the owners twice a week for three weeks; they reported that the mare no longer showed the same levels of stereotypic behaviour as before the therapy (it was reduced to less than 1 h/day).

Unfortunately, at last contact with the owners, the team received the information that the patient had been euthanized due to a fracture involving the metacarpophalangeal joint, at the 4th week post-treatment. The fracture was traumatic in nature and was unlikely to be related to the previous treatment course of CBD.

3. Discussion

This clinical case described a 22-year-old mare suffering from chronic crib-biting and wind-sucking, the two most common oral stereotypic behaviours shown by horses when subjected to stressful activities or environmental deprivation, and the successful reduction of stereotypic behaviour with administration of CBD. Once horses under natural conditions, spend the major part of their time foraging, environmental restriction and captivity play a major role in the development of stereotypies (Koolhaas et al., 2010; Mason, 2006). The story of the patient as a retired sports horse with social and space restrictions, matched with the factors associated with the development of behavioural disorders in horses. The clinical finding of tooth erosion was consistent with that of the study of Cooper and McGreevy (2007); muscular hypotrophy may be a consequence of malabsorption and decreased food intake, which would be compatible with the evidence of Nicol et al. (2002).

Cannabidiol was chosen as the treatment of choice due to its efficacy in behavioural disorders in other mammalian species, including humans (Bonaccorso et al., 2019; Elsaid et al., 2019; García-Gutiérrez et al., 2020). Williams et al. (2022) found that the oral administration of a pure crystalline cannabidiol product at 0.35 mg/kg or 2.0 mg/kg once daily was well tolerated by horses. Ellis and Contino (2021) reported the successful treatment of a horse with allodynia with a dose of 0.5 mg/kg twice a day of CBD.

In the current report, the Authors' hypothesis used two main pathways to explain the success of the CBD treatment: 1) the direct activity of CBD on the receptors within the basal ganglia, specifically the serotonergic and dopaminergic receptors, and 2) CBD anxiolytic effects, by binding with serotoninergic receptors and CB1R, attenuating acute autonomic response and diminishing fear.

1) Cannabidiol is the major non-psychotropic component of *Cannabis sativa* and has attracted interest due to its therapeutic potential in several diseases which have been investigated in animal models (Fernandez-Ruiz et al., 2011). It has many activities within the central nervous system (CNS), such as anxiolytic, antidepressant, antipsychotic, anticonvulsant, antinausea, antioxidant, anti-inflammatory, analgesic, and antineoplastic activity. It also exerts protective action in animal models of epilepsy, anxiety, psychosis, and diseases of the basal ganglia, such as Parkinson's and Huntington's diseases (Ligresti et al., 2016).

Horses which present stereotypies have increased activity within the mesoaccumbens dopamine pathway, and the development of environmentally-induced stereotypy may be associated with changes in motivational systems within the animal. Therapies using agonists/antagonists which will either regulate its activity and/or its expression may achieve therapeutic results in those patients suffering from neurochemical disorders at the basal ganglia level. It is known that, in humans and rats, activating presynaptic cannabinoid CB1 receptor can reduce the glutamate release in the dorsal and ventral striatum (nucleus accumbens) and alter synaptic plasticity; it can modulate neurotransmission in the basal ganglia and the mesolimbic reward system (Salamone et al., 1997).

McBride and Hemmings (2005) supported an existing body of knowledge which indicated that stereotypies were mediated by means of a dopaminergic striatal pathway, and that oral stereotypies, in particular, were mediated within the ventral striatum. Therefore, events known to cause high activation (interaction with ligands, e.g., phytocannabinoids) of the mesoaccumbens pathway should be associated with both the development of new stereotypies and the elicitation of a stereotypic response in the stereotypic-established animal. Franklin et al. (2021) identified the mechanisms associated with the up-regulation of dopamine receptor 2 (D2 receptor) expression in a neuronal cell model (Embryonic Rat Hypothalamic, CLU213 cells) after repeated exposure to cannabinoid agonists. Cannabidiol has a slight affinity for the 5-HT1A receptor, and some of its effects are at least in part inhibited by 5-HT1A receptor antagonists, moreover, there is evidence of its modulation of 1-adrenergic and dopamine D2 receptors and its long-term increase in GABA-A receptor binding or the allosteric modulation of opioid receptors (Ligresti et al., 2016). It is also worth noting that the mesoaccumbens dopamine pathway is considered to be the primary neural centre for the initiation and control of the appetitive phase of goal-directed behaviours (Salamone et al., 1997), which may justify the significant increase in the horse's appetite.

2) The anxiolytic effects of CBD are well known (Ligresti et al., 2016; Mason, 2006); CBD, by reducing anxiety, reduces the levels of stress, a key factor involved in stereotypies of horses (Dezfouli et al., 2013). Draeger et al. (2021) showed a decrease in the horse's reactivity after supplementation with CBB. By reducing anxiety, CBD reduces the levels of stress, a key factor involved in stereotypies of horses. The Authors' assumption was that lowering the reactivity of the horse could also manipulate how the horse responded to environmental challenges, therefore decreasing stress, and improving animal behaviour and welfare. It is important to point out that the study carried out by Draeger et al. (2021) evaluated the horses after 6 months of supplementation, and that no horse with a stereotypy was assessed. In the current study,

the mare was treated with cannabinoid therapy for only 1 month, with significant improvement observed within two weeks of treatment initiation.

It should be noted that currently, no cannabis-derived veterinary medicinal products are authorised in the EU or North America. Off-label use of human medicinal products might be allowed to be used in animals in certain EU countries or in the US, only when using EU or USFDA-approved products, respectively. It is the responsibility of the veterinarian to understand their legal obligations (De Briyne et al., 2021).

4. Conclusion

This case highlighted the potential use of CBD in cases in which traditional therapies for behavioural disturbances had no success. It was the desire of the Authors that the description of this case would help to stimulate additional research into the use of phyto- and endo-cannabinoids, not only in equines but also in other veterinary species. The dosage used in the horse in this report was approximately 0.5 mg/kg/day and was shown to be effective in successfully managing and treating the behavioural disorder, yet little information is available on the best dosing regimen of horses. Significant research and clinical trials are needed to establish the bioavailability, dosage, and drug interactions in equine cases, and the potential use for specific pathologies.

The results after 30 days of therapy were positive and no regression in behaviour was seen by the owners after the treatment ended. To the best of the Authors' knowledge, this is the first published case describing the successful treatment and management of a chronic crib-biting, wind-sucking horse with the oral administration of CBD, enhancing welfare and life quality.

Limitations

The main limitations of the present case report were the number of horses, the absence of a post-therapy follow-up longer than 30 days due to euthanasia, and the lack of video camera use instead of personal.

Founding

This research received a grant from NBF Lanes, Milano.

Ethical statement

The authors declare that the owners of the equine were previously requested to authorizy the case publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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