

Treatibles Takakura CBD Meeting

2022.5.27

Chie MOGI, D.V.M., Ph. D.

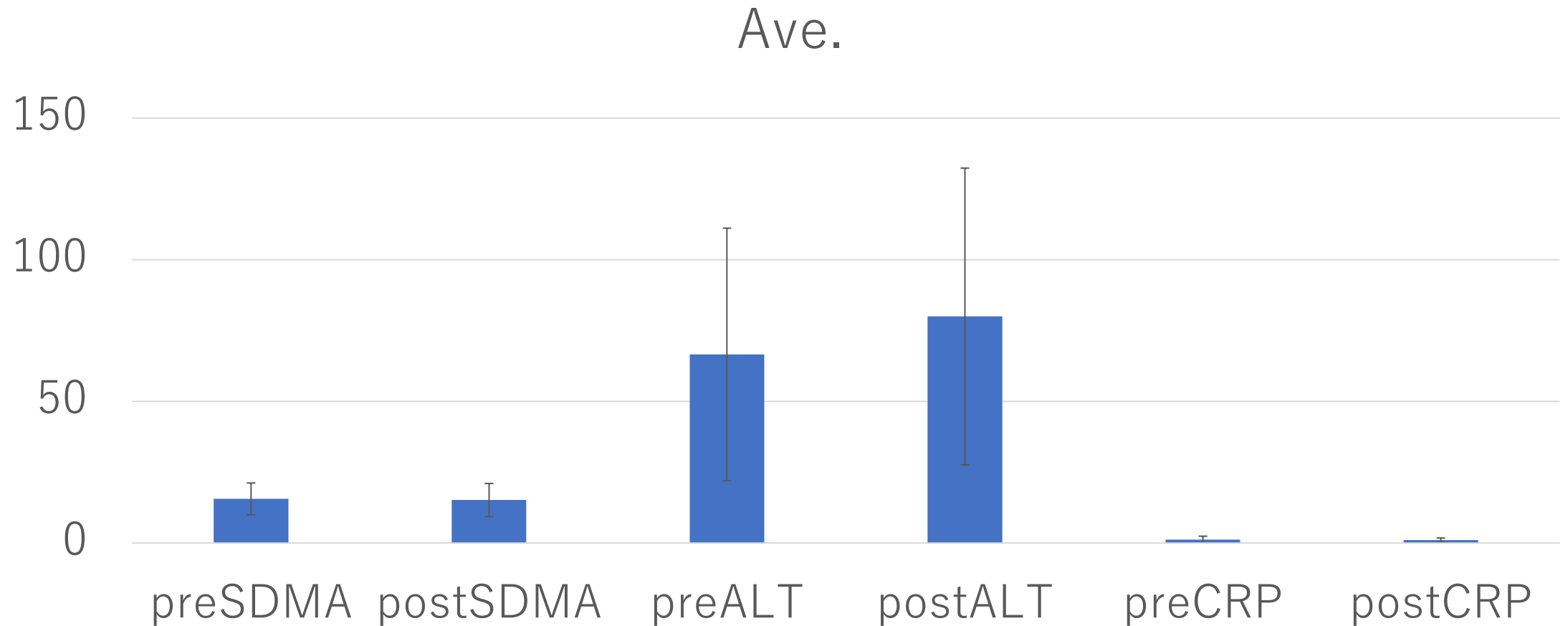
Clinical parameters after CBD use

- Five dogs Age average 11.4 ± 3.8 years (5-15 years)
- CBD products [treatibles] Organic hemp oil 250mg
- Blood biochemical tests
- Inflammatory response: CRP
- Haemostasis: SDMA
- Blood oxidation indices: d-ROMs and measurement with BAP reagents (<http://www.wismerll.co.jp/reagent/index.html>)



reference value	checklist	Fos Terrier 15y 1.0mg/kg		Chihuahua 13y 0.132mg/kg		Old English Sheep dog 12y 0.36mg/kg		Shiba Inu 5y 0.4mg/kg		Airedale terrier 12y 1.0mg/kg	
		11月7日	11月21日	11月11日	12月2日	11月18日	12月22日	11月11日	12月9日	11月6日	12月4日
70.0-143.0	GLU	118	122	79	75	115	106	109	109	90	96
0.0-14.0	SDMA	22	23	21	20	14	12	10	10	11	11
0.5-1.8	CREA	1.1	1.2	0.7	0.8	0.84	0.98	1.4	1.2	0.93	0.88
7.0-27.0	BUN	43	44	26	29	22.1	22	21	18	20.7	25.1
7-37	BUN/CREA	39	35	35	37	26.3	22.4	15	15	22.3	28.5
2.5-6.8	PHOS	5.3	5.1	4.7	4.8	3.6	4.1	3.4	3.2		
7.9-12.0	CA	9.5	9.1	9.7	9.7	9.8	10.9	10.3	10.5		
5.2-8.2	TP	6.4	6.3	6.6	6.4	6.4	7.3	7	6.9	6.8	6.7
2.2-3.9	ALB	2.4	2.3	2.9	2.8	2.7	3.1	3.5	3.4	3.1	2.9
2.5-4.5	GLOB	4	3.9	3.7	3.6			3.5	3.5		
	ALB/GLOB	0.6	0.6	0.8	0.8			1	1		
10.0-125.0	ALT	139	159	79	81	42	95	45	35	28	30
23.0-212.0	ALKP	136	138	137	107	158	228	37	37	229	149
0.0-11.0	GGT	17	20	6	4	1	7	0	2		
0.0-0.9	TBIL	0.3	0.2	0.2	0.2			0.3	0.2		
110.0-320.0	CHOL	255	266	245	210			287	262	178	215
500.0-1500.0	AMYL	871	727	929	758	829	851	587	590		
200.0-1800.0	LIPA	1303	1229	703	888	175	97	520	610		
0.0-1.0	CRP	3.1	1.7	0.3	0.3	0.8	0.9	0.3	0.3	1.8	2

Indicators of renal, hepatic and immune function



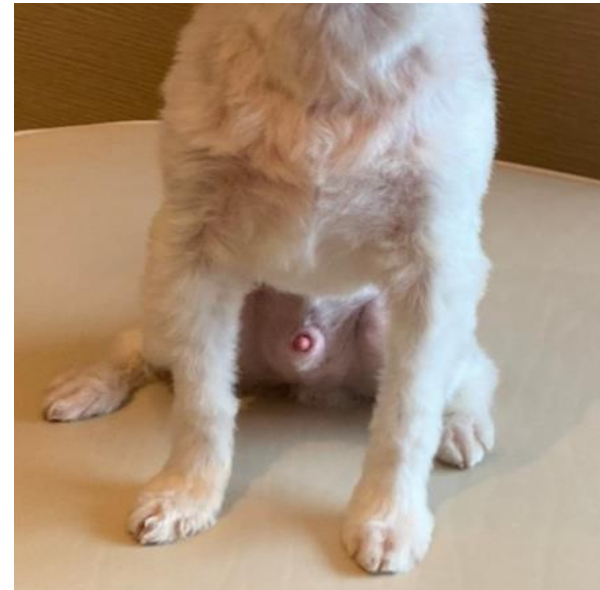
No significant changes were observed.

Maltese with constant licking disorder (continuous licking).

- Neutered male, 4 years 0 months old, 2.5 kg Continuous licking of penis, abdomen and hind legs when eating, dysphoria (picking up food while walking), defensive aggressive behaviour
- Sweet Potato Soft Chewables - 3 mg CBD for Dogs (Treatibles / AD Remedies, Inc., TN, U.S.A), three times a day (3.2mg/kg/day), From day 91, one piece was taken at 8.00 am and 5.00 pm respectively (2.1 mg/kg/day).

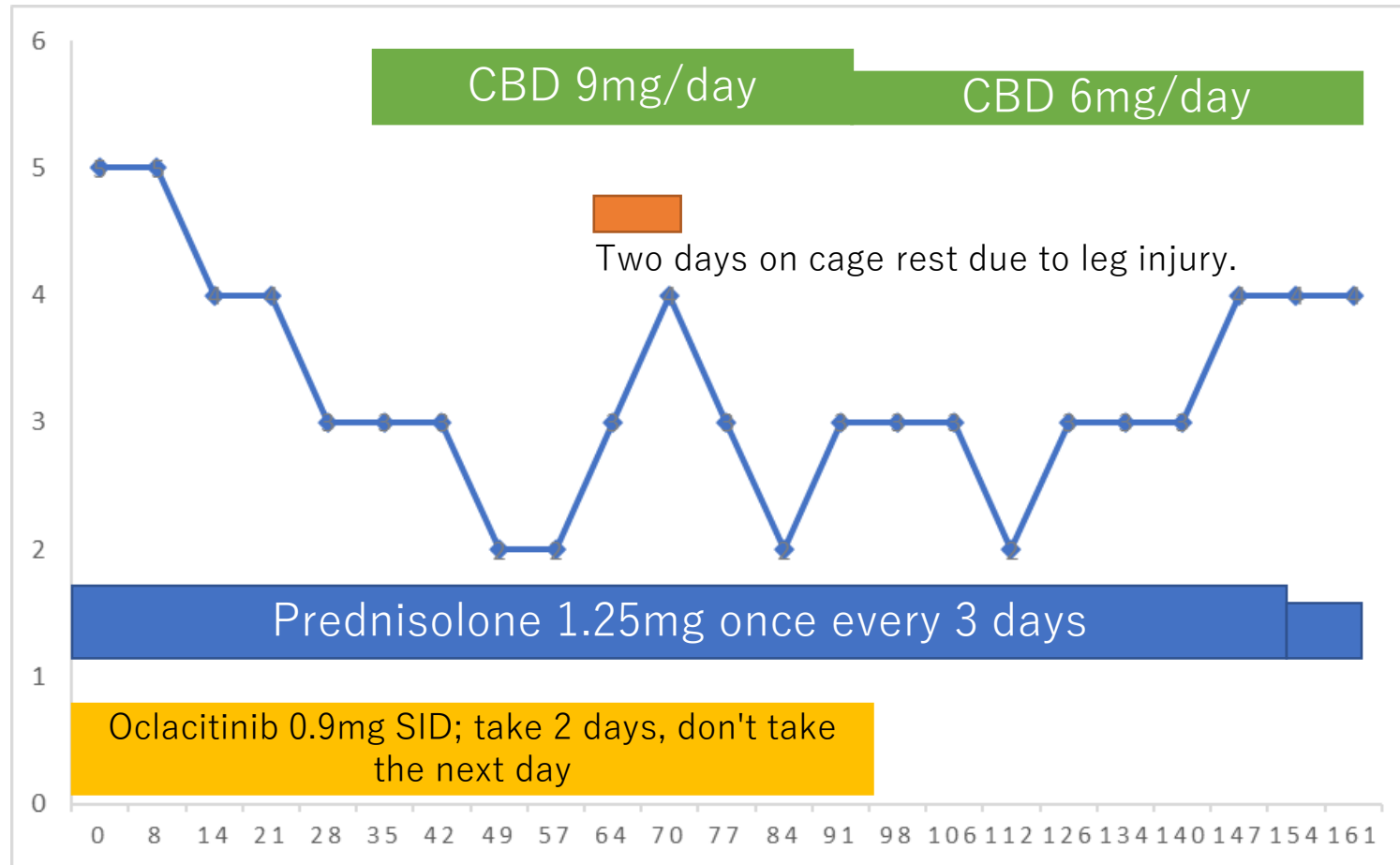


Day42

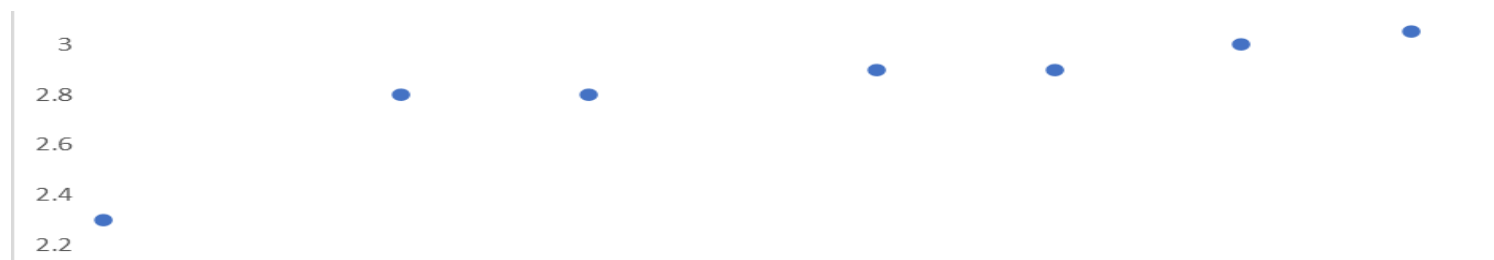


Day147

PVAS



BW(kg)



 *Journal of Alternative Complementary & Integrative Medicine*

 *Category: Medicine*

 *Type: Case Report*

Use of Prednisolone, CBD and Behavior Modification as a Treatment for Atopic Dermatitis in a Canine: A Case Report

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Case Report

Avulsion fracture of patella

Mix, 11-year-old neutered male.

Knee injury during a walk, almost immobile.

Diagnosed as avulsion fracture on x-ray

Undergoing conservative treatment



Treatibles. Organic hemp cream. Two hours after application to the knee, the patient was able to climb stairs and urinate independently.

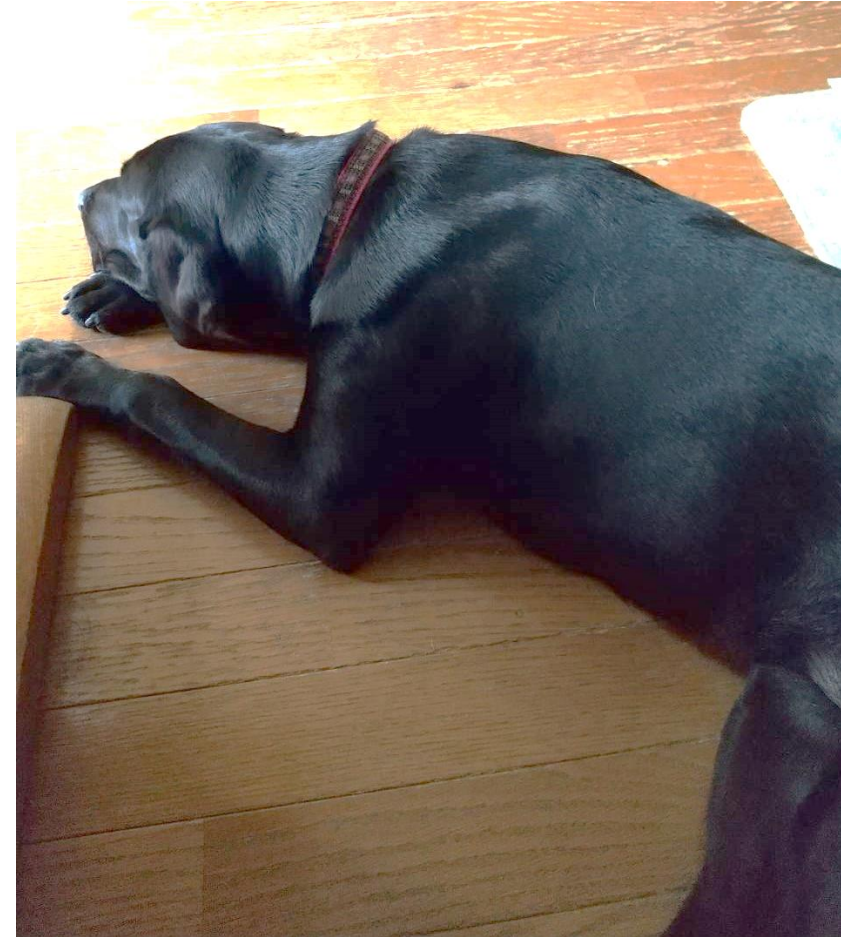
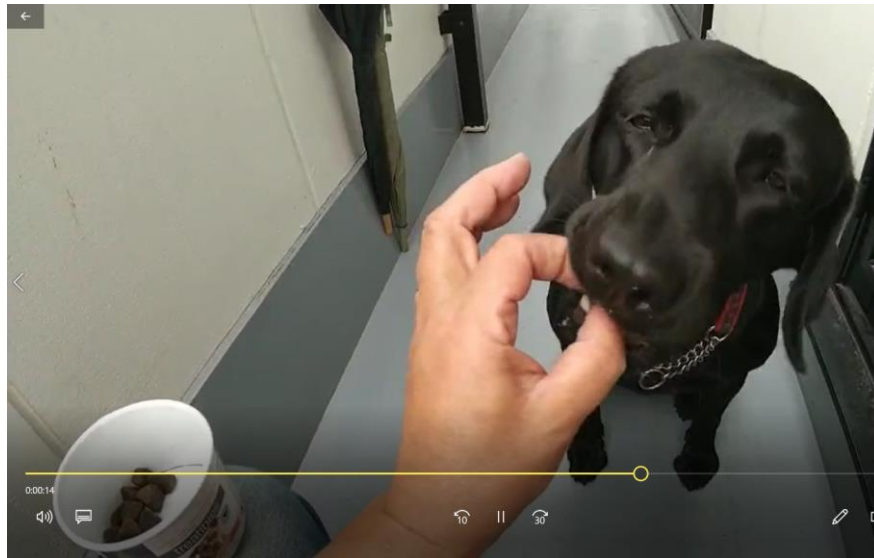
Case Report

Separation anxiety

Labrador, 1 year old

Shelter dog

Strong attachment to owner and excessive barking due to demands



20 minutes after eating a Treatibles Soft Chew Calm (sweet potato), she lay down and started sleeping.

Case studies of CBD interventions in high-senior years.

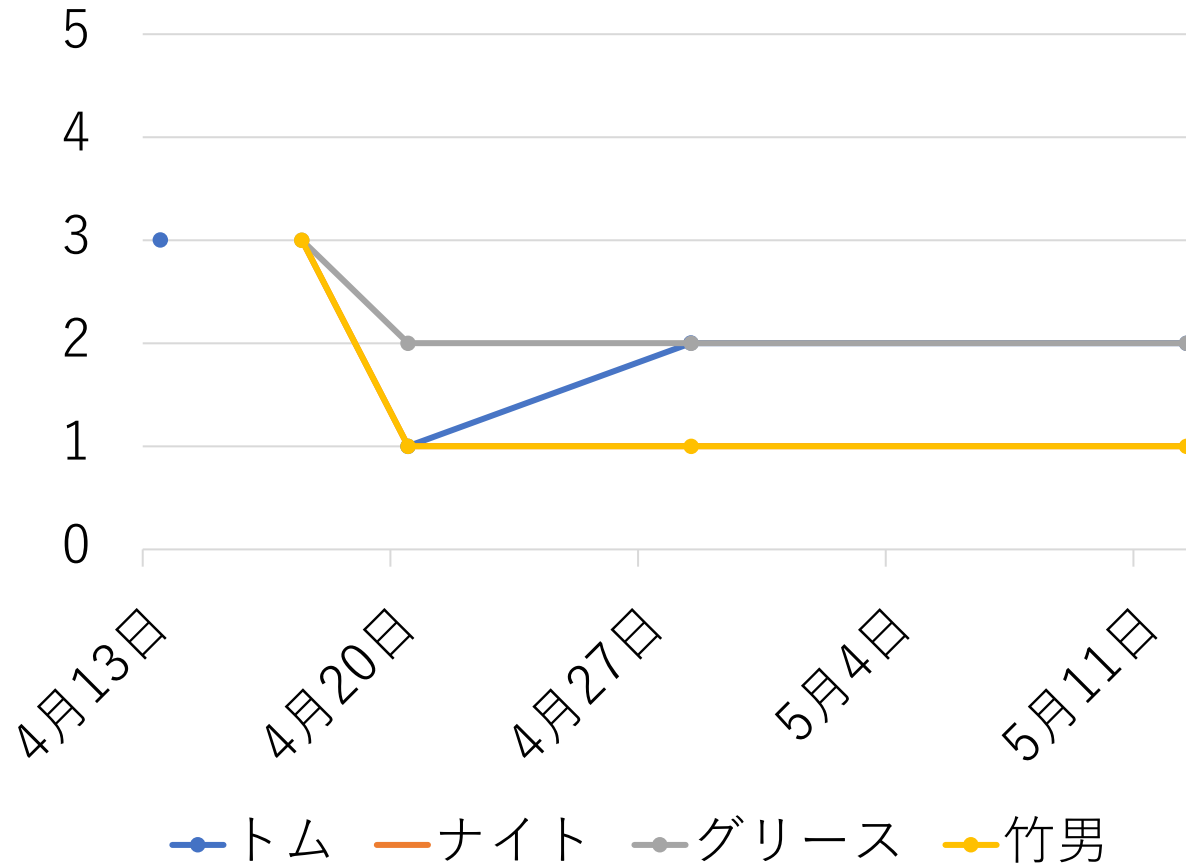
Four toy poodles (Dog Salon Taroimo)

knight	16y Male	Treatibles Hard Chew Ease	1.2mg/kg/day
Tom	15y Male	Treatibles Hard Chew Ease	1.2mg/kg/day
Greece	16y Female	Mary's Tales - 300mg CBD Hemp oil	1.2mg/kg/day
Takeo	15y Male	Mary's Tales - 300mg CBD Hemp oil	1.36mg/kg/day

Survey scores (behavioural concerns)



Greece, 16y
Female



Knight, 16y
Male

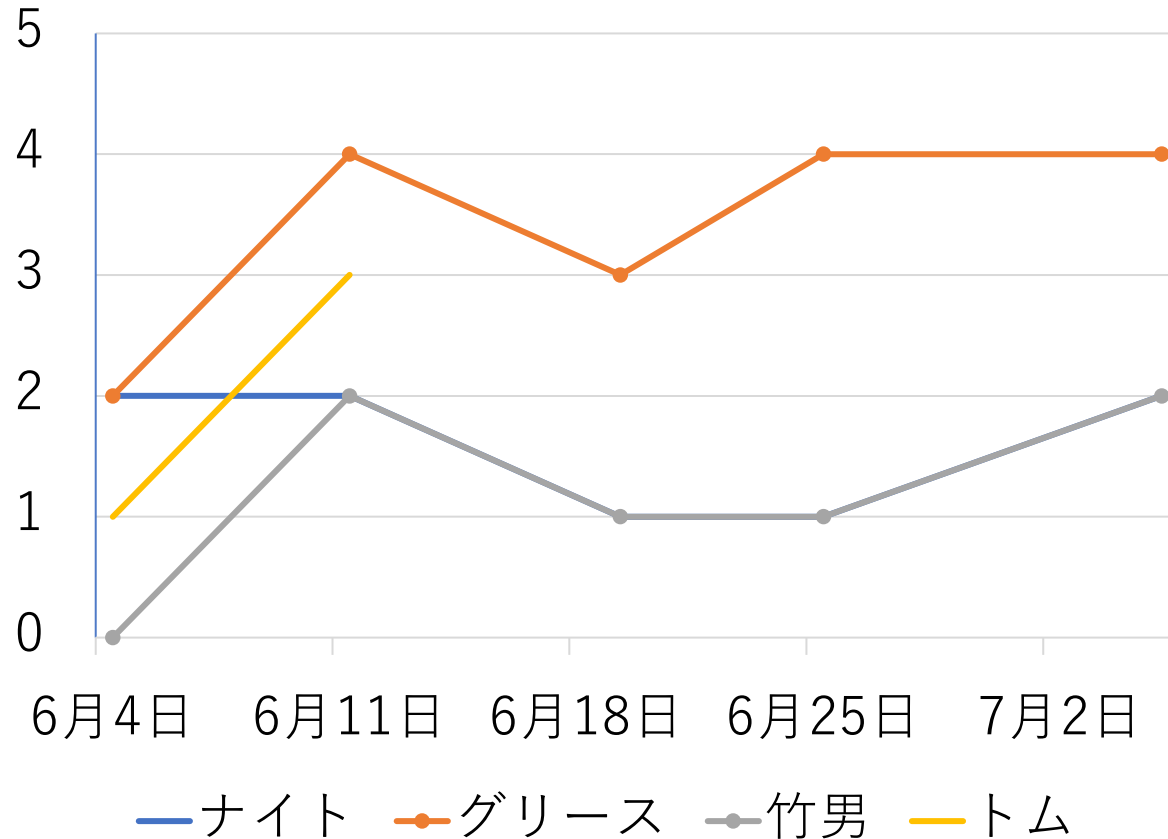
In combination with cognitive function improvement supplement (Activate)

Survey scores (behavioural concerns)

CBD alone Investigation started 7 days after deactivation of Activate.



Tom, 15y Male



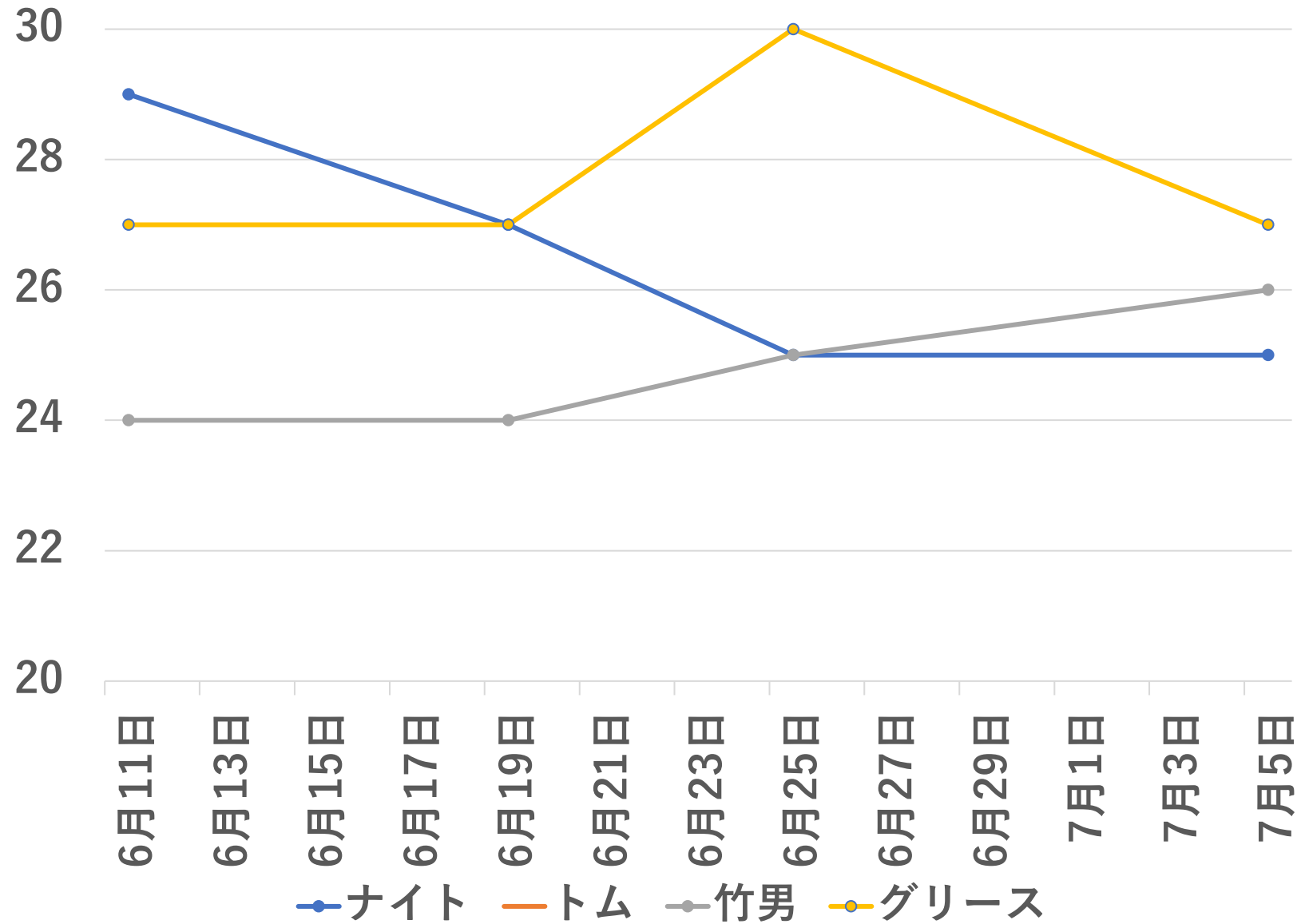
Takeo, 15y Male

Knight	No more whimpering during defecation, good appetite
Greece	Recently, nighttime crying has increased again. Good appetite.
Takeo	Good appetite

Summary of physical examination and blood findings (Tougasaka Veterinary Hospital)

- Weight slightly decreased in all three animals.
- Appetite maintained high.
- Blood test findings: No significant changes in all three dogs.
 - Knight: No change in renal or hepatic function. Mild anaemia progresses. May be associated with chronic disease.
 - Greece: Renal function and anaemia levels unchanged. Liver enzymes (ALP) elevated. SDMA lowered. BUN unchanged. CRP slightly elevated.
 - Takeo : Renal function and anaemia levels unchanged. Liver enzymes (ALP) elevated. BUN elevated. SDMA down. ALT rising slightly. CRP slightly lower.

Pain assessment



Epilepsy case

Lakeland terrier, 4y, male,

Concomitant antiepileptic drug zonisamide

Changed from Mary's 300 to Treatibles 250

Mary's 300 2019/6/18 start at 8 drops BID
1.56mg/kg/day, seizure interval 49.5 days.

Day 454 Treatible 250mg 8 drops start 0.68mg/kg/day,
seizure interval 82.5 days.

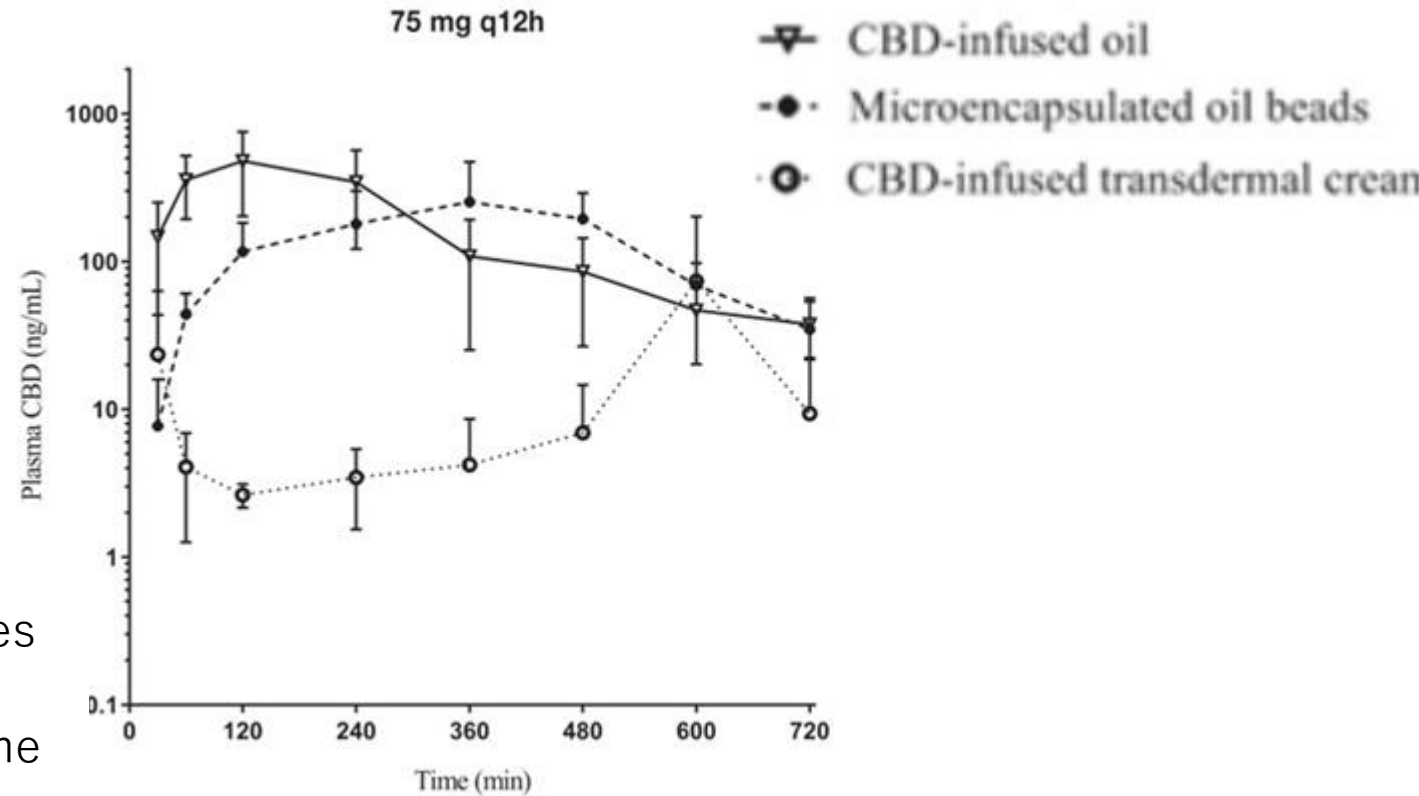
Day 571 dose up to 16 drops BID 1.36mg/kg/day added
1.6mg prn, seizure interval 54 days.



2021/9/24: Day 829

Differences in blood concentration transitions according to route of drug delivery.

- Oral
- Transdermal
- Inhalation (not for pets)



CBD oil has an average residual time of 217 minutes and a half-life of 200 minutes.

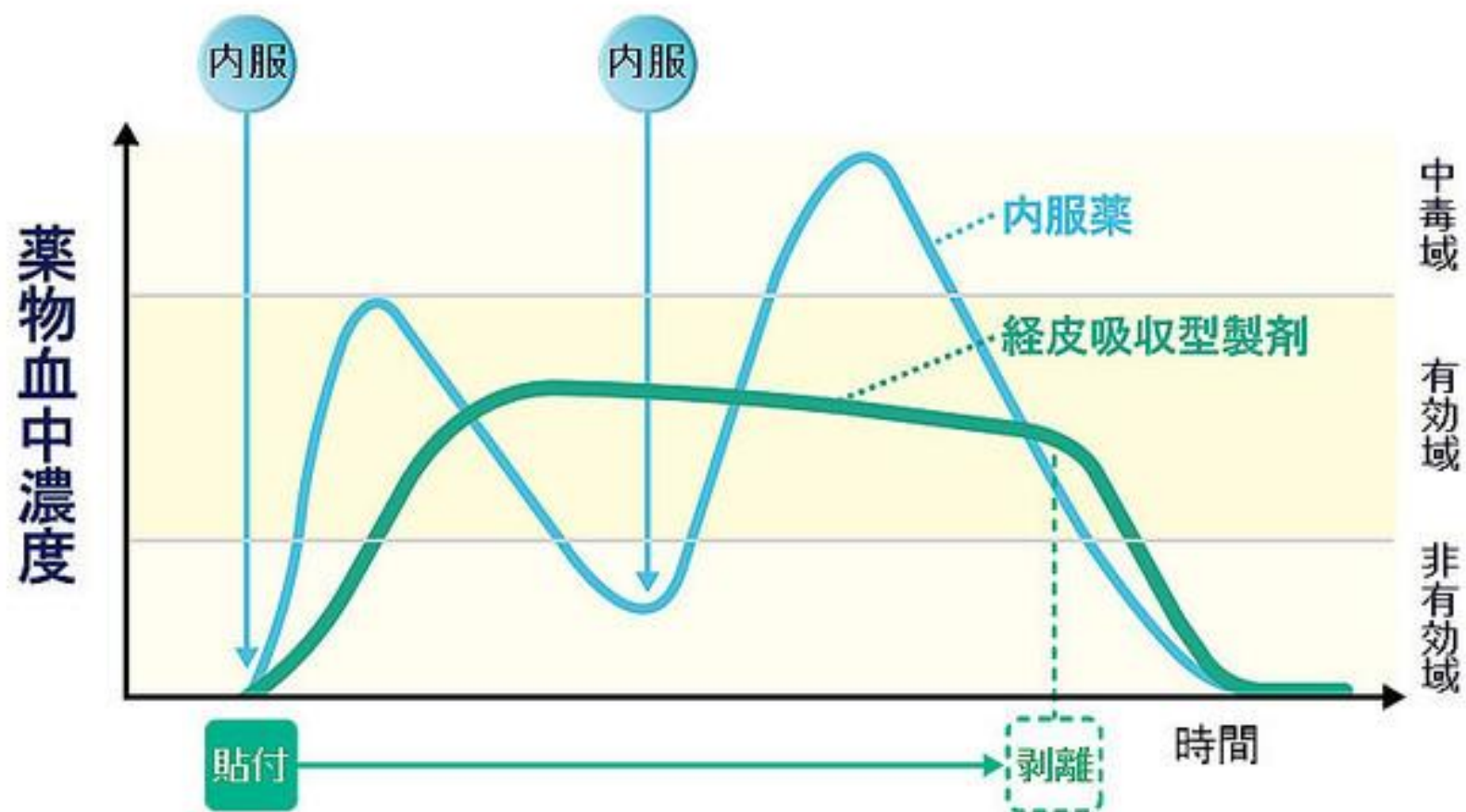
The transdermal cream has an average residual time of 298 minutes and a half-life of 128 minutes.

Bioavailability is 8.6 for the transdermal cream compared to 100 for CBD oil.

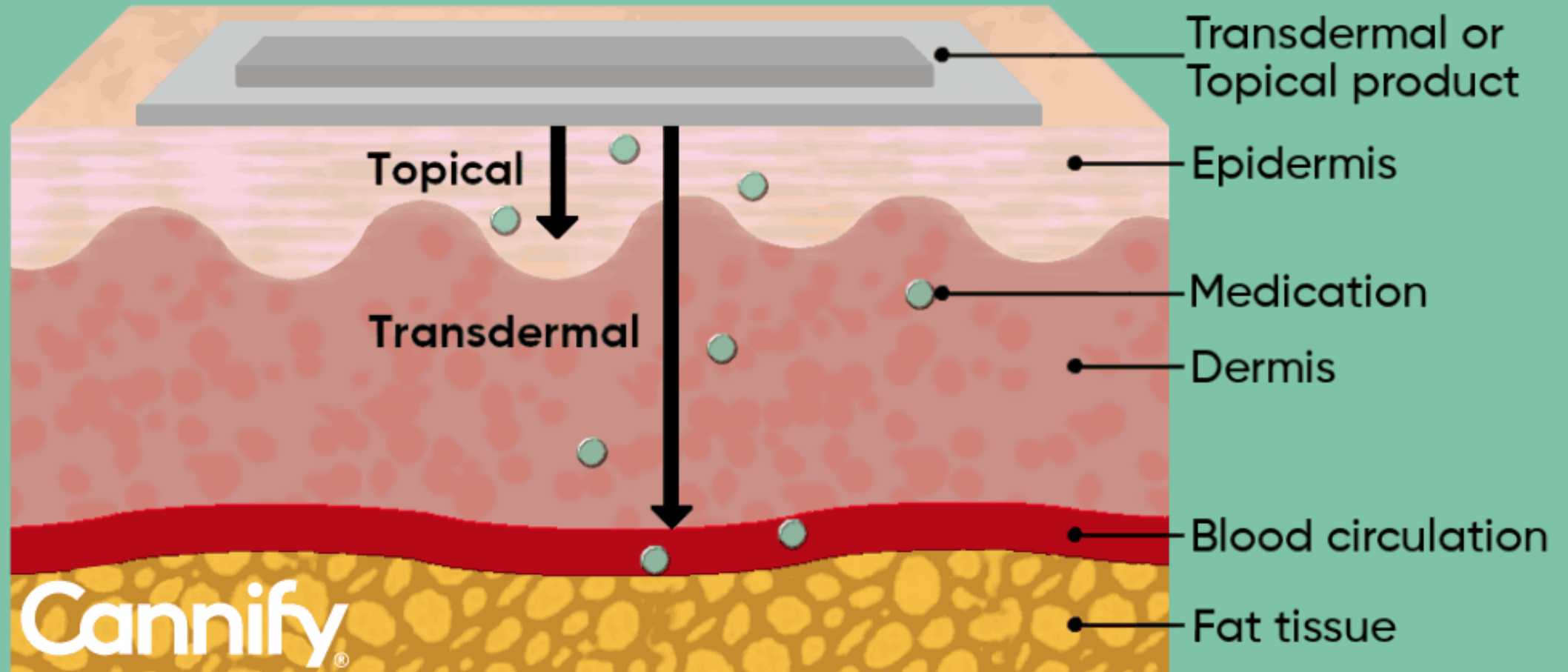
Oral administration has a first-pass effect in the liver and most of it is broken down.

Bartner, L. R., McGrath, S., Rao, S., Hyatt, L. K., & Wittenburg, L. A. (2018). Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. *Canadian Journal of Veterinary Research*, 82(3), 178-183.

経皮吸収型製剤と内服薬の血中濃度イメージ



Cross-section of the skin



<https://www.cannify.us/education/cannabis-and-the-body/cannabinoid-clinical-pharmacology/what-your-body-does-to-cannabis-pharmacokinetics/thc-absorption/>

Advantages of transdermal formulations

- The bioavailability of the drug is increased.
- Stable effective blood concentration range can be maintained for a longer period of time.
- Less prone to fluctuations in efficacy and reduced side-effects.
- Easier to use, as it does not require the time and effort of forced administration. ◦

Original Article

Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis

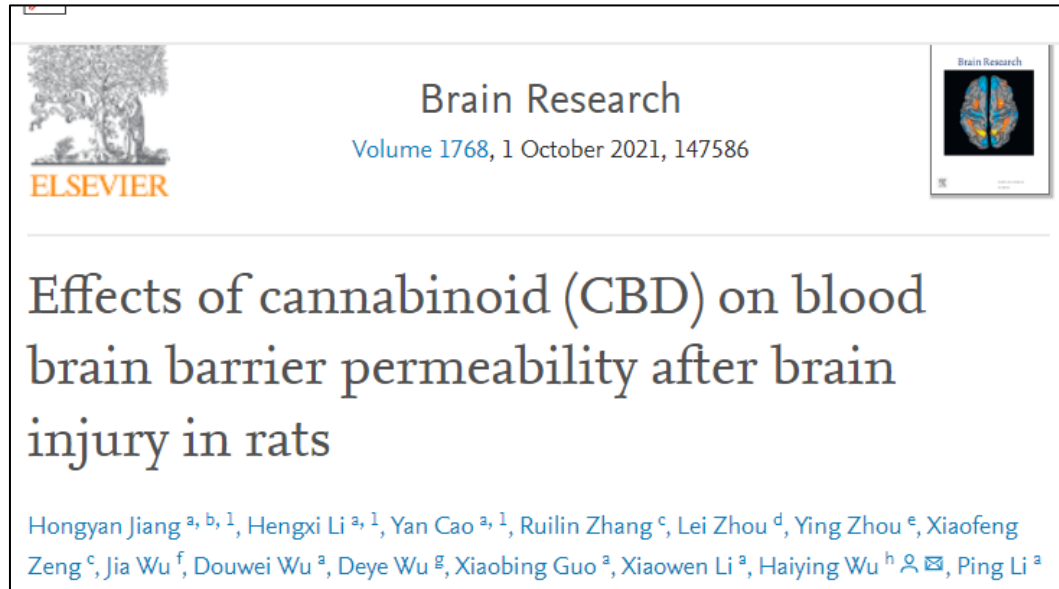
D.C. Hammell, L.P. Zhang, F. Ma, S.M. Abshire, S.L. McIlwrath, A.L. Stinchcomb, K.N. Westlund 

First published: 30 October 2015 | <https://doi.org/10.1002/ejp.818> | Citations: 106

Funding sources:

This work was supported by the American Cancer Society award (RGS-00-027-04-CDD) to A.L. Stinchcomb, University of Kentucky start-up funds to K.N. Westlund and AllTranz, Inc. Cannabidiol was a generous gift provided by NIDA.

Entourage effect of terpenes.



- Cannabidiol reduced the protein levels of proinflammatory cytokines (TNF- α and IL-1 β) and increased the expression of tight junction proteins (claudin-5 and occludin).
- CBD administration significantly mitigated water content in the brain after blood–brain barrier disruption and ameliorated the neurological deficit score after injury.

<https://doi.org/10.1016/j.brainres.2021.147586>

Advances in Pharmacological Activities of Terpenoids

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and Xiuling Yu¹ 

Abstract

Terpenoids, the most abundant compounds in natural products, are a set of important secondary metabolites in plants with diverse structures. Terpenoids play key roles in plant growth and development, response to the environment, and physiological processes. As raw materials, terpenoids were also widely used in pharmaceuticals, food, and cosmetics industries. Terpenoids possess antitumor, anti-inflammatory, antibacterial, antiviral, antimalarial effects, promote transdermal absorption, prevent and treat cardiovascular diseases, and have hypoglycemic activities. In addition, previous studies have also found that terpenoids have many potential applications, such as insect resistance, immunoregulation, antioxidation, antiaging, and neuroprotection. Terpenoids have a complex structure with diverse effects and different mechanisms of action. Activities and mechanisms of terpenoids were reviewed in this paper. The development and application prospect of terpenoid compounds were also prospected, which provides a useful reference for new drug discovery and drug design based on terpenoids.

<https://doi.org/10.1177%2F1934578X20903555>

Terpene Benefits are...

- Humulene.
 - Antioxidant, antibacterial, analgesic, appetite suppressant.
- Alpha and beta pinene.
 - Anticancer and anti-inflammatory effects. Crosses the blood-brain barrier, increases BDNF production and has antidepressant effects.
- Linalool.
 - Calming effect. Strong analgesic and bactericidal effect. Activates immune cells and has anti-inflammatory properties.
- Beta-caryophyllene.
 - Chronic pain relief, anxiolytic and antidepressant effects.
- Myrcene.
 - Sedative, analgesic action; facilitates CBD to pass through the blood-brain barrier.
- Limonene.
 - Relieves symptoms of anxiety; promotes transdermal absorption of CBD.

Weak anxiolytic effect of CBD without THC.

- When considering exogenous cannabinoid administration, cannabinoid receptor 1 (CB1) agonists have a biphasic, dose-dependent effect on anxiety such that low doses are anxiolytic while high doses are anxiogenic, a phenomenon that is evident in both rodent models and humans.
- <https://doi.org/10.1016/j.neuropharm.2021.108626>

Product trial impressions of
Treatibles new products

Leonberger: Sora, 6y, male, 132 lb

Treatibles Soft / Hard chew strong



Soft 7mg: 4 capsules twice a day
Hard 10mg: 2 tablets twice a day, once a day
Sora is not bothered by temperature changes and remains normal. There are no major changes. He is rather relaxed at home as usual. When I thought she was walking faster than usual, there was an incident when I saw a small dog in front of he. I didn't start to run, but I felt that he was in front of me, even though he usually walks leisurely behind me.

Norwich Terrier 11y, male

Treatibles Soft Chew



- He had a strong, fearless character, but from about the age of nine he became dependent on people and sensitive to sounds and other noises.
- He was afraid of thunder and earthquakes, and when the neighbour's house was being rebuilt, he would not sleep at all, but stay still and frozen in a prone position, making frightened noises.
- He did not like the taste of soft chews and ate them when covered with venison sprinkles.
- One piece didn't make any difference, so I added two more and he calmed down. Even though he was frightened, he started to come when I called him, so he must feel a bit more at ease. The next day I gave him two pieces in the morning, but he seemed the same and was frightened all the time while I heard the construction noise.

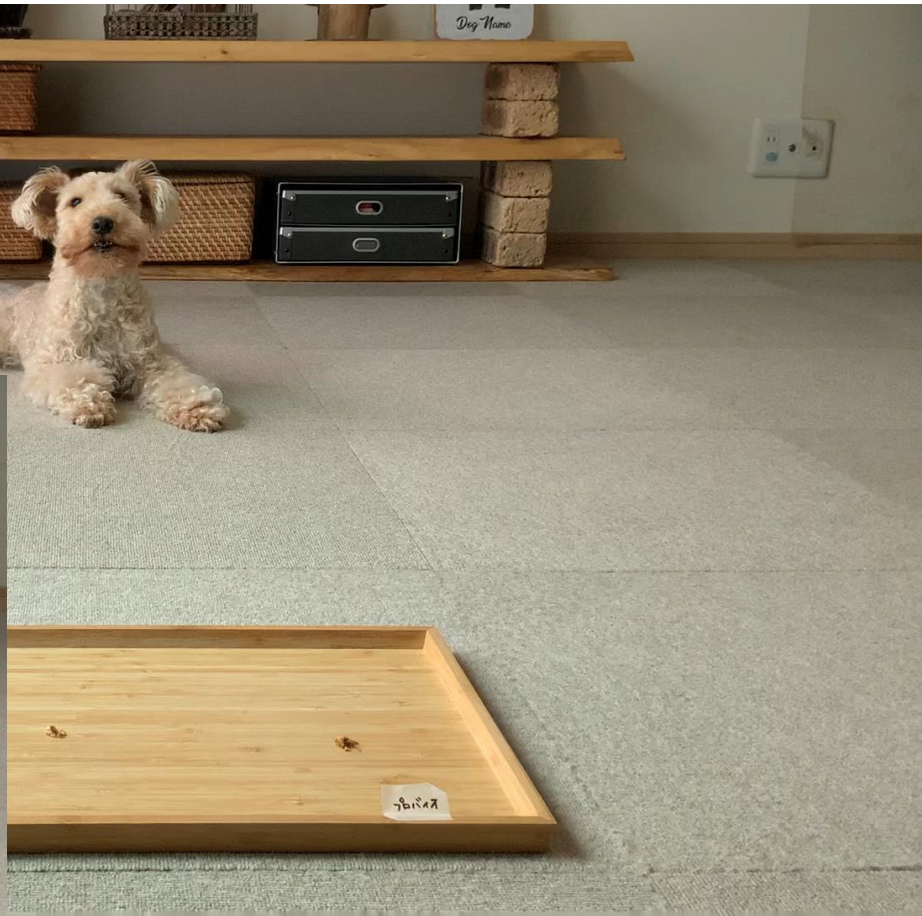
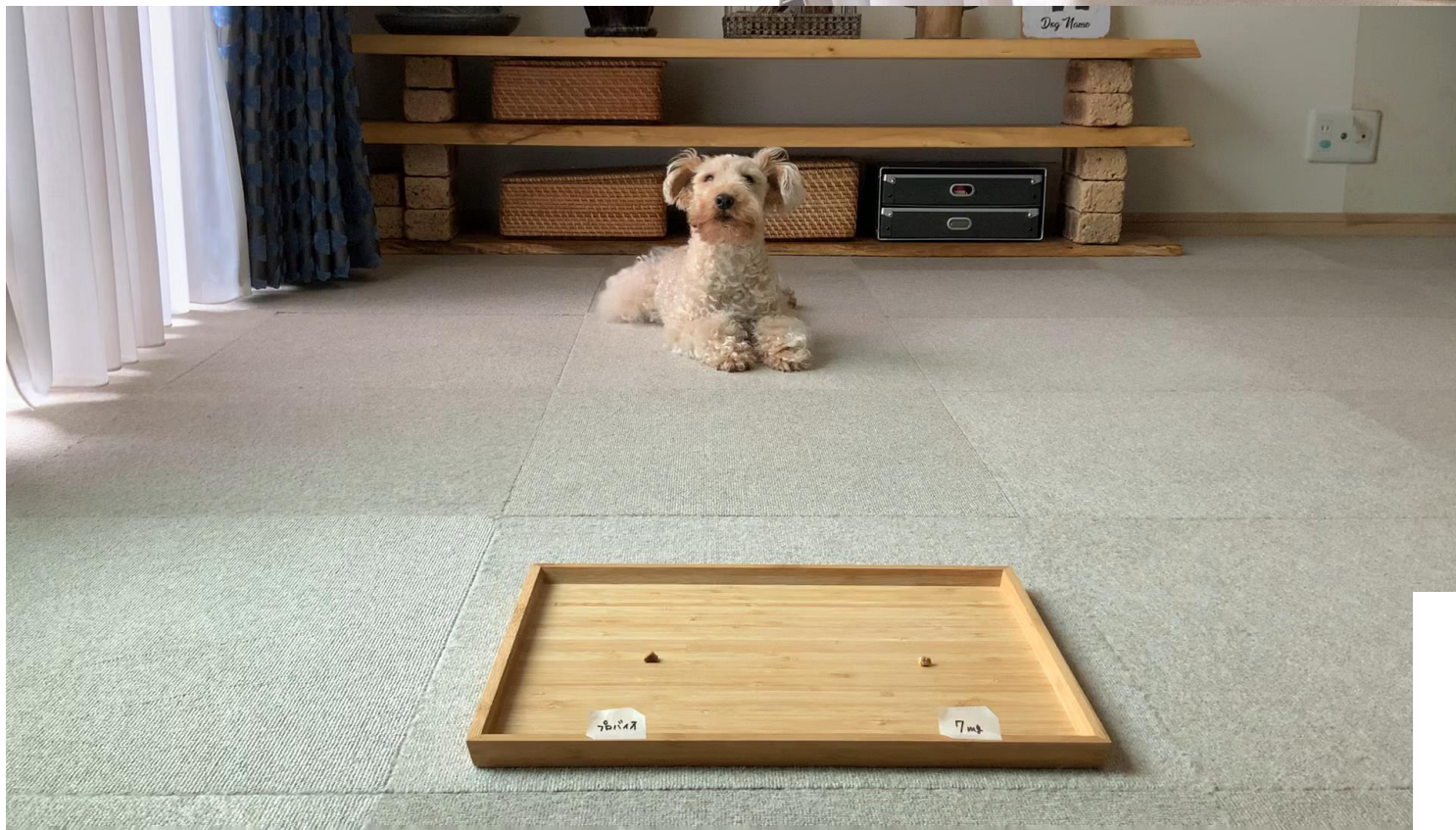
Norwich Terrier, 12y, female, Hind limb lameness

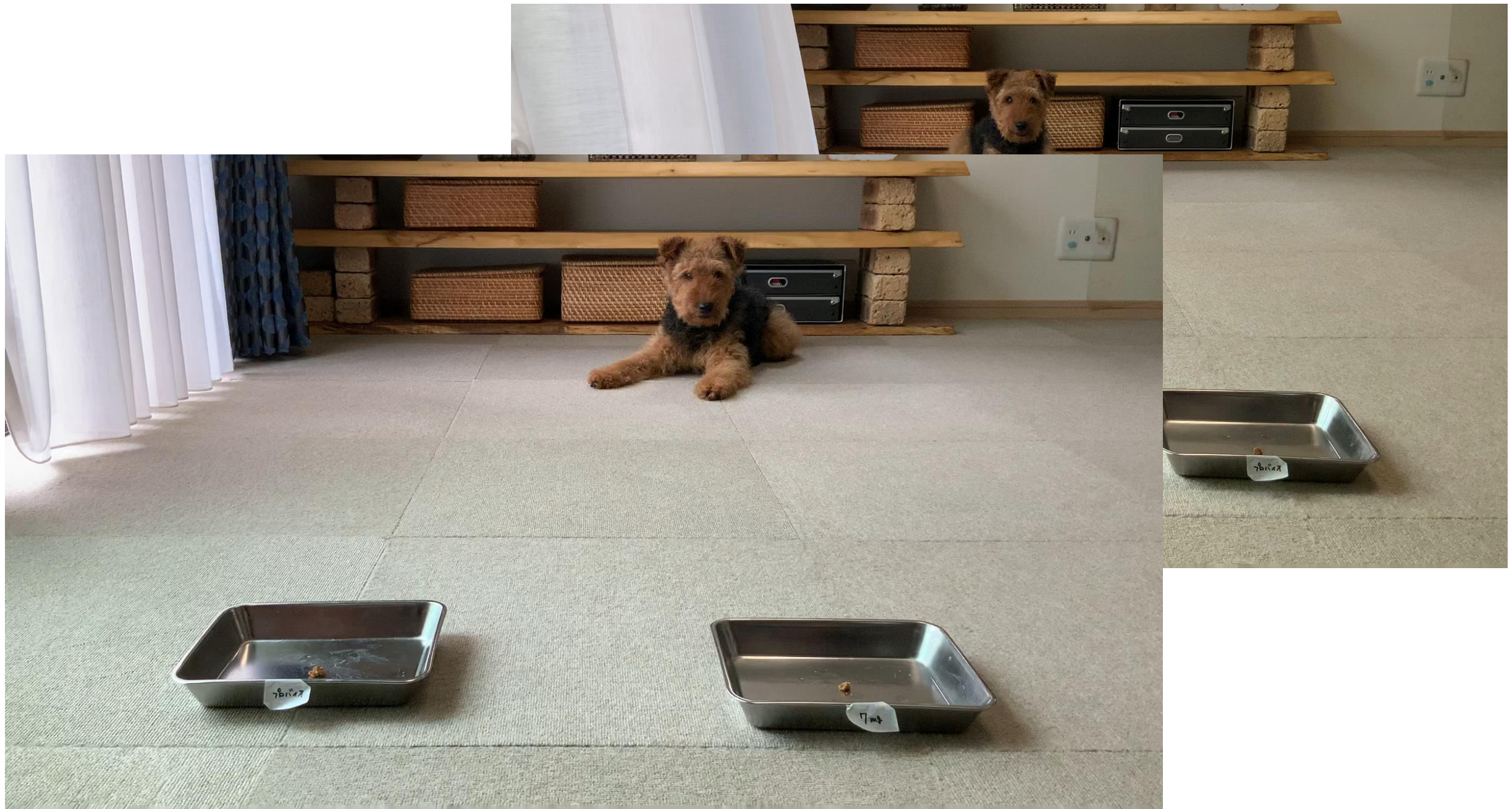
Treatibles CBD Unflavored oil



- Lameness has been observed since last year or so and her hind legs are unstable and she does not want to walk much anymore.
- She is currently doing better than before with physical therapy and Acupuncture and moxibustion treatment, but it sometimes getting.
- She has a great CBD effect on her mobility.
- When I would drive out in the car with her in my carry-on and get out, she used to stand up and get out when I opened the top lid, but since her leg went wrong, she never stood up...
- Now she can stand up and play with Shadow and she bounces around like she used to. It's very effective.
- I've reduced the dosage a little since the day before yesterday, but she's still as healthy as ever. I'm very happy.

Comparison of probiotic products



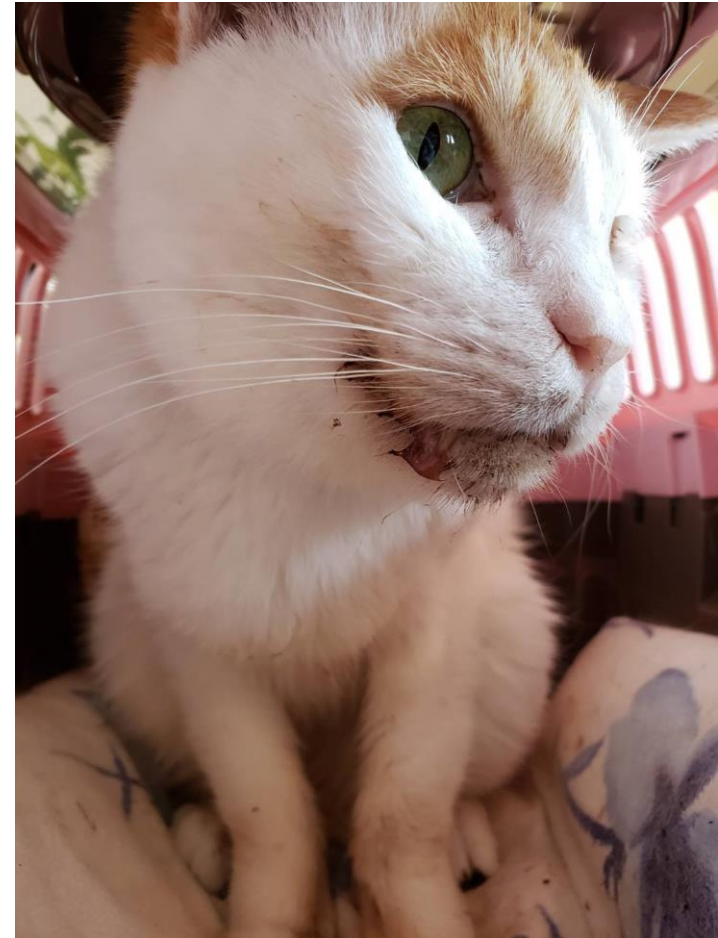


Cats with mouth ulcers

Soft chews for cats



Without antibiotics



A few days after CBD started, without antibiotics

Treatibles Soft Chews for cats

- 7 cats that would not eat
- It was impossible to ingest the food as it was, so the owners sprinkled their own liquid treats on it and it was eaten.
- There was concern that soft chews for cats were not highly palatable.
- Leading Japanese breeder of American (Domestic) Shorthairs indicated that she thought they would prefer chicken-flavoured products.