

# Oral THC: CBD cannabis extract in main symptoms of Alzheimer disease: agitation and weight loss

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## Abstract

**Objectives.** Ten million new cases of dementia are recorded annually worldwide, with agitation and idiopathic weight loss being the most common symptoms. Several pharmacological therapies have emerged in recent years, but the clinical use of cannabis extracts in older patients with AD is constantly growing. This retrospective, analytical, observational, spontaneous trial aimed to enhance the clinical action of THC: CBD cannabis extract administration in AD patients with severe symptoms such as agitation, weight loss, cognitive impairment, and sleep disturbance.

**Methods.** Thirty patients (9 men and 21 women) diagnosed with mild, moderate, or severe AD, aged 65-90 years, appealing to our Second Opinion Medical Consultation (Modena, Italy), were enrolled and required to use oil-diluted cannabis extract, Bedrocan® (22% THC, 0.5% CBD, Olive Oil 50 ml), twice a day for 12 weeks. The efficacy of cannabinoid therapy was evaluated at baseline and 12 weeks after therapy, employing three self-administered questionnaires completed by the parents of the enrolled patients: NPI-Q, CMAI, and MMSE.

**Key findings.** The NPI-Q demonstrated a reduction ( $p < 0.0001$ ) in agitation, apathy, irritability, sleep disturbances, and eating disturbances, consequently improving caregiver distress. Levels of physically and verbally aggressive behaviours, measured using the CMAI questionnaire, were lower ( $p < 0.0001$ ) in all patients. The MMSSE questionnaire confirmed a significant decrease ( $p < 0.0001$ ) in cognitive impairment in 45% of the patients.

**Conclusion.** Our anecdotal, spontaneous, and observational study demonstrated the efficacy and safety of oil-diluted cannabis extract in patients with AD. The limitations of our study are: 1) small patient cohort, 2) absence of control group, 3) self-administered questionnaires that are the most practical but not objective instruments to assess the neurologic functions of AD patients. *Clin Ter 2023; 174 (1):53-60*  
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**Key words:** Bedrocan®, CBD, agitation, weight loss, cannabis, Alzheimer disease, AD, galenical preparation, THC, extract, oil

## Introduction

In 2019, 36 million people worldwide were affected by dementia, accounting actually for 60-80% of AD cases (1, 2).

This number, owing to demographic changes and population aging, could reach 115 million by 2050 (3). In 1906, the German psychiatrist and pathologist Alois described Alzheimer's disease as a neurodegenerative disorder, distinguished by declined cognitive memory, language, and perceptual-motor abilities that have a negative effect on daily living activities (4, 5). Behavioural and psychological changes such as apathy, disinhibition, anxiety, insomnia, and hallucinations, caused mainly by inflammation, oxidative stress, and impaired function of degradation pathways, are frequently added (6-8). The most common symptoms were agitation and idiopathic weight loss. Agitation usually affects 20% of AD cases, increasing to 50% after admission to long-term care facilities. It definitely worsens the life quality requiring more accurate surveillance and a greater institutionalization rate (9, 10). Weight loss is confirmed in one-third of patients, it involves an increased risk of falls and worsens rapid cognitive decline (11-13). AD can also be classified into two types: 1) sporadic AD, which dominates in >95% of patients, and 2) familial early onset form (FAD), which is determined mainly by mutations of genes encoding  $\beta$ -amyloid precursor protein (APP) and presenilin-1 and -2 (PS1 and PS2) and is evidenced in <5% of cases (14, 15). Both forms of AD are histologically characterized by dysfunctional deposition of  $\beta$ -amyloid protein (A $\beta$ ) (Ab1-42 and Ab1-40) in extracellular senile plaques in different brain zones, including the hippocampus, cerebral prefrontal cortex, and amygdala, and by tau hyperphosphorylation in major brain zones involved in memory and cognition (16-21).

The main therapeutic approach makes acetylcholine available by inhibiting acetylcholinesterase (22).

The degeneration of acetylcholine determines cholinergic deficits in AD patients, particularly in the hippocampus and neocortex (23). The main acetylcholinesterase inhibitors are donepezil, galantamine, and rivastigmine, which inhibit both AChE and butyrylcholinesterase. Nevertheless, several clinical trials with a placebo group, based on common pharmacological AD treatments with cholinesterase inhibitors, showed that these inhibitors are efficient mostly for mild-to-moderate AD stage but not in severe stage (24).

The cannabis plant (*Cannabis sativa* L.), including cannabidiol (CBD) and  $\Delta$ -9-tetrahydrocannabinol (THC),

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has been constantly growing in older people with AD (25, 26). These components show neuroprotective action against excitotoxicity and acute brain damage by activating two main cannabinoid G-protein coupled receptors, CB1 and CB2 (21, 27-30). In fact, CB1 receptors appear in glial cells and neurons and modulate excitatory and inhibitory neurotransmission (31). Furthermore, CB1 plays a protective role against excitotoxicity and the induction of repair mechanisms in response to neuronal damage (32, 33). Indeed, stimulation of CB1 receptors reduces the neurotoxic effect of A $\beta$  (34-36) and regression of A $\beta$ -induced memory impairment (37-39). Esposito et al. (40) highlighted the anti-inflammatory action due to reduced levels of inducible nitric oxide synthase (iNOS) and interleukin 1 beta (IL-1b). Eubanks et al. (41) demonstrated the clinical role of exogenous THC as a novel AD drug candidate, discovering that THC could prevent acetylcholinesterase-induced A $\beta$  aggregation by means of enzymes in a crucial zone affecting amyloid production (41).

In 1997, 15 patients with dementia who refused nutrition were treated with cannabis product (2,5 mg THC twice daily) for 42 days, showing reduced Cohen-Mansfield Agitation Inventory (CMAI) scores (42). In 2006, Walther et al. (43) assessed the effect of dronabinol (2,5 mg daily, at 19.00h, for 14 days) on sleep and behavioural disturbances in 5 AD patients with AD, confirming, by Actigraphy and Neuropsychiatric Inventory (NPI) scale, a significant improvement in agitation, appetite, and irritability, compared to baseline, with no side effects (43). Hospitalized AD patients were treated sporadically with various cannabis compounds: THC (2.5–30 mg/dose) and/or CBD, disclosing marked benefits on neuroleptic drug sparing, reduced agitation, increased appetite, sleep quality, and nursing care demands (44). Woodward et al. (45) analysed the outcomes of dronabinol therapy (7 mg/day for 7 weeks) in 13 patients with AD with behavioural or appetite disturbances and evidenced an improved sleep time and percentage of food consumed during the therapy (45). Herrmann et al. reported the therapeutic effect (1-2 mg daily for 6 weeks) of a synthetic THC analogue, nabilone, in 39 AD patients with agitation, observing an improvement in CMAI, PAS and CGI scores (46).

Therefore, the described studies suggest that oral cannabis products have therapeutic effects on patients with AD.

The aim of our retrospective, anecdotal, observational, spontaneous trial was to enhance clinical action of oral THC:CBD cannabis extract administration in AD patients with severe symptoms, such as agitation, weight loss, cognitive impairment, sleep disturbance etc., and its adverse effects. In particular, the objective of this study was to investigate the therapeutic action of this oral cannabis extract in AD patients for at least 3 months. We specifically examined: -The efficacy of oral cannabis extract in agitation, -The efficacy of oral cannabis extract in sleep disturbance, -The efficacy of oral cannabis extract in cognitive impairment, and -Potential occurrence of adverse effects.

## Materials and methods

This anecdotal, spontaneous, and observational study, without control group, was approved by the local ethics

committee Second Opinion Local Institutional Review Board (IRB) and conducted in accordance with the ethical standards of the Declaration of Helsinki.

Patients. Thirty patients (9 men and 21 women) diagnosed with mild, moderate, or severe Alzheimer disease, aged 65-90 years, directed to our Second Opinion Medical Consulting, from February 2018-January to 2020, accompanied by their respective caregivers, were included in this investigation (Table 1). The Second Opinion Medical Network is a consultation referral web and medical office system enclosing a wide panel of specialists, to whom any patient with any illness or syndrome that is not adequately satisfied by the diagnosis or therapy can be applied for an individual clinical audit (47-50).

The main symptoms of the enrolled patients were agitation, appetite loss with consequent weight loss, sleep disturbances, and cognitive impairment.

Inclusion and exclusion criteria. The inclusion criteria were as follows: mild/moderate/severe AD symptoms for at least 24 weeks and seeking adequate therapy; behavioral disorders (NPI-score >2), agitation (CMAI-score >4), and cognitive impairment (Mini Mental State Examination [MMSE] score < 10). The exclusion criteria were the presence of severe cardiac insufficiency, unstable heart rhythm, orthostatic hypotension, antidepressant and anxiolytic therapy, and a history of psychotic disorder.

The patients were required to undergo cannabis oil extract sublingually, twice daily for 12 weeks.

The specific personnel of the Second Opinion Medical Consulting Network evaluated monthly tolerability and side effects, such as hypertension, tachycardia through mail, telephone, WhatsApp, Skype, or visit if required.

The efficacy of cannabinoid therapy was evaluated at baseline and 3 months after therapy using three self-administered questionnaires completed by the parents of enrolled patients: NPI, CMAI, and MMSE. The first determines the severity of 12 neuropsychiatric symptoms, such

*Table 1. Patient's clinical and demographic characteristics. Data are presented as the mean (SD). AD, Alzheimer disease; BMI, Body mass index, MMSE, Mini-Mental State Examination*

No. of patients	30
Male, No	9
Female, No	21
White race, No	30
Geographic region, Italy, No	30
Age, years	69,36
Weight, kg	64,76
BMI, kg/m <sup>2</sup>	<25
Education, years	11.6
MMSE score of <10	24
Patients with mild AD, No	2
Patients with moderate AD, No	10
Patients with severe AD, No	18
Disease duration	6,3
Family history AD	5
Type galenic oil preparation	Oral THC:CBD cannabis extract

as hallucinations, agitation, depression, anxiety, euphoria, apathy, irritability, aberrant motor behaviors, nighttime behavioral and appetite/eating disorders, and caregiver upset. The severity scale ranges from to 1-3 points (1=mild, 2=moderate, and 3=severe), while the scale for evaluating caregiver distress has scores ranging from to 0-5 (0 = no distress, 1=minimal distress, 2=mild distress, 3=moderate distress, 4=severe distress, and 5=extreme distress) (51). The CMAI determines the frequency of agitated behaviors and consists of 29 items typically associated with agitation, including physically aggressive (e.g., hitting, pushing, kicking, cursing), and non-aggressive actions (e.g., pacing, inappropriate dressing or undressing), verbally aggressive (swearing), and non-aggressive habits (uncooperative, constant request for attention), measured before a 14-days period on a 7-point scale (0 = never occurred, 1 = less than once a week, 2= once or twice a week, 3 = several times a week, 4 = once or twice a day, 5 = several times a day, 6 = several times an hour) (52-54). In conclusion, the MMSE is the main instrument used to screen for cognitive impairment in patients with AD, considering several domains of cognitive function such as time and place orientation, concentration, naming familiar items, repeating a common expression, and reading/writing a sentence. Lower score of scale indicates significant impairment (30-26= normal, 20-25: mild, 10-19: moderate, 0-9:severe) (55, 56).

Pharmacological Interventions. The full cannabis plant extract, Bedrocan®, is obtained from Bedrocan International

Table 2. Oral cannabis product's dosage

oil-diluted cannabis extract dosage	
1th week	15 drops/day
2th week	15 drops/day
3th week	23 drops/day
4th week	23 drops/day
5th week	30 drops/day
6-7th weeks	30 drops/day
8th week	30 drops/day
9th week	23 drops/day
10th week	23 drops/day
11th week	15 drops/day
12th week	15 drops/day

BV (Veendam, The Netherlands) and the oil-diluted cannabis extract is prepared by the galenical Pharmacy Dr. Ternelli (Bibbiano, Reggio Emilia, Italy). Bedrocan® that contains 22% THC (220 mg/g) and 0,4% CBD (4mg/g), is prepared from standardized cannabis plant material (Cannabis flos) by means of Sifap-Sifo or Pellati-Ternelli extraction and diluted in oil (1 g of cannabis in 10 g of olive oil). The dosage usually begins with low dose (15 drops) and titrates upwards to the recommended maximum dose of 1 ml/day (30 drops) followed by a reduction down to 0.5 ml/day at month 3 (Table 2).

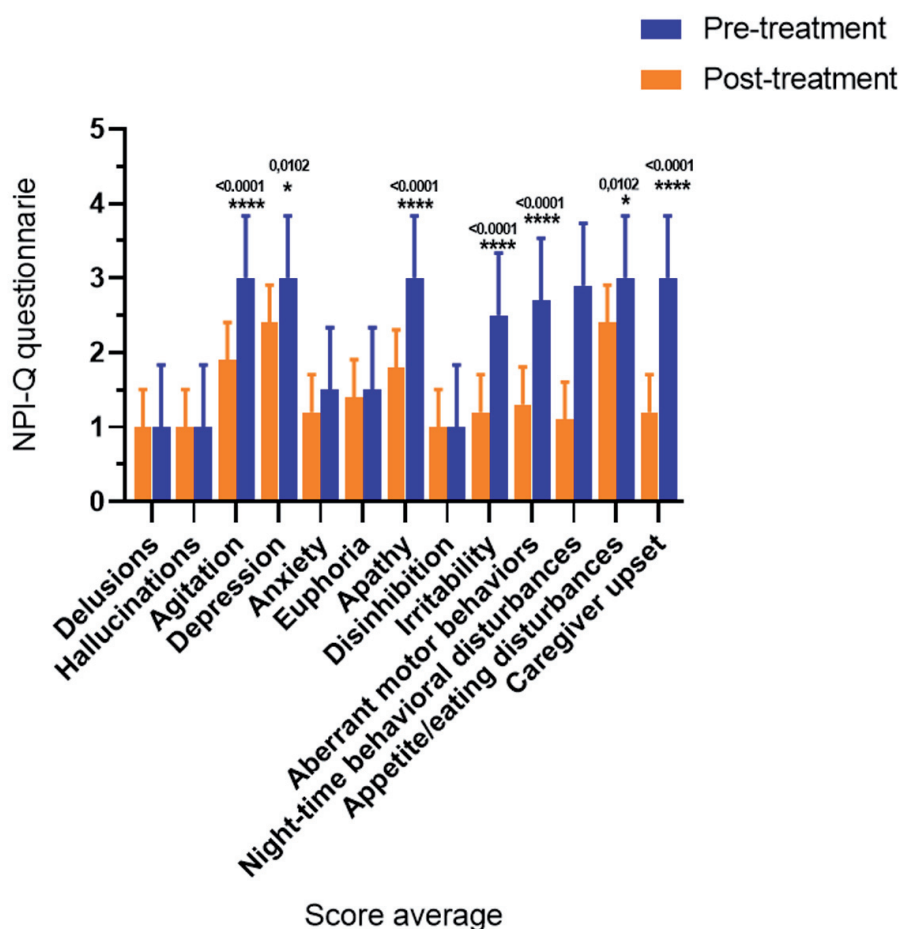


Fig.1. Graphical representation of NPI-Q questionnaire before and after treatment. The bar graph shows the results of NPI-Q text before (blue colour) and after (orange colour) treatment with oil-diluted cannabis extract. Data are presented as the mean ± standard deviation (SD). There were significant differences between pre- and post-treatment. \*\*\*\*P<0.0001 pre vs. post-treatment

No medical treatment was administered in combination with chemotherapy. The patients in the treatment with quetiapine fumarate 0.25 mg for sleep disturbance ( $n = 3$ ) stopped the drug one week before the oil-diluted cannabis extract therapy.

**Statistical analysis.** Statistical analyses were performed using GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA). The data were analyzed using an unpaired t-test with Welch's correction.  $p < 0.05$  was considered significant.

## Results

All enrolled patients completed the cannabis treatment for three months. None of the patients complained of mild, moderate, or severe adverse effects. The NPI questionnaire showed a significant reduction ( $p < 0.0001$ ) in typical behavioural problems, particularly significant decrease of agitation, apathy, irritability, sleep disturbance, and eating disturbances, consequently improving caregiver distress (Fig.1). Levels of physically and verbally aggressive behaviours, measured using the CMAI questionnaire, were lower ( $p < 0.0001$ ) in all clinical cases (Fig.2). Some 'performing repetitive behaviors', such as repeating a question or an action, tapping fingers, were observed more commonly.

The MMSE questionnaire confirmed severe cognitive impairment (score  $< 10$ ) before cannabis treatment, which was reduced to mild/moderate (score: 15-17) in 45% of the patients. The majority (70%) of the clinical cases showed an increase in appetite, probably due to the known effects of CB1 agonism (Fig.3).

However, caregiver feedback (son/daughter, wife/husband, brother/sister) about the treatment was extremely positive overall. They reported definite improvement in daily behavior: the patient appeared quieter, less excitable and irritable, more adherent to environmental situations, and even more properly laughing and smiling.

At the end of cannabis treatment, the patients significantly reduced their behavioral disorders, including screaming, tearing clothes, and claiming for common daily living activities, such as washing, dressing, climbing stairs, and eating alone. One woman (88 years old) with persistent agitation stopped therapy after 30 days.

## Discussion

The results of our clinical trial suppose the effectiveness and in particular the safety of galenic (CBD/THC) preparation in two main symptoms of AD, such as agitation and weight loss.

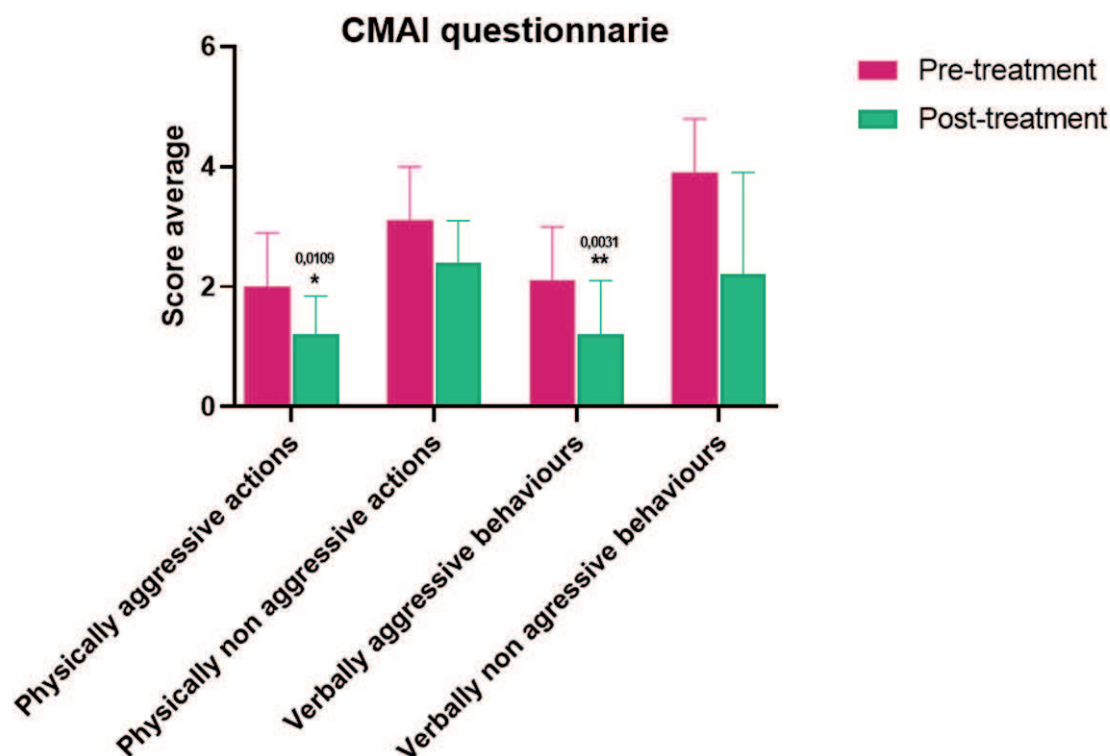


Fig. 2. Graphical representation of CMAI questionnaire before and after treatment. Bar graphs showing the CMAI questionnaire results for the pretreatment (fuchsia bar) and posttreatment (green bar) group. Data are presented as the mean  $\pm$  standard deviation (SD).



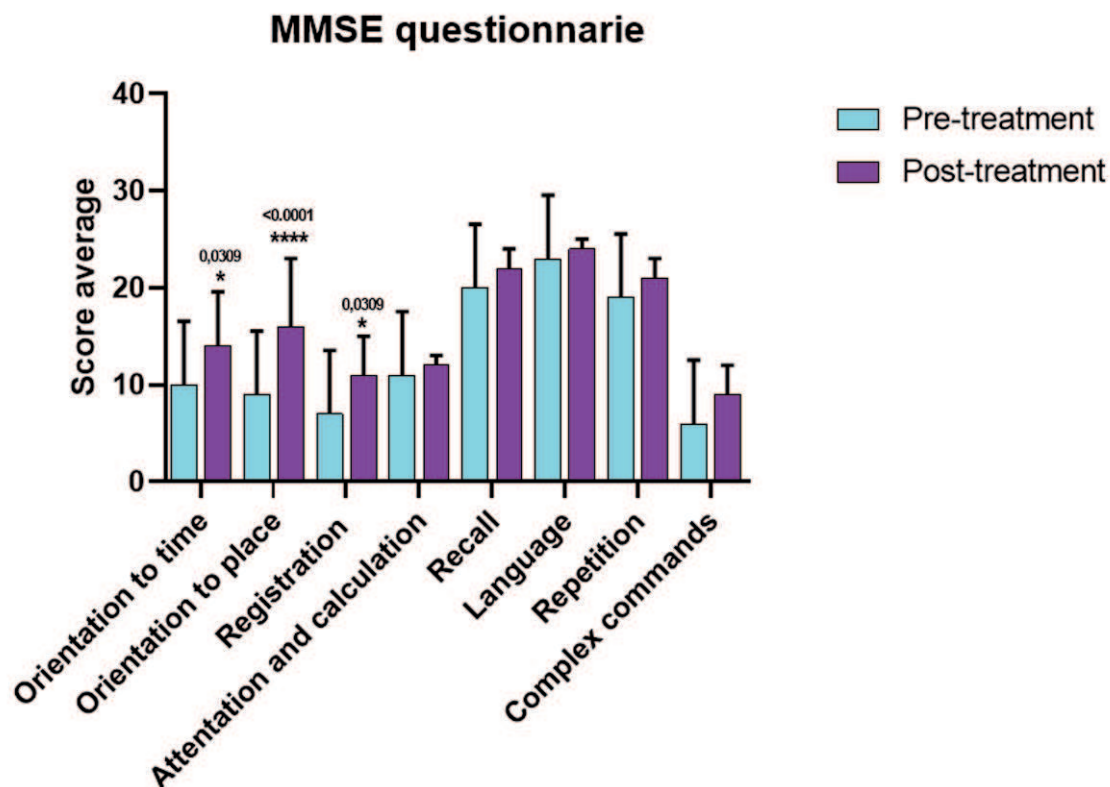


Fig. 3. Graphical representation of MMSE questionnaire before and after treatment. Data are presented as the mean  $\pm$  standard deviation (SD). Differences in symptoms such as orientation to time or to place and registration were considered statistically significant relative to the pre-treatment group. \*\*\*\* $P < 0.0001$  pre vs. post-treatment

Despite the many confirmatory experimental researchers, the clinical evidence of the effectiveness of cannabinoids (CBD and/or THC) in AD has not been confirmed statistically, because of the small sample size of the treated patient groups and some bias in the homogenous meta-analysis of individual studies. For example, we can report a recent (2021) metanalysis of Kuharic and coworkers (57) that included 4 clinical trials: 126 patients, the majority with AD syndrome and/or vascular or mixed dementia treated with natural THC (Namisol) or two types of synthetic THC analogue (dronabinol and nabilone) for a period of treatment over 3 weeks. The authors found low-certainty evidence suggesting there may be little or no clinically important effect of cannabinoids on overall behavioural and psychological symptoms of dementia assessed with NPI scale. There were no significant differences between groups in terms of adverse events, with the exception of sedation which was more frequent among participants taking nabilone ( $N = 17$ ) than placebo ( $N = 6$ ).

Many neurophysiological investigations have shown that high THC concentrations inhibit cholinergic transmission in the limbic system and cortex, impairing memory and cognition; however, the side effects observed after THC-based therapy are similar to those observed after cholinergic antagonists, such as 4-DAMP, cyclizine, gallamine, and methdilazine, as studied by Varvel et al. (58).

Cao et al. (59) examined the toxicity of THC in N2a-variant amyloid- $\beta$  protein precursor ( $A\beta$ PP) cells incubated with a low dose of compound (100  $\mu$ L in 2 $\times$  concentrations

for each well = 2.5 nM) and confirmed that this compound could reduce the synthesis of the AD pathological marker, slowing down or stopping the progression of the disease.

Similar results were observed in old mice (12-18 months) with cognitive symptoms (memory deficit and increased learning capacity) treated with a low dose of THC (60). The improved cognitive functions, with consequently improved expression of synaptic marker proteins and hippocampal spine density, were similar to those of untreated mice with the same symptoms, according to other studies (61-64).

In our observational and spontaneous study, we chose cannabis oil because it can be administered in different food options (bread, breadstick, crackers, etc.), compared with an oral spray that is poorly adsorbed in elderly patients, or cannabis tincture (alcoholic), responsible for mucositis or oral ulcers (65).

Our treatment reduced behavioural misconduct, such as agitation and cognitive impairment, probably because of the direct effect of cannabis on  $A\beta$  processing, which could increase the level of available acetylcholine and anticipate acetylcholinesterase-induced  $A\beta$  aggregation.

Many patients showed a significant improvement on NPI and MMSE scores, in according to the 14-week randomized double-blind crossover trial of Herrmann et al (46), demonstrating that the cannabis therapy can be associated with a relevant reduction in agitation over 8 weeks. This therapy could also act against another typical night-time behaviour, in AD syndrome, that is the nocturnal motor activity, as showed by Walther et al (43). Our results, in fact,

corroborate improvements in NPI total score, as well as in subscores for aberrant motor, and night-time behavioural disturbances ( $P < 0.05$ ).

During the treatment period, we observed an increased quality of life for each patient, and consequently, a decrease in caregiver burden and costs of medical care and assistance.

## Conclusion

Our analytical, spontaneous, and observational study demonstrated the efficacy and safety of THC:CBD cannabis extract in patients with AD.

The main limitation of our study was the small clinically cohort of patients. Given the small size of the patient sample, we cannot exclude error rates (Type 1 and Type 2 errors) and cannot ensure that our results may be replicated in future research with larger sample size. Considering the low size of our patient sample and related low statistical power, our study should be viewed as an anecdotal one and to help as an input for larger studies. Other limitations of our study are as follows: 1) the absence of a control group, and 2) self-administered questionnaires that are the most practical but not objective instruments to assess the neurologic functions of AD patients.

In conclusion, the lack of clinical studies in this area validates further trials, particularly randomized controlled studies, to assess the pharmacokinetics and pharmacodynamics of cannabis treatment in different clusters of AD symptoms.

## Declaration section Funding

Funding information was not applicable/no funding was received.

## Conflicts of interest

The Authors declare that there is no conflict of interest

## Data transparency

The authors affirm that this manuscript is an honest, accurate, and transparent account of this study.

Being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained

## Data availability

The authors declare that data supporting the findings of this study are available in the article.

## Ethics approval

Approval was obtained from the local ethics committee Second Opinion Local Institutional Review Board (IRB), named: Second Opinion Medical Network, the number of Approval is 7/2021

## Authors contribution

The authors confirm their contribution to the paper as follows: study conception and design: MV; data Collection and writing BP,

## Consent to participate

The participants consented to the submission of the case report to the journal. Each Patient signed

Informed consent regarding publishing his data and photographs" statement in the ethics approval and consent to participate section.

## Consent for publication

Each patient gave its consent for the publication of identifiable details, which can include photographs and/or case history and/or details within the text ("methods, results") to be published in the above Journal.

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All methods were performed in accordance with the relevant guidelines and regulations, according to a statement in the ethics approval and consent to participate.

## References

1. Ranson JM KE, Hamilton W, Lang I, Llewellyn DJ. Case-finding in clinical practice: An appropriate strategy for dementia identification? *Alzheimer's & dementia* (New York, N Y). 2018; 4:288-96
2. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology*. 2013; 80(19):1778-83
3. Andersen F, Viitanen M, Halvorsen DS, et al. Co-morbidity and drug treatment in Alzheimer's disease. A cross sectional study of participants in the dementia study in northern Norway. *BMC geriatrics*. 2011; 11:58
4. Li H, Liu Y, Tian D, et al. Overview of cannabidiol (CBD) and its analogues: Structures, biological activities, and neuroprotective mechanisms in epilepsy and Alzheimer's disease. *European Journal of Medicinal Chemistry*. 2020; 192:112163
5. Deckers K, van Boxtel MP, Schiepers OJ, et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. *International journal of geriatric psychiatry*. 2015; 30(3):234-46
6. Keller JN, Hanni KB, Markesbery WR. Impaired proteasome function in Alzheimer's disease. *Journal of neurochemistry*. 2000; 75(1):436-9
7. I.F. Defining Alzheimer as a commonage-related neurodegenerative process notinevitably leading to dementia. *ProgNeurobiol* 2012; 397:38-51
8. Sultana R, Butterfield DA. Role of oxidative stress in the progression of Alzheimer's disease. *Journal of Alzheimer's disease : JAD*. 2010; 19(1):341-53
9. McKeith I, Cummings J. Behavioural changes and psychological symptoms in dementia disorders. *The Lancet Neurology*. 2005; 4(11):735-42
10. Zuidema SU, de Jonghe JFM, Verhey FRJ, et al. Agitation in Dutch Institutionalized Patients with Dementia: Factor Analysis of the Dutch Version of the Cohen-Mansfield Agitation Inventory. *Dementia and Geriatric Cognitive Disorders*. 2007; 23(1):35-41

11. Soto ME, Secher M, Gillette-Guyonnet S, et al. Weight Loss and Rapid Cognitive Decline in Community-Dwelling Patients with Alzheimer's Disease. *Journal of Alzheimer's Disease*. 2012; 28:647-54
12. White H, Pieper C, Schmader K. The Association of Weight Change in Alzheimer's Disease with Severity of Disease and Mortality: A Longitudinal Analysis. *Journal of the American Geriatrics Society*. 1998; 46(10):1223-7
13. Gillette-Guyonnet S, Nourhashémi F, Andrieu S, et al. Weight loss in Alzheimer disease. *The American Journal of Clinical Nutrition*. 2000; 71(2):637S-42S
14. Hardy J. Amyloid, the presenilins and Alzheimer's disease. *Trends in neurosciences*. 1997; 20(4):154-9
15. Price DL, Sisodia SS. Mutant genes in familial Alzheimer's disease and transgenic models. *Annual review of neuroscience*. 1998; 21:479-505
16. Ferrer I. Defining Alzheimer as a common age-related neurodegenerative process not inevitably leading to dementia. *Progress in Neurobiology*. 2012; 97(1):38-51
17. Selkoe DJ. Preventing Alzheimer's Disease. *Science*. 2012; 337(6101):1488-92
18. Akiyama H, Barger S, Barnum S, et al. Inflammation and Alzheimer's disease. *Neurobiology of aging*. 2000; 21(3):383-421
19. Masliah E, Sisk A, Mallory M, et al. Comparison of neurodegenerative pathology in transgenic mice overexpressing V717F beta-amyloid precursor protein and Alzheimer's disease. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 1996; 16(18):5795-811
20. Jantzen PT, Connor KE, DiCarlo G, et al. Microglial activation and beta -amyloid deposit reduction caused by a nitric oxide-releasing nonsteroidal anti-inflammatory drug in amyloid precursor protein plus presenilin-1 transgenic mice. *The Journal of neuroscience: the official journal of the Society for Neuroscience*. 2002; 22(6):2246-54
21. Ramírez BG, Blázquez C, del Pulgar TG, et al. Prevention of Alzheimer's Disease Pathology by Cannabinoids: Neuroprotection Mediated by Blockade of Microglial Activation. *The Journal of Neuroscience*. 2005; 25(8):1904-13
22. Talarico G, Trebbastoni A, Bruno G, et al. Modulation of the Cannabinoid System: A New Perspective for the Treatment of the Alzheimer's Disease. *Current neuropharmacology*. 2019; 17(2):176-83
23. Perry E, Walker M, Grace J, et al. Acetylcholine in mind: a neurotransmitter correlate of consciousness? *Trends in neurosciences*. 1999; 22(6):273-80
24. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *The Cochrane database of systematic reviews*. 2006; (1):Cd005593
25. Iuvone T, Esposito G, Esposito R, et al. Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on beta-amyloid-induced toxicity in PC12 cells. *Journal of neurochemistry*. 2004; 89(1):134-41
26. Esposito G, De Filippis D, Carnuccio R, et al. The marijuana component cannabidiol inhibits beta-amyloid-induced tau protein hyperphosphorylation through Wnt/beta-catenin pathway rescue in PC12 cells. *Journal of molecular medicine (Berlin, Germany)*. 2006; 84(3):253-8
27. Piomelli D. The molecular logic of endocannabinoid signaling. *Nature reviews Neuroscience*. 2003; 4(11):873-84
28. van der Stelt M, Veldhuis WB, Maccarrone M, et al. Acute neuronal injury, excitotoxicity, and the endocannabinoid system. *Molecular neurobiology*. 2002; 26(2-3):317-46
29. Mechoulam R, Shohami E. Endocannabinoids and traumatic brain injury. *Molecular neurobiology*. 2007; 36(1):68-74
30. Assogna M, Casula EP, Borghi I, et al. Effects of Palmitoylethanolamide Combined with Luteoline on Frontal Lobe Functions, High Frequency Oscillations, and GABAergic Transmission in Patients with Frontotemporal Dementia. *Journal of Alzheimer's disease: JAD*. 2020; 76(4):1297-308
31. Howlett AC. Cannabinoid Receptor Signaling. In: Pertwee RG, editor. *Cannabinoids*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2005; 53-79
32. Fagan SG, Campbell VA. The influence of cannabinoids on generic traits of neurodegeneration. *British Journal of Pharmacology*. 2014; 171(6):1347-60
33. Mitew S, Kirkcaldie MTK, Dickson TC, et al. Altered synapses and gliotransmission in Alzheimer's disease and AD model mice. *Neurobiology of aging*. 2013; 34(10):2341-51
34. Noonan RT, Klompas A, Gowran A, et al. Endocannabinoids prevent beta-amyloid-mediated lysosomal destabilization in cultured neurons. *J Biol Chem*. 2010; 285:38543-54
35. Chen X, Zhang J, Chen C. Endocannabinoid 2-arachidonylglycerol protects neurons against  $\beta$ -amyloid insults. *Neuroscience*. 2011; 178:159-68
36. Janefjord E, Määg JLV, Harvey BS, et al. Cannabinoid Effects on  $\beta$  Amyloid Fibril and Aggregate Formation, Neuronal and Microglial-Activated Neurotoxicity In Vitro. *Cellular and Molecular Neurobiology*. 2014; 34(1):31-42
37. Aso AS-P, Vegas-Lozano E, Maldonado R, et al. Cannabis-based medicine reduces multiple pathological processes in A $\beta$ PP/PS1 mice. *Alzheimers Dis*. 2015; 43:977-91
38. Haghani M, Shabani M, Javan M, et al. CB1 Cannabinoid Receptor Activation Rescues Amyloid  $\beta$ -Induced Alterations in Behaviour and Intrinsic Electrophysiological Properties of Rat Hippocampal CA1 Pyramidal Neurones. *Cellular Physiology and Biochemistry*. 2012; 29(3-4):391-406
39. Aso EP, Juvés S, Maldonado R, et al. CB1 agonist ACEA protects neurons and reduces the cognitive impairment of A $\beta$ PP/PS1 mice. *J Alzheimers Dis*. 2012; 30:439-59
40. Esposito G, De Filippis D, Steardo L, et al. CB1 receptor selective activation inhibits beta-amyloid-induced iNOS protein expression in C6 cells and subsequently blunts tau protein hyperphosphorylation in co-cultured neurons. *Neuroscience letters*. 2006; 404(3):342-6
41. Eubanks LM, Rogers CJ, Beuscher AE, et al. A molecular link between the active component of marijuana and Alzheimer's disease pathology. *Molecular pharmaceutics*. 2006; 3(6):773-7
42. Volicer L, Stelly M, Morris J, et al. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *International journal of geriatric psychiatry*. 1997; 12(9):913-9
43. Walther S, Mahlberg R, Eichmann U, et al. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology*. 2006; 185(4):524-8
44. Hergenrath J. *Cannabis and Dementia*. Columbus, OH: Cannabis Expertise. 2017
45. Woodward MR, Harper DG, Stolyar A, et al. Ellison JM. Dronabinol for the treatment of agitation and aggressive behavior in acutely hospitalized severely demented patients with noncognitive behavioral symptoms. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2014; 22(4):415-9

46. Herrmann N, Ruthirakuhan M, Gallagher D, et al. Randomized Placebo-Controlled Trial of Nabilone for Agitation in Alzheimer's Disease. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2019; 27(11):1161-73
47. Palmieri B, Iannitti T, Capone S, et al. Second opinion clinic: is the Web Babel Syndrome treatable?. *La Clinica terapeutica*. 2011; 162(6):575-83
48. Di Cerbo A, Palmieri B. The economic impact of second opinion in pathology. *Saudi medical journal*. 2012; 33(10):1051-2
49. Palmieri B, Capone S, Fistetto G. Second opinion consultation: is Babel-web syndrome curable? *Recenti progressi in medicina*. 2011; 102(1):43
50. Palmieri B, Iannitti T. The Web Babel syndrome. *Patient education and counseling*. 2011; 85(2):331-3
51. Musa G, Henríquez F, Muñoz-Neira C, et al. Utility of the Neuropsychiatric Inventory Questionnaire (NPI-Q) in the assessment of a sample of patients with Alzheimer's disease in Chile. *Dement Neuropsychol*. 2017; 11(2):129-36
52. Cohen-Mansfield J, Billig N. Agitated behaviors in the elderly. I. A conceptual review. *J Am Geriatr Soc*. 1986; 34(10):711-21
53. Cohen-Mansfield J, Libin A. Assessment of agitation in elderly patients with dementia: correlations between informant rating and direct observation. *International journal of geriatric psychiatry*. 2004; 19(9):881-91
54. Koss E, Weiner M, Ernesto C, et al. Assessing patterns of agitation in Alzheimer's disease patients with the Cohen-Mansfield Agitation Inventory. *The Alzheimer's Disease Cooperative Study. Alzheimer disease and associated disorders*. 1997; 11 Suppl 2:S45-50
55. Vertesi A, Lever JA, Molloy DW, Sanderson B, Tuttle I, Pokoradi L, et al. Standardized Mini-Mental State Examination. Use and interpretation. *Can Fam Physician*. 2001; 47:2018-23
56. O'Caomh R, Molloy DW. Comparing the Diagnostic Accuracy of Two Cognitive Screening Instruments in Different Dementia Subtypes and Clinical Depression. *Diagnostics (Basel, Switzerland)*. 2019; 9(3)
57. Bosnjak Kuharic D, Markovic D, Brkovic T, et al. Cannabinoids for the treatment of dementia. *The Cochrane database of systematic reviews*. 2021; 9(9):Cd012820
58. Varvel SA, Hamm RJ, Martin BR, et al. Differential effects of delta 9-THC on spatial reference and working memory in mice. *Psychopharmacology*. 2001; 157(2):142-50
59. Cao C, Li Y, Liu H, et al. The potential therapeutic effects of THC on Alzheimer's disease. *Journal of Alzheimer's disease: JAD* 2014; 42(3):973-84
60. Bilkei-Gorzo A, Albayram O, Draffehn A, et al. A chronic low dose of  $\Delta(9)$ -tetrahydrocannabinol (THC) restores cognitive function in old mice. *Nature medicine*. 2017; 23(6):782-7
61. Zanettini C, Panlilio LV, Alicki M. Effects of endocannabinoid system modulation on cognitive and emotional behavior. *Frontiers in behavioral neuroscience*. 2011; 5:57
62. Aso E, Sánchez-Pla A, Vegas-Lozano E, et al. Cannabis-based medicine reduces multiple pathological processes in A $\beta$ PP/PS1 mice. *Journal of Alzheimer's disease: JAD*. 2015; 43(3):977-91
63. Tselnicker I, Keren O, Hefetz A, et al. A single low dose of tetrahydrocannabinol induces long-term cognitive deficits. *Neuroscience letters*. 2007; 411(2):108-11
64. Amal H, Fridman-Rozevich L, Senn R, et al. Long-term consequences of a single treatment of mice with an ultra-low dose of Delta9-tetrahydrocannabinol (THC). *Behavioural brain research*. 2010; 206(2):245-53
65. Broers B, Patà Z, Mina A, et al. Prescription of a THC/CBD-Based Medication to Patients with Dementia: A Pilot Study in Geneva. *Medical Cannabis and Cannabinoids*. 2019; 2(1):56-9