



Case Series

Neuropsychiatric Symptoms in Dementia. The Added Value of Cannabinoids. Are they a Safe and Effective Choice? Case Series with Cannabidiol 3%

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Abstract

Introduction: The behavioral and psychological symptoms of dementia (BPSD) are still among the most difficult symptoms in the management of dementia. It is estimated that BPSD affect up to 90% of all dementia subjects over the course of their illness, and is independently associated with poor outcomes, including distress among patients and caregivers, long-term hospitalization, early institutionalization, misuse of medication, and increased health care costs. **Method:** People with Dementia (PwD) and severe neuropsychiatric symptoms as assessed by the Greek version of Neuropsychiatric Inventory (NPI score >30) were recruited from the database of the Greek Association of Alzheimer's disease and Related Disorders. They were assigned to a prospective experimental study with cannabidiol (CBD) drops (KANNABIO CARE DROPS 3%®). The reassessment was performed either by a structured telephone interview or by clinical reassessment on site fifteen days after the initiation of the CBD administration. **Results:** The follow-up assessment showed improvement of the BPSD in 11 out of 17 of our patients, as was evaluated by the NPI (a decrease from a mean 65.54 to 19.73) in fifteen days after CBD initiation. These results were presented regardless of the underlying pathophysiology (Alzheimer's, Frontotemporal, or Lewy Body Dementia). **Conclusion:** Our case series is one of the largest in the current literature regarding cannabinoids and BPSD. We suggest that CBD may be an effective and safe choice for managing the BPSD. Future clinical trials are needed to reassure these findings.

Keywords: Cannabinoids; Dementia; Neuropsychiatric symptoms; Cannabidiol; Behavioral and Psychological symptoms of Dementia (BPSD)

Introduction

Over 50 million people worldwide were living with dementia in 2020. This number will almost double every 20 years, reaching 82 million in 2030 and 152 million in 2050 [1] (www.alzint.org). Whilst there have been limited success of clinical trials and disease modifying drugs, the behavioral and psychological symptoms of dementia (BPSD) are still among the most difficult symptoms in the management of PwD. BPSD includes emotional, perceptual, and behavioral disturbances [2]. It is estimated that BPSD affects over 90% of all dementia subjects over the course of their illness, and is independently associated with poor outcomes, including distress among patients and caregivers, long-term hospitalization, early institutionalization, misuse of medication, and increased health care costs [3]. The prevalence of non-cognitive BPSD in patients with Alzheimer's Dementia (AD), which is the most common form of Dementia, is 56–98% in the community and up to 91–96% in hospitals or long-term care facilities [4]. BPSD are caused by brain circuitry disruptions, which are theorized to increase the PwD's vulnerability to 3 categories of triggers: those related to the (1) patient (e.g., pain, hunger, and infection), (2) caregivers (e.g., competing priorities, unrealistic expectations, and negative communications), and (3) environment (e.g., overstimulation and limited light exposure). Non-biological determinants of BPSD identified that pre-morbid neuroticism, pre-morbid post-traumatic stress disorder, and problematic caregiver communication styles contribute to BPSD [2]. The experts' opinion regarding the pharmaceutical management of BPSD has not been altered significantly during the last decades [5,6]. They recommend using an atypical antipsychotic for agitation associated with delirium, psychosis, aggression, or anger. They would also consider divalproex to manage anger with a risk of physical aggression. Selective serotonin reuptake inhibitors were recommended for the treatment of depression or anxiety in PwD. Benzodiazepines or atypical antipsychotics were viewed as short-term options for acute anxiety. Trazodone was recommended for insomnia. Clinical experience has shown that BPSD with the above pharmaceutical options are not always effectively controlled, leaving the patient and his/her environment in an unbearable distress, and leading to faster institutionalization. Therefore, their use should be minimum, at low doses with slow titration [7]. It is also suggested that they should be removed as fast as possible after symptoms regulation with close monitoring [8]. Cannabinoids have been shown to have neuroprotective properties, reduce neuroinflammation, and enhance neurogenesis [9,10]. Evidence suggests that the utilization of marijuana products containing both Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) or CBD

alone have been effective and safe for use in older people with agitation associated with dementia. Cannabinoids were shown to be well tolerated, with few short-term side effects. This effect differs from first-line medications utilized for BPSD, which can have unwanted side effects. However, the evidence is still weak and further research regarding the safety, efficacy, and variability of these products in older people is needed [11,12]. Our study presents seventeen patients with severe BPSD, not well controlled by common pharmaceutical choices that were assigned to the clinical protocol with CBD 3% extract of industrial cannabis, as a therapeutic approach. To our knowledge, this is the longest case series published with CBD 3% Industrial Cannabis extract for BPSD.

Methodology

This was a prospective experimental study. PwD from different origins (Alzheimer's, Lewy Body, Frontotemporal, Parkinson's Disease Dementia, and Down Syndrome) with severe BPSD as assessed by the Greek version of Neuropsychiatric Inventory (NPI score >30) were recruited from the database of the Greek Association of Alzheimer's Disease and Related Disorders (GAADR). After a detailed informative discussion with their primary carer-givers and family members, they were assigned to an open clinical trial with CBD drops (KANNABIO CARE DROPS 3%®). The patient and the primary caregiver signed an informed consent. The CBD botanical Extract product [containing full spectrum organic hemp extract, premium organic extra virgin olive oil, natural terpenes and 300mg CBD+CBDA (1mg CBD+CBDA/drop), THC <0.2%] was supplied by the producer, KANABIO Social Cooperative Enterprise (SCE) for free for research purposes. The extract comes from biological cultures of industrial cannabis in Volos, Greece, produced and vialled in certified (ISO) laboratories in Greece and abroad. The patient received one drop t.i.d. with gradual titration to a maximum number of 10 drops daily (3 in the morning-3 in the afternoon-4 at night on the eighth day). The study protocol was approved by the bioethics committee of the Greek Association of Alzheimer's Disease and Related Disorders (protocol no 61/14-10-2020). The NPI reassessment was performed either by a trained psychologist with a structured telephone interview or by clinical reassessment on site fifteen days from the CBD initiation.

Cases Patient #1

A 76-year-old woman with AD and main symptoms aberrant motor disturbances and appetite/eating changes visited the Day Care Centre of the GAADR. The most recent neuropsychological assessment was on 12/10/2020 (MMSE: 5 HAMILTON:5, FRSSD from her caregiver: 30, and the NPI on 20/11/2020 was 42). The patient was treated with metformin 850mg, Levothyroxine 25mg, Aniracetam 1500 mg, Clopidogrel 75mg q.d., Donepezil 5mg q.d., Memantine 10mg b.i.d., Folic acid 5mg q.d., hydroxocobalamin 1mg

IM and cholecalciferol 25.000IU/ week per os, with no significant effect on her behavioral symptoms. Non-pharmacological therapies such as physical activity, music therapy, and reminiscence therapy and psychoeducational intervention had modest effects on her behavior. The patient initiated CBD 3 % on 20/11/2020 and they titrated CBD to 10 drops/day according to protocol. The patient's daughter reported significant improvement, especially of the aberrant motor disturbances. On 2/1/2021, the NPI was decreased to 16. In particular, the patient was noted to have better orientation inside the house, not going outside, and proper use of the toilet.

Patient #2

A 78-year-old man with AD and main symptoms agitation, depression, anxiety, irritability as well as nighttime sleep disturbance visited the Day Care Centre of the GAADR. The most recent neuropsychological assessment was on 22/09/2020 (MMSE:20, HAM:1, FRSSD:7) and the NPI on 23/11/2020 was 36. His medical treatment consisted of Bromazepam 3mg q.d., Atorvastatin 20mg q.d., Irbesartan- hydrochlorothiazide 150/12,5 q.d., Hydroxyzine dihydrochloride 25mg q.d., cholecalciferol 25.000IU/ week, Donepezil 5mg q.d. He was previously treated with paroxetine, but at his last examination, he had no depressive symptoms. However, neither medications nor non-pharmacological treatments had positive outcomes in the above BPSD. The patient initiated CBD 3% on 23/11/2020 and they titrated the dose to 10 drops/day, according to protocol. The patient's caregiver referred to a significant improvement, especially on anxiety and depression symptoms, and the NPI was decreased significantly from 36 to 7 on 2/12/2020.

Patient #3

This is a 72-year-old man with Parkinson's disease Dementia (PDD) with main symptoms anxiety, apathy, irritability, hallucinations-delusions and night time sleep disturbance. The most recent neuropsychological assessment was on 9/9/2020 (MMSE: 22, HAM: 28, FRSSD from Caregiver: 16) and the NPI on 26/11/20 was 48. His medical treatment at this point consisted of Rivastigmine TTS 9.5mg/24h q.d., Memantine 10 b.i.d., Levodopa-Benserazide, Escitalopram 20 1x1, Folic acid 5, pitavastatin 2mg q.d., Aspirin/Clopidogrel 100/75mg, Metoprolol, Vortioxetine 5mg q.d. He was previously treated with olanzapine, quetiapine, prazepam, trazodone, and venlafaxine in an effort to ameliorate BPSD. He also participated in non-pharmacological interventions. However, all these interventions did not reduce the negative behavioral symptoms. The patient initiated CBD 3 %, on 23/11/2020 and they titrated the dose to 10 drops/day according to protocol. Even though the patient's primary caregiver reported presence of hallucinations and delusions, they claimed a significant improvement in anxiety, apathy, irritability and nighttime sleep disturbance, with a decrease of NPI from 48 to 34 on 15/12/2020.

Patient #4

An 86-year-old woman with Lewy Body Dementia (LBD) and main BPSD symptoms agitation, depression, anxiety, irritability as well as nighttime sleep disturbance visited the Day Care Centre of the GAADR. The most recent neuropsychological assessment was on 21/09/2020 (MMSE: 14, HAMILTON: 12, FRSSD from her caregiver: 17) and the NPI on 31/12/2020 was 64. The interventional program comprised of pharmacological (Alprazolam 0.25mg b.i.d., Rivastigmine TTS 9.5mg/24h q.d., Atorvastatin 20mg, Metformin 850mg, Memantine 10mg b.i.d., Sertraline 100mg q.d., Metoprolol, cholecalciferol 25.000IU/ week, hydroxocobalamin inj IM, Amlodipine 5mg q.d., Hydroxyzine dihydrochloride 25mg b.i.d) and non-pharmacological interventions. She was previously treated with haloperidol, quetiapine, pipamperone, risperidone, alprazolam, and sulpiride in an effort to ameliorate the BPSD. However, all these interventions did not reduce the behavioral symptoms. The patient initiated CBD 3 %, on 03/12/2020 and they titrated the dose to 10 drops/day, according to protocol. On 5/1/2021, the NPI decreased from 64 to 28 and the patient was calm on 10 drops/day.

Patient #5

A 75-year-old man with Frontotemporal Dementia (FTD) and main BPSD symptoms agitation, delusions, anxiety, irritability and abnormal aberrant motor disturbances visited the Day Care Centre of the GAADR. The most recent neuropsychological assessment was on 28/02/2020 (MMSE: 3, HAMILTON: 18, FRSSD from his caregiver: 26) and the NPI on 28/12/2020 was 86. The patient was treated with Nebivolol 5mg q.d., Rivastigmine TTS 13,3mg/24h, Magnesium-Potassium, hydroxocobalamin inj IM, Quetiapine 25 t.i.p. He was previously treated with citalopram. However, these medications had no positive outcomes. The patient initiated on CBD 3% on 28/12/2020 and they titrated the dose to 10 drops/day, according to protocol. On 30/1/2021 the NPI was remarkably decreased from 86 to 9. Apart from some mild aberrant motor disturbances, the patient's primary caregiver reported improvement, especially on the patient's agitation, delusions/hallucinations, anxiety, irritability and behavioral disinhibition.

Patient #6

A 73 -year-old man with severe AD and main symptoms hallucinations-delusions, depression, nighttime sleep disturbance and apathy visited the Day Care Centre of GAADR. The most recent neuropsychological assessment was on 31/07/2020 (MMSE:8, FuCAS:94, GDS:0, SAST:15, NPI:39, CDR:14, ADCS-ADL:31, ROCFT:13). However, the NPI on 15/12/2020 was 57 and his family asked for help. His medical treatment consisted of Quetiapine 25mg t.i.d., Memantine 20mg q.d. and Insulin for Diabetes Mellitus. He was previously treated with citalopram, venlafaxine, risperidone and mirtazapine. Neither the above

medications nor common non-pharmacological interventions had positive outcomes for his BPSD. The patient initiated on CBD 3% on 5/1/2020 and they titrated the dose to 10 drops/day, according to protocol. On 31/01/2021, the patient's caregiver stated that he was calmer and had an improvement in his sleep, with a considerable decrease of NPI from 57 to 24.

Patient #7

A 78-year-old man with AD and main BPSD symptoms hallucinations, agitation, anxiety, depression, disinhibition, appetite/eating changes and night time sleep disturbance visited the Day Care Centre of the GAADR. The most recent neuropsychological assessment was on 11/12/2020 (MMSE: 21, HAM: 14, NPI: 18) and the NPI on 5/1/2021 was 92. His medical treatment consisted of Metformin 850mg, Atorvastatin 20mg q.d., Bromazepam 3mg q.d., Hydroxyzine dihydrochloride 25mg t.i.d., Homotaurine t.i.d., Donepezil 5mg, q.d., and Quetiapine 25mg q.d. He also participated in non-pharmacological interventions. He was previously treated with venlafaxine and amitriptyline-perphenazine. However, all the above interventions did not reduce the behavioral symptoms. The patient initiated on CBD 3 %, on 5/1/2020 and they titrated the dose to 10 drops/day, according to protocol. The primary caregiver reported significant improvement in almost all the behavioral symptoms and the NPI was decreased from 91 to 31 on 20/1/2021.

Patient #8

A 58-year-old man with FTD and main BPSD symptoms agitation, depression and apathy visited the Day Care Centre of the GAADR. His neuropsychological assessment on 7/01/2021 was: MMSE: 28, MoCA: 23, CDR: 3, FRSSD Caregiver: 14, FRSSD Patient: 5 and the NPI on 07/01/2021 was 16, however with intense agitation. The patient was treated with Memantine 10mg b.i.d., Nebivolol 5mg q.d., Escitalopram 20mg q.d., Aniracetam, Sach 1500mg q.d., Hydroxyzine dihydrochloride 25mg q.d. and with non-pharmacological interventions. He was previously treated with citalopram, risperidone, and mirtazapine. Patient initiated CBD 3 %, on 7/1/2021. They titrated the dose to 10 drops/day, according to protocol. The NPI on 30/1/2021 was 26 and the primary caregiver reported a significant improvement in patient's mood. However, the symptoms of apathy and the occasionally present hallucinations-delusions remained unchanged.

Patient #9

A 75-year-old man with PDD and main BPSD symptoms delusions, depression, anxiety, abberant motor disturbances and nighttime sleep disturbance visited the Day Care Centre of the GAADR. The most recent neuropsychological assessment was on 25/2/2020 (MMSE: 22, GDS: 2, FRSSD from his caregiver: 14) and the NPI on 5/1/2021 was 84. The medical treatment contained Cholecalciferol 2000IU q.d., hydroxocobalamin inj

IM, Levodopa-Carvidopa-Entacapone occasionally, Rasagiline 1mg q.d., Sertraline 100mg q.d., Pravastatin/fenofibrate 40/160mg q.d. However, neither medications nor non-pharmacological treatments had positive outcomes. The patient initiated on CBD 3% on 11/01/2021. They titrated the dose according to the protocol. On 20/01/2021, the NPI decreased from 84 to 14. The patient's caregiver stated a general improvement, especially on the patient's sleep and abberant motor disturbances. Moreover, she mentioned that patient's pain was also reduced and thus reduced the need for painkillers. However, because the patient would get excessively sleepy during the day, the dose was decreased in the morning hours.

Patient #10

A 94-year-old woman with AD and main BPSD symptoms delusions, irritability, abberant motor disturbances, appetite/eating changes and nighttime sleep disturbance visited the Day Care Centre of the GAADR. Her recent neuropsychological assessment on 22/12/2020: MMSE: 15, HAMILTON: 32, FRSSD from the caregiver: 22) and the NPI on 04/01/2021 was 58. The patient was treated with Hydroxyzine dihydrochloride 25mg q.d., Citalopram 20mg q.d., Memantine 10 b.i.d., Betahistine 8mg t.i.d., Folic Acid 5mg q.d., cholecalciferol 25.000IU/ week, Alphatocopherol acetate 10mg q.d., glyceryl trinitrate q.d., Donepezil 10mg q.d., Diltiazem, Simvastatin 20mg q.d., Irbesartan 150mg q.d. She was previously treated with mirtazapine and bromazepam. She also participated in non-pharmacological interventions. However, neither medications nor non-pharmacological treatments had positive outcomes. The patient initiated on CBD 3% on 04/01/2021. They titrated the dose according to the protocol. On 13/01/2021, the NPI was impressively decreased to 3 and the caregiver mentioned great improvement in all the behavioral symptoms. The patient was very calm, but sometimes she became lethargic.

Patient #11

An 83-year-old woman with AD/ Depression and main BPSD symptoms agitation, anxiety, irritability and nighttime sleep disturbance visited the Day Care Centre of the GAADR. Her latest neuropsychological assessment was on 7/01/2021 (MMSE: 23, HAMILTON: 14, FRSSD from the caregiver: 7) and the NPI on 7/1/2021 was 46. Her medical treatment consisted of rivastigmine 2mg/ml syr. 3ml b.i.d., pramipexole 0.18mg t.i.d., empagliflozin 10mg q.d., valsartan -hydrochlorothiazide el 150mg/12.5mg, metoprolol 5mg q.d., rosuvastatin 5mg q.d., clopidogrel 75mf q.d., glimepiride 4mg 1/2tb q.d., INN-insulin degludec/liraglutide 100U+ 3.6mg/ml q.d., Oxybutynin hydrochloride 5mg q.d., pantoprazole 40mg q.d., solifenacin 5mg q.d. She was previously treated with Flunitrazepam, Sertraline and Hydroxyzine dihydrochloride. She also participated in non-pharmacological interventions. However, all the above interventions did not manage

the behavioral symptoms. The patient initiated on CBD 3 %, on 07/01/2021. They titrated the dose according to the protocol. On 20/01/2021, the NPI was decreased from 46 to 16. The caregiver mentioned the patient was very calm, stopped crying and her sleep got better.

Patient #12

A 79-year-old woman with AD and main BPSD symptoms agitation, irritability, apathy, appetite/eating changes and nighttime sleep disturbance visited the Day Care Centre of the GAADR. Her latest neuropsychological assessment was on 22/12/2020 (MMSE: 0, HAMILTON: 13, FRSSD from her caregiver: 26 and NPI: 33). Her medical treatment included Memantine 10mg bid and Donepezil 10 mg qd. She was previously treated with Citalopram and Hydroxyzine Dihydrochloride without any response. The patient initiated CBD 3 %, on 30/12/2020. Unfortunately, they stopped due to side effects. They stopped even after the second attempt on 13/1/2021 because the patient became very aggressive and anxious. The patient lives in an island far away from our Day Center and her family had no opportunity to communicate with us because of COVID-19 in order to understand what were the problems with CBD.

Patient #13

A 60-year-old man with Dementia Down Syndrome and epilepsy, with main symptoms hallucinations-delusions, depression, anxiety, apathy, irritability and nighttime sleep disturbance visited the Day Care Centre of the GAADR. The most recent neuropsychological assessment was on 3/10/2019 (MMSE: 0, HAMILTON: 12, FRSSD from his caregiver: 33) and the NPI was 72 on 18/12/2020. The patient was treated with Hydroxyzine dihydrochloride 25mg 1x3, Rosuvastatin 20mg qd, Rivastigmine patch 9,5mg qd, Memantine 10mg b.i.d., Quetiapine 25mg q.d., Calcium gluconate q.d., Co Q10 q.d., Levothyroxine 75mg q.d., Risperidone 1mg q.d., Mirtazapin 30mg q.d., and Lamotrigine 100mg b.i.d. with no significant effect on his behavioral symptoms. He was previously treated also with paroxetine, alprazolam and citalopram. The patient initiated CBD 3 %, on 18/12/2020. They titrated the dose according to the protocol. The NPI on 5/1/2021 decreased from 72 to 12 with an improvement to his nighttime sleep disturbance. However, as the dose increased to 10 drops per day the patient has caregiver mentioned side effects such as agitation and one epileptic seizure, so the administration stopped on 12/1/2021.

Patient #14

A 75-year-old woman with LBD and main BPSD symptoms, delusions, anxiety, irritability, abberant motor disturbances and appetite/eating changes visited the Day Care Centre of the GAADR. The most recent neuropsychological assessment was

on 09/12/2020 (MMSE: 17 HAM: 19, FRSSD from her caregiver: 27 and the NPI was 71). The patient was treated with Olmesartan Medoxomil 20/12 q.d., Macrogol 13.3gr b.i.d., Vildagliptin-Metformin 50/100 q.d., Rivastigmine TTS 9,5 mg q.d., Levodopa-Benserazide (200+50mg) 1/2tb b.i.d, Citalopram 40mg q.d., Hydroxyzine dihydrochloride 25mg t.i.d. with no significant effect on her behavioral symptoms. The patient initiated CBD 3 %, on 09/12/2020. They titrated the dose according to the protocol only for 4 days. On 08/01/2021, the NPI was 71 and the caregiver stated that they did not notice any change in her behavior and they stopped CBD after 4 days, on 13/1/2021. However, it has to be emphasized that the patient did not have a 24/7 care-giver or family member by her side and they did not follow the protocol.

Patient #15

A 74-year-old woman with AD and main symptoms anxiety, depression, sleep, appetite/eating changes and abberant motor disturbances visited the Day Care Centre of the GAADR. The latest neuropsychological assessment was on 12/02/2020 (MMSE: 10, GDS: 1, NPI: 41, FRSSD from her caregeiver: 14) and the NPI on 05/01/2021 was 54. The patient was treated with Alendronate sodium trihydrate- Cholecalciferol 70 mg/ 140mcg, Calcium carbonate 500mg, Atorvastatin-ezetimibe 10/40mg, Donepezil 5mg q.d., Memantine 10mg b.i.d., with no significant effect on his behavioral symptoms. She was previously treated with bromazepam. The patient initiated on CBD 3 %, on 11/01/2021. They titrated the dose according to the protocol. The caregiver on 20/01/2021 stated that they did not notice considerable change in her behavior as she was depressed and more anxious. The NPI was 52 and caregiver reported that they stopped CBD after 8 days, on 19/1/2021.

Patient #16

A 94-year-old woman with LBD and main symptoms anxiety, nighttime sleep disturbance, apathy, irritability and lifting of suspensions visited the Day Care Centre of the GAADR. The latest neuropsychological assessment was on 30/10/2020 (MMSE: 17, HAM: 18, FRSSD from her caregiver: 26) and the NPI on 11/1/2021 was 69. The patient was treated with Paracetamol, Rivastigmine 9.5/24h TTS, Hydroxyzine dihydrochloride 25mg t.i.d., Diacerein, Folic Acid 5mg q.d., hydroxychloroquine 200mg q.d., Omeprazole 20mg, cholecalciferol 25.000IU/ week, with no significant effect on her behavioral symptoms. The patient was previously treated with mirtazapine, diazepam, olanzapine, quetiapine, zolpidem in different periods in an effort to ameliorate the BPSD. The patient initiated on CBD 3 %, on 11/1/2021. They titrated the dose according to the protocol. The caregiver on 20/01/2021 said that the patient was more anxious. In addition, they noticed high blood pressure. She stopped CBD after 3 days on 23/01.2021 due to the above side effects.

Patient #17

A 64-year-old woman with FTD and main BPSD symptoms, abbe, depression, apathy, as well as hallucinations-delusions visited the Day Care Centre of the GAADR. The most recent neuropsychological assessment was on 19/10/20 (FuCAS: 119, CDR: 16, ADCS-ADL: 9, FRSSD from her caregiver: 26) and the NPI on 28/12/2020 was 57. Her medical treatment consisted of Esomeprazole 40mg q.d., Pregabalin 150mg t.i.d., Trazodone 150mg q.d., Olanzapine 5mg q.d., biperiden b.i.d., Haloperidol 5mg b.i.d. She was also treated with levomepromazine previously. However, the above treatments had no positive outcomes. The patient initiated on CBD 3% on 31/12/2020. They titrated the dose according to the protocol. The patient's caregiver did not notice a significant important improvement and he stopped CBD administration after 20 days, as he mentioned the patient was disorganized. The NPI had a minimum decrease from 57 to 51 on 6/4/2021.

Discussion

To our knowledge, this is the largest case series regarding PwD with different forms of dementia (9 AD, 3 LBD, 2 FTD and 2 PDD, 1 Down Syndrome) with severe BPSD (NPI score >30), treated with CBD 3% extract of Industrial Cannabis. Our seventeen patients were 9 females and 8 males, with a mean age of 80, 70 years. Eleven out of the seventeen had a positive outcome with an average decrease of NPI from 65.54 to 19.73 in a very short time. The feedback of the families was also positive in most of the cases. We also observed a decrease of daily analgesic drug consumption and a referred rigidity reduction/ mobility improvement of a PDD patient. The most common adverse event was agitation and in few cases somnolence which was improved by removing or lowering the CBD dose. As described above, the least manageable symptoms with CBD were the perceptual disturbances. The cases that did not respond had various backgrounds (AD, LBD, FTD, and Down syndrome), so we cannot conclude regarding the underlying pathophysiology. Previous experimental studies with cannabis products have also observed positive results regarding the BPSD [13-15]. Few randomized controlled trials (RCTs) have focused on medical cannabis for the older adult population. Existing studies have small sample sizes (N <100) and indicate a lack of high-quality evidence for the efficacy and safety of medical cannabis for older adults [16], while only five [17-21] have been conducted with PwD. Three out of five had the BPSD as primary endpoints [17,18,21], and all of them used THC or its synthetic analogue (nabilone). On the other hand, CBD has been used as a treatment for psychiatric disorders and although available trials reported potential therapeutic effects, there is still limited evidence regarding the safety and efficacy of CBD for the treatment of psychiatric disorders of PwD [22].

So, what is the underlying theory indicating this treatment effect? Cannabis sativa L. has been used for decades for medical purposes. However, its clinical use has been limited due to the effects on the central nervous system and the possibility of drug abuse and addiction [23]. The plant exudes two principal components, Δ^9 - tetrahydrocannabinol (THC) and cannabidiol (CBD). The structure and configuration of CBD was discovered in the 60s and has gained particular attention due to the lack of psychotropic activity, its antipsychotic, anxiolytic, antiseizure, as well as anti- inflammatory properties and its excellent tolerability in humans. Cannabidiol exerts complex actions at multiple receptors within the endocannabinoid system (ECS). The ECS consists of cannabinoid receptors, endogenous ligands and enzymes within the brain and immune system. The two principal cannabinoid receptors are cannabinoid receptor type-1 (CB1) and cannabinoid receptor type-2 (CB2), both distributed throughout the brain with greater expression in the neocortex, basal ganglia, and hippocampus. The CB1/CB2 receptor systems have a mechanistic role in memory, appetite/eating changes, and stress response. Cannabidiol acts as a non-competitive antagonist at CB1 receptors and an inverse agonist at CB2 receptors. Cannabidiol inhibits the reuptake and enzymatic degradation of the endogenous cannabinoid anandamide (N-arachidonylethanolamine or AEA), which has a well-established effect on neuronal/synaptic function. Cannabidiol also exerts agonistic activity at the 5-HT_{1a} receptors. This action is hypothesized to mediate antidepressant, anxiolytic and cognitive effects [13,24-26].

BPSD are a significant problem in everyday clinical practice due to the prevalence, severity of symptoms, burden on the caregiver, and difficulties in treatment. Many existing clinical guides recommend the use of non-pharmacological methods as the first course of action, and that pharmacotherapy should be used as a secondary option or when there is severe presentation of symptoms. In practice, a range of drugs is used, although most are antipsychotics [7]. Antipsychotics provide only modest improvements and are associated with increased mortality [27]. There is no FDA- approved treatment for BPSD until today. There is currently only one FDA-approved CBD (Epidiolex®) prescription drug being used to treat two rare genetic epilepsy syndromes [28] and Nabiximols (Sativex®) [29] is currently approved in Europe and Canada for severe spasticity in MS. However, CBD seems to have many off-label uses in neurological diseases such as chronic pain, essential tremor, Parkinson's disease, Anxiety related disorders, trigeminal neuralgia, and epilepsy [28]. Moreover, based on its pharmacology, cannabis components (THC±CBD) may provide benefits on brain tumors, brain injury, AD, chronic traumatic encephalopathy and brain injury [30]. At this time, recommendations for the routine use of CBD targeting BPSD cannot be suggested. The evidence regarding CBD's role in BPSD will be investigated by ongoing and future Randomized Controlled

studies [25]. There is limited evidence for use of CBD in dementia with most of the research available in AD. However, the experience from our patients indicate that CBD can be a treatment option in BPSD, with the advantage of fast, at least short-term results, well tolerated and cost-effective compared to the prescribed medical Cannabis (Sativex®), which is currently available only to patients with chronic pain due to cancer in Greece (off-label use).

Consent for publication

Written informed consent was obtained from all the subjects and their caregivers for publication of this case report series. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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